AN UNUSUAL CASE OF HAEMOCHROMATOSIS

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Idiopathic haemochromatosis[1-3] is a relatively rare disease, believed to be due to an inborn error of metabolism, in which there is excessive absorption of iron from dietary sources. This eventually leads to massive storage of iron in the tissues and associated evidence of damage to the organs. About 30% of the cases of the disease are in chronic alcoholics. The clinical syndrome consists of cirrhosis of the liver, diabetes, skin pigmentation, and hypogonadism. Cardiac complications may occur.

The plasma iron is raised and the plasma protein (transferrin) is more than 90% saturated. In 50% of cases haemosiderin is present in the skin, with the deposits most marked in the dermis.[4] The diagnosis is confirmed by liver biopsy, which shows a septal cirrhosis and haemosiderin deposition in the parenchymal liver tissue.

Since the major organs showing tissue damage in this disease are those in which iron deposits are greatest, for the last few years phlebotomy has been used to remove the excess iron in the hope that the progressive damage in the tissues will be halted. Phlebotomy is followed by mobilization of storage iron.[5-11] Clinically it may also be followed by a decrease of skin pigmentation,[5-10] but serial postphlebotomy biopsies of the skin have not been reported. Postphlebotomy biopsies of the liver have shown a variable picture, ranging from a reduction in the amount of iron to a complete absence of iron.[5,12] After phlebotomy the plasma iron is reduced, and the percentage saturation of the transferrin falls once iron stores are exhausted.

The following case is presented to illustrate the extent to which iron can be mobilized from the tissues as a result of repeated large haemorrhages.

CASE REPORT

A 37-year-old European male was admitted to a hospital in May 1957 complaining of swelling of the legs and abdomen. As a child he had had jaundice at the ages of 5 and 8 years. When 23 he was told by a doctor that he had an enlarged liver. He was an alcoholic and for the last 5 years had been drinking 2 - 3 bottles of brandy a day.

He had a brother aged 35 who was a known haemochromatotic, this diagnosis having been confirmed by liver biopsy. The brother was not an alcoholic. A paternal aunt and the paternal grandfather were both diabetic.

On examination the patient was found to have ascites, marked ankle oedema, jaundice, and a five-finger nodular hepatomegaly. A reversal of the albumin-globulin ratio and abnormal flocculation tests were found. Six months later he developed diabetes and was noted to be markedly pigmented.

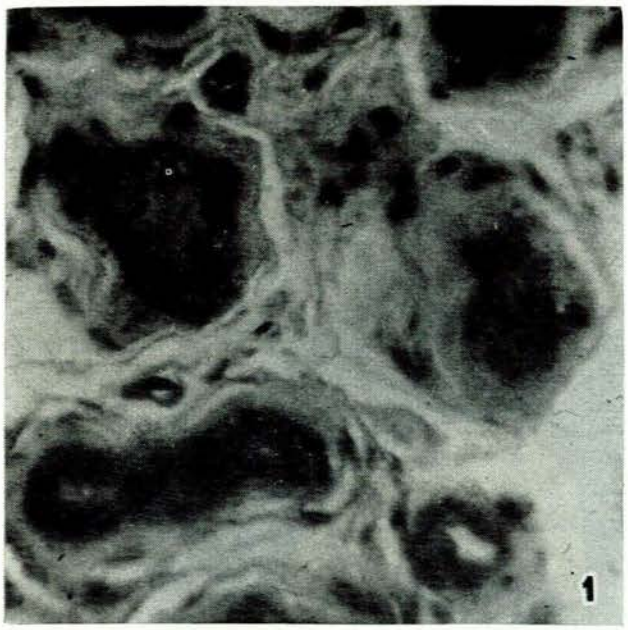

Fig. 1. Skin biopsy. Well-marked haemosiderin deposition in the sweat glands of the skin of the shoulder. (Perls' Prussian-blue reaction×960.)

He had also become impotent. A biopsy of skin from the shoulder area showed haemosiderin in the basal epithelial cells and also around the sweat glands (Fig. 1). The plasma iron on two occasions was 250 and 240 micrograms per 100 ml. (normal range 70 - 150).

