HAEMOCHROMATOSIS IN A FAMILY, AND ITS OCCURRENCE IN TWO WOMEN

BY

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Haemochromatosis is an uncommon disease which occurs principally in men. Houston (1953) was able to review 512 reported cases, of which only 33 were women. A familial incidence of the disease is not well known, although its occurrence has been reported on a number of occasions (Sheldon, 1935; Lawrence, 1935, 1949; Rogers, 1950; Houston and Zilkha, 1955; Houston, 1957). In this paper a family is reported in which two brothers have haemochromatosis in classical form, and their sister, who has neither symptom nor sign of the disease, has a raised serum iron. Two female patients who have the classical triad of cirrhosis, diabetes, and skin pigmentation are also reported.

Case Reports

Case 1.—This patient was born in 1900. Symptoms of diabetes developed in 1950, but he did not receive treatment until 1951, when he was admitted to the Dumfries and Galloway Royal Infirmary in diabetic precoma. Enlargement of the liver was observed at this time and did not regress when his diabetes was stabilized. Skin pigmentation became obvious about three years later, but a skin biopsy showed no increase in iron. Skin pigmentation continued to increase, however, and by 1957 there was no doubt about the diagnosis. The liver was enlarged 5 in. (12.5 cm.) below the right costal margin and was firm. The skin had a slate-grey hue. Diabetes required 80 units of insulin zinc suspension for control. Serum iron was 554 $\mu\text{g./100 ml.}$, but liver function tests were normal. Regular venesection was begun at this time and improvement has taken place.

Case 2.—Born in 1906, the brother of Case 1. He was admitted to hospital in 1957 complaining of weight loss and vague ill-health of one year's duration. He did not admit to thirst or polyuria, but the urine contained sugar, and a glucose-tolerance curve was typical of diabetes mellitus. On examination he was found to have slight skin pigmentation and hepatic enlargement to just below the right costal margin. Haemochromatosis might not have been considered had his brother not been known to the medical unit, for the signs were not striking. Serum iron, however, was greatly increased at 332 $\mu\text{g./100 ml.}$, and regular venesection has been employed with benefit and without the occurrence of anaemia. His diabetes is controlled by diet alone. Liver-function tests are normal.

Case 3.—Born in 1897, the sister of Cases 1 and 2. She was examined at my request and had no complaint other than joint pain due to long-standing rheumatoid arthritis. The only positive features on examination were related to the arthritis. She had six full-time pregnancies between 1920 and the early 1930's, and the menopause took place in 1947. The urine was free of sugar and liver-function tests were normal, but the serum iron was raised to 190 $\mu\text{g./100 ml.}$ (normal range 78–170 $\mu\text{g./100 ml.}$).

Case 4.—A married woman born in 1897 developed diabetes in 1948 shortly after emigrating from Glasgow to South Africa. Her skin had always been dark, but it became much darker at this time. In 1950 she was admitted to the medical wards of the University of Witwatersrand in diabetic coma, and during this admission a diagnosis of haemochromatosis was clearly established by liver biopsy and radioactive iron studies. Diabetes was extremely difficult to control, and the daily dose of soluble insulin

varied from 400 to 600 units. In 1953 she returned to Glasgow and was admitted to the professorial medical unit in the Royal Infirmary for stabilization of diabetes. The menstrual history, obtained at this time, was that periods had been scanty for many years and had ceased completely in 1947 at the age of 50. She had never been pregnant. On examination the liver was enlarged 2 in. (5 cm.) below the right costal margin and the skin was obviously pigmented. Serum iron was 248 $\mu\text{g./100 ml.}$ and the serum iron-binding capacity was nil. Liver-function tests were normal. The patient has been treated most successfully over a period of eight years by repeated venesection, and signs of the disease have regressed. Insulin requirements, however, are still very high.

Case 5.—A woman born in 1892 was admitted to the Dumfries and Galloway Royal Infirmary in 1955 for stabilization of diabetes. She was found to have dusky skin pigmentation and hepatic enlargement of 3 in. (7.5 cm.). Serum iron was 379 $\mu\text{g./100 ml.}$ and a glucose-tolerance curve was typical of diabetes mellitus. Liver-function tests were normal. The patient began to menstruate at the age of 10, and the menopause took place while she was in her early thirties. She had three sons, all of whom were stated to be well, but unfortunately none was available for examination. Treatment by repeated venesection has been successfully carried out.

Discussion

Haemochromatosis is due to an inborn error of metabolism whereby excessive amounts of iron are absorbed from the small intestine and stored throughout the body, notably in liver, spleen, marrow, pancreas, heart muscle, pituitary, and skin. Symptoms and signs of the disease are uncommon before middle life in men and generally occur at a greater age in women. Physiological loss of iron by menstruation and pregnancy is the accepted explanation for the paucity of female patients, but it is probable that this loss merely delays the recognition of haemochromatosis and that the fundamental abnormality of iron absorption is present in both sexes.

