of iron by venesection would reduce the amount of iron inhibiting the enzymes and allow more efficient tissue metabolism and consequent increase of well-being. It would permit organ damage to be reversed in some cases as in Case 1.

We believe that this explanation of the improvement in haemochromatosis is a reasonable one and fits in with the facts available. What is more difficult is to explain why some cases do not respond so well and why progressive fibrosis or diabetes mellitus may develop during mobilization of iron. At present one can only suggest that a critical irreversible stage has been passed in those cases, whatever that means.

Summary

Two cases of haemochromatotic heart failure which were treated by venesection and removal of iron deposits are described. The diagnosis of haemochromatosis was made in one patient before heart failure developed, and progressive deterioration was arrested in a dramatic fashion by venesection, but death after obstructive jaundice occurred 20 months after treatment began. The second case had a similar clinical picture but failed to improve to such a degree, although the liver returned to normal size, and the patient went back to work. A brief review of the literature dealing with the results of venesection, together with an attempt to correlate the results of treatment and the mechanism of symptom formation, has been made.

While venesection remains the treatment of choice in haemochromatosis the results are not completely satisfactory.

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INCREASED THYROID FUNCTION IN HAEMOCHROMATOSIS

BY

R. S. WILLIAMS,* M.B., M.R.C.P.
Late Captain, R.A.M.C.
From the Queen Alexandra Military Hospital, Millbank

In at least 90% of cases of haemochromatosis there is deposition of iron in the thyroid, often associated with considerable fibrosis (Sheldon, 1935), but, in spite of this, thyroid function is rarely disturbed.

Occasional cases of hypothyroidism have, however, been reported. In 1935 Darnall described a case of haemochromatosis showing some clinical features of hypothyroidism which he regarded as secondary to pituitary deficiency. Two cases were reported by McAllen *et al.* (1957). In one which was grossly myxoedematous the radio-iodine test was unchanged after a course of thyrotrophic hormone, indicating a primary failure of the thyroid gland. The other, though not clinically hypothyroid, showed diminished thyroid function with the radio-iodine test, but on repeating the test after a course of thyrotrophic hormone there was a hyperthyroid response, showing that most of the depression of thyroid function was due to anterior pituitary failure.

The occurrence of increased thyroid function is even more remarkable. Althausen and Kerr (1927, 1933), in describing the various endocrine disturbances in haemochromatosis, noted three cases with a raised basal metabolic rate. One of these had suggestive signs of thyrotoxicosis with a goitre, slight exophthalmos, and lid lag, although examination of the thyroid after its removal showed no histological evidence of toxicity. There were no clinical signs of hyperthyroidism in the other two cases, but