The patient, then, with a family history of haemochromatosis, presented clinically with cirrhosis of the liver, diabetes, skin pigmentation, and hypogonadism. Haemosiderin was found by skin biopsy and the plasma-iron levels were significantly raised. A diagnosis of idiopathic haemochromatosis was made.

Towards the end of 1959 he was admitted on 3 separate occasions to a country hospital for control of haemorrhage from tooth sockets following dental extractions. At this time no investigations were carried out. He was not transfused nor was he given any iron therapy. In January 1960 he was admitted for jaundice and epistaxis. The plasma iron was 290 micrograms per 100 ml. After phlebotomy of 1,000 ml. of blood the plasma iron dropped to 199 micrograms.

Six weeks later he was transferred for the first time to the Johannesburg General Hospital to be treated for diabetes. On examination he was found to have a slate-grey skin pigmentation, firm, non-tender, five-finger hepatomegaly, gonadal atrophy, and sparse axillary and pubic hair. The plasma iron ranged from 240 to 250 micrograms per 100 ml. and the plasma protein (transferrin) was fully saturated. A skin biopsy showed an increase of melanin in the epidermis but no haemosiderin was seen. After 3 weeks in hospital he was discharged on 120 units a day of protamine zinc insulin. Throughout his stay in hospital his diabetes was very difficult to control.

In May 1960 he was readmitted for epigastric pain and melaena. The estimated blood loss was five pints. The haemoglobin was 8 G. per 100 ml., the plasma iron was 300 micrograms per 100 ml., and the transferrin was 93% saturated. The platelet count and Coombs test were normal. The prothrombin index was 67%. The haemoglobin rose to 11·6 G. per 100 ml. without any transfusion or iron therapy, but the plasma iron dropped to 57 micrograms per 100 ml. and the saturation of the transferrin was low. A barium swallow revealed no varices, but occult blood was consistently present in the stools.

As an outpatient over the following 5 months, 5 litres of blood were removed by phlebotomy. The blood smears showed normochromic red blood cells and the mean corpuscular haemoglobin concentration ranged from 30 - 34%.

In May 1961 he was again admitted for jaundice and bruising. He said he had had numerous nose and mouth bleeds on the pillow at home. Occult blood was still present in the stools but once again no varices were demonstrated by barium swallow. The haemoglobin rose from 12 G. per 100 ml. on admission to 15 G. at the time of discharge. No iron therapy or transfusions were given.

Three months later he had a severe haematemesis and melaena. The blood loss was estimated at about 5 pints. The haemoglobin was 8 G. per 100 ml. and the plasma iron 160 micrograms per 100 ml. He was transfused for the first time and a Blakemore tube was passed to control the bleeding. While in hospital he had two further episodes of haematemesis and melaena. He received a total of 4 pints of blood and at the time of discharge his haemoglobin was 15·2 G. per 100 ml.

The final hospital admission occurred in October 1961, again for haematemesis and melaena. He had been bleeding excessively before admission and the haemoglobin had dropped to 7·5 G. per 100 ml. The prothrombin index was 45% and the plasma iron 46 micrograms per 100 ml. In spite of appropriate therapy he continued to bleed profusely and died after a tremendous haematemesis and melaena.

The serial changes in plasma-iron levels that occurred during the patient's illness are shown in Fig. 2. In view of the fact

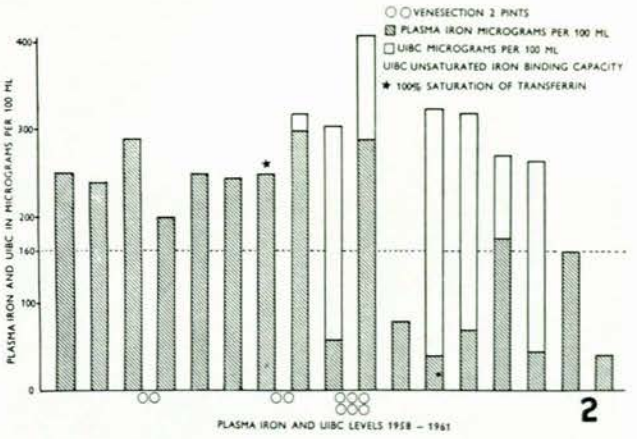

Fig. 2. Serial changes in level of plasma iron and unsaturated iron-binding capacity during patient's illness.

that his brother was known to have the disease, other members of the patient's family were studied. The results of the measurements of plasma iron and the unsaturated iron-binding capacity are shown in Fig. 3.