Assuming that the reproductive life of a woman extends between the ages of 13 and 50, and that the average menstrual loss each month contains 25 mg. of iron (Fowler and Barer, 1935), then approximately 11 g. of iron is removed from the body by menstruation alone, the approximate equivalent to the iron contained in 44 pints (25 litres) of blood. In addition, each pregnancy would account for a further loss of 0.5 g. of iron, even when allowance is made for the absence of the menses. These figures can be compared with the quantity of iron in the tissues of a patient with haemochromatosis, estimated to lie between 20 and 60 g. (Sherlock, 1955). It can therefore be understood how physiological iron loss will retard the progress of the disease, and it is probably significant that many of the reported female patients with haemochromatosis had absent or scanty menstruation. Houston (1953) could find only three female patients in whom a diagnosis was made before the age of 45 years, and one of these had had amenorrhoea for 13 years prior to her death.

In Cases 4 and 5 both patients have abnormal menstrual histories in that periods were abnormally scanty in Case 4, while in Case 5 the menopause occurred at a very early age. In the latter case haemochromatosis was not recognized until 30 years after menstruation had ceased. In Case 3 the patient, who had a normal menstrual history and a family of six, would appear to have so delayed the progression of the disease that, at

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the age of 61, she still has neither symptom nor sign, although the serum iron is raised.

Until recent years there was no effective treatment for haemochromatosis. The various therapeutic regimes, such as a low-iron diet, or a diet rich in phosphorus to delay the absorption of iron, met with little or no success; this was not surprising, as large quantities of iron had accumulated in the body by the time that the disease was productive of symptoms. The only rational method of effecting improvement is to remove iron from the tissues, and this can readily be achieved by repeated venesection, each pint (570 ml.) of blood containing about 250 mg. of iron. After venesection, mobilization of body iron is rapid, and 20 to 40 pints (11.4 to 22.7 litres) of blood can be removed in as many weeks without the development of a hypochromic anaemia. The good results of this treatment were first reported by Finch (1949) and have been confirmed by other workers (Davis and Arrowsmith, 1952; Finch and Finch, 1955; McAllen, Coghill, and Lubran, 1957). The recognition of a familial incidence of the disease will enable the diagnosis to be made in the relatives of such patients at a stage before the development of symptoms. If a raised serum iron is accepted as evidence that haemochromatosis exists in a subclinical form, treatment by controlled venesection may prevent the occurrence of clinical disease. It is therefore important to examine the relatives of these patients and to make periodic estimations of their serum iron.

During the past six years, as part of a study of portal cirrhosis, I have been interested in eight patients with haemochromatosis. Three of these patients had duodenal ulceration of some severity. One man presented with a perforated ulcer; a second man died from haemorrhage when a large chronic ulcer eroded an artery; a third man had a 20-year history of chronic dyspepsia, and cirrhosis was first observed when a gastrojejunostomy was performed. This association has not previously been commented on, although four of the seven male patients with haemochromatosis reported by McAllen, Coghill, and Lubran (1957) also had duodenal ulceration. Sheldon (1935) cited only one instance of this in his review of 311 cases. It is possible that this observation is but a reflection of an increasing incidence of duodenal ulceration in men during the twentieth century, but the occurrence is reported here as it may have some relevance, particularly as the duodenum is believed to be the principal site of iron absorption.

Summary

The cases of two brothers with haemochromatosis are reported. Their sister, aged 61, has a raised serum iron but is at present asymptomatic. As repeated venesection may halt the progress of this disease, it is suggested that the relatives of patients with haemochromatosis should be examined and serum iron estimations made.

The cases of two women with classical haemochromatosis are reported. In both instances the diagnosis was made after the menopause.

The occurrence of duodenal ulceration in three out of eight patients with haemochromatosis is commented on.

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"LIPOSTABIL": A PILOT STUDY

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A number of preparations have been introduced recently for the treatment of diseases associated with abnormal lipid metabolism. Their purpose is to reduce abnormally high cholesterol levels and in other respects to restore a more normal blood lipid pattern. These preparations are mainly intended for the treatment of patients with ischaemic heart disease, and this report gives the results of a pilot trial with one of them ("lipostabil"). Each capsule contains: alpha- and beta-lecithins of soya bean, 175 mg.; 3-4-5 polyoxyethylene-sorbitolmono-oleate, 100 mg.; potassium theophyllinate potassium thiocyanate, 50 mg.; (addition compound).

Material and Methods

Ten patients with ischaemic heart disease were studied, and in most of them the disease was severe. One died, and a second developed severe congestive failure, so that our results relate only to the remaining eight patients. Details of these are given in Table I. Four had an abnormally high serum cholesterol (more than 340 mg./100 ml.), while the other four had wide pre-beta-lipoprotein bands (Besterman, 1957). The width of these bands has been expressed arbitrarily as 0-3 (Smith, 1957). In addition, two of these patients had xanthomatosis tendinosum and a third had xanthelasma.

TABLE I.—Details of Cases

Case No.	Age and Sex	Condition Present	Initial Cholesterol (mg./100 ml.)	Width of Pre-beta Band
1	M 59	Myocardial infarction and angina	263	2
2	M 46	" " "	267	2
3	M 55	" " "	264	2
4	M 50	Angina	278	1
5	F 53	Angina; xanthelasma	500	1
6	M 44	Myocardial infarction; xanthomatosis tendinosum	385	½
7	M 56	Angina; xanthomatosis tendinosum	485	½
8	M 66	Angina	368	0