Autopsy Report

The postmortem examination was carried out 14 hours after death. No obvious skin pigmentation was noted. The lungs were congested and oedematous. The heart (380 G.) showed no pathological change. The oesophageal veins were dilated and prominent. The entire bowel was filled with fresh blood, but no fresh bleeding point was found. The liver was grossly enlarged (2,460 G.) and nodular. It was pale, and on section showed a well-marked cirrhosis, with nodular areas of regeneration. The pancreas was white and fibrotic. The spleen was enlarged (375 G.). The capsule was thickened and on section the spleen was soft, with prominent trabeculae.

Histology

Liver. Broad bands of fibrous tissue surrounded the portal tracts and traversed the parenchymal tissue. Bile-duct proliferation was not marked. The reticulum stain demonstrated scattered areas of collapse, with two or three portal tracts

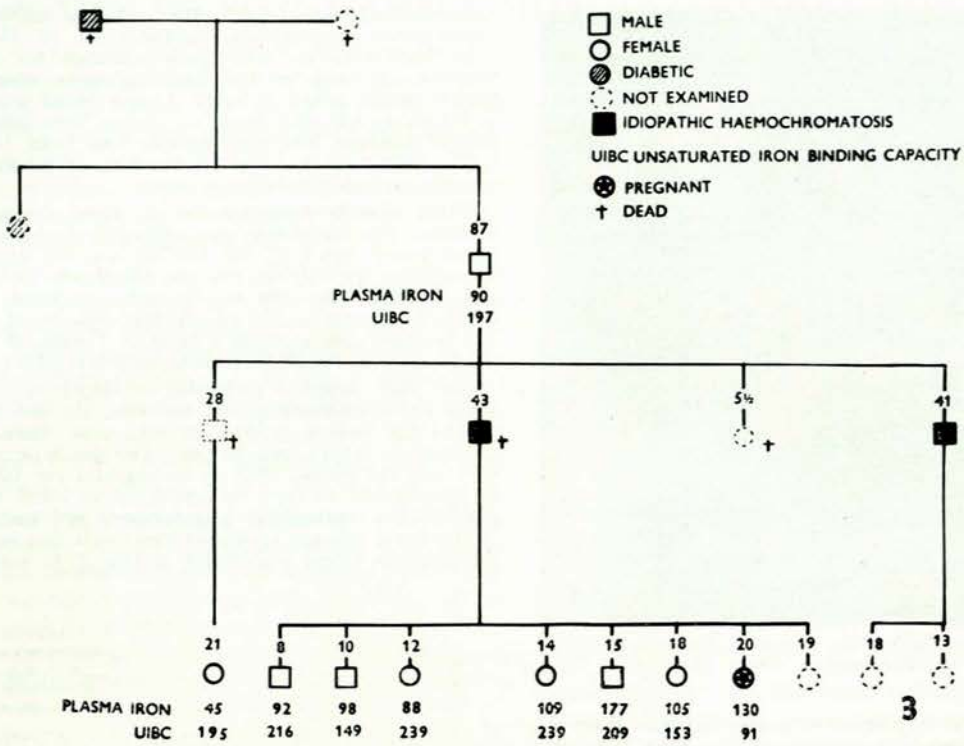

Fig. 3. Plasma iron and unsaturated iron-binding capacity of other members of the patient's family.

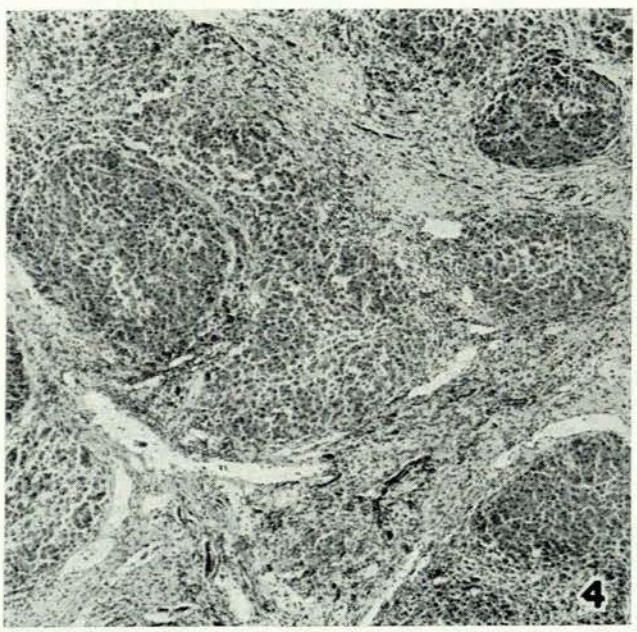

Fig. 4. Postmortem histology. Nodules of regenerating liver cells, fatty change, broad bands of connective tissue, and some bile-duct proliferation, are demonstrated in this lower-power field. (H. & E.×50.)

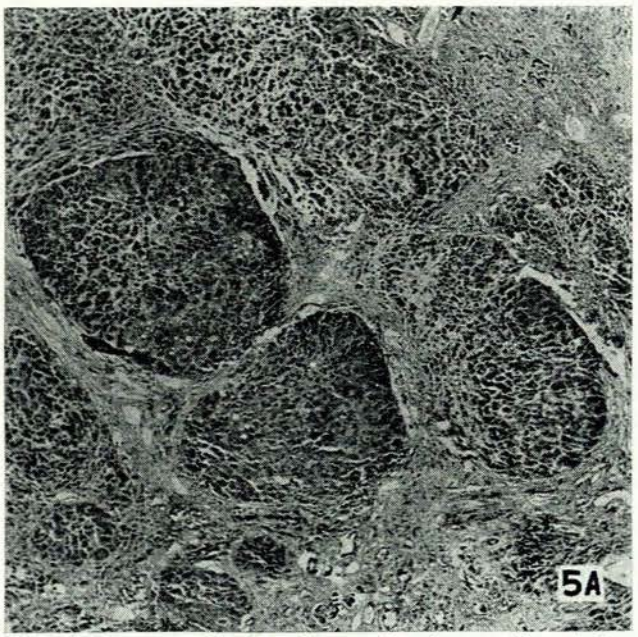

Fig. 5A. Postmortem histology. The complete absence of iron is demonstrated in this lower-power view of the liver. Compare with the control Fig. 5B. (Perls' reaction×50.)

adherent to each other. The surviving parenchymal tissue showed fatty change with fatty cyst formation. The nodules of regenerating tissue were irregular in size and shape (Fig. 4).

Pancreas. Intralobular and interlobular fibrous tissue was considerably increased. The islets showed a mild degree of fibrosis.

Testes. The lamina propria of the tubules was thickened and there was a complete absence of normal spermatogenesis.

Histopathology

Liver. Perls' stain was used to demonstrate the presence of iron, but though numerous sections were examined no iron was found either in the fibrous tissue, reticulum cells, or liver cells (Figs. 5A and 5B). Lipofuscin was detected in moderately increased amounts in the parenchymal cells (P.A.S. technique and Mallory's method). This pigment, derived

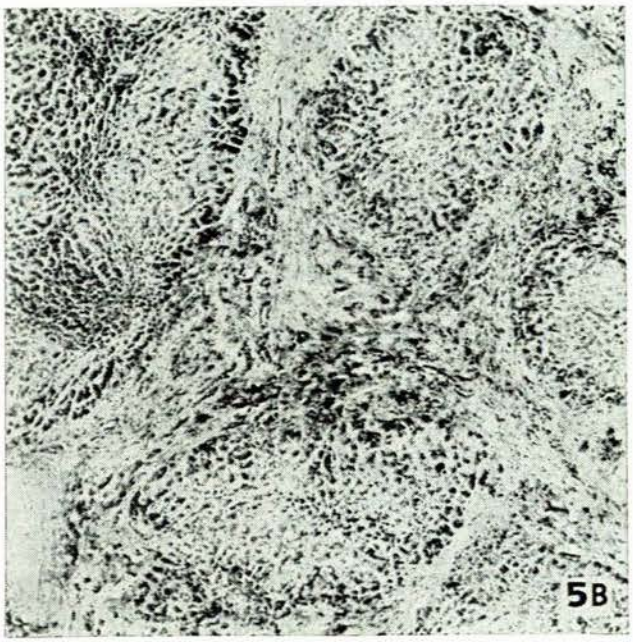

Fig. 5B. A liver of a case of haemochromatosis used as a control. Note the large amounts of iron (appearing black in this picture) in the parenchymal cells, Kupffer cells, and connective tissue. (Perls' reaction×50.)

from lipids or lipoproteins, is sometimes increased in haemochromatosis.

Pancreas. Small amounts of iron were present both in the acinar cells and in the epithelial cells of the islets of Langerhans.

Pituitary, adrenals, thyroid, testes, and prostate. Occasional scattered deposits of iron were present in the epithelial cells and blood vessels of the pars intermedia of the pituitary, the zona glomerulosa of the adrenal, and the epithelial cells lining the thyroid follicles. The testes and epididymis were devoid of iron but the prostate contained small amounts.

Spleen, lymph glands, and bone-marrow. With the exception of the bone-marrow, where normal amounts were present, no iron was found in the reticular endothelial system.

Skin. Sections of skin from the anterior chest wall, arm, and thigh, showed a moderate increase in melanin but no iron was present.

Specimens of liver, pancreas, thyroid and testes were dry ashed and the iron contents estimated. The results were as follows (mg. % dry weight): liver 0·01, thyroid 0·037, testes 0·036, adrenal 0·065, pancreas 0·097. These are all within normal range.

DISCUSSION

This case report serves to illustrate the difficulties associated with the diagnosis of haemochromatosis. Despite the fact that the clinical and biochemical findings conformed in every way to the accepted pattern of idiopathic haemochromatosis, there was an almost complete absence of iron in the tissues at postmortem.

Although phlebotomies had been carried out, only about 2·5 G. of iron had been removed from the patient by this route. However, he had suffered from repeated pathological bleeding episodes and presumably most of the excessive iron present in the body was mobilized in this way. The total loss of blood cannot be calculated because the amount lost in melaena, haematemesis and epistaxis cannot be estimated. The tissue stores of iron in haemochromatosis vary between 20 and 40 G. An average loss of 30 ml. of blood per day would mobilize 5·5 G. of iron per annum, or 22 G. over 4 years. We believe that this estimate is compatible with the patient's history and would account for the postmortem findings. Losses greater than this (induced by phlebotomy) have been reported in the literature.[8,10,11]

The diffuse type of septal cirrhosis of the liver that was seen in this case, with collapse of some of the lobules, is found in cases with a secondary type of lobular collapse. The diffuse septal cirrhosis found in classical haemochromatosis is altered by the changes associated with dietary deficiency and alcoholism, so that a mixed histological picture results. It was of some interest that even in the fibrous tissue of the cirrhotic liver no iron was observed. The complete mobilization of iron from the fibrous tissue of the liver has not, to the best of our knowledge, been previously reported as a postmortem finding in a treated haemochromatotic, although the photomicrographs of at least one of Davis and Arrowsmith's biopsies[5] shows cirrhosis without iron after phlebotomy. The presence of small amounts of iron in the other tissues of our patient suggests that there must have been iron in the liver at some stage, for iron deposition in the epithelial tissues probably follows the iron deposition in the liver.[12,14]

That iron was continually mobilized and used is evidenced by the fact that at no stage in the clinical history did the patient have a hypochromic anaemia, despite phlebotomy and the enormous blood loss. This is a well documented feature[4,6] in cases with large iron stores. It is also of interest to note that the depletion of iron stores did not improve the diabetes, which was difficult to control at all times.

SUMMARY

A case of idiopathic haemochromatosis is described. The history was traced over a number of years and the family investigated. Although the clinical and biochemical findings conform to a diagnosis of haemochromatosis, the pathological findings do not confirm the clinical diagnosis. This discrepancy is discussed.

We are greatly indebted to Dr. T. H. Bothwell for his invaluable advice in the preparation of this paper; we are also indebted to Dr. G. S. Getz. In addition we should like to thank Dr. Pericles Menof for his encouragement and permission to publish this case, Dr. Peter Jacobs, the photographic staff of the Department of Medicine, and Mrs. J. E. Bailey of the Department of Pathology.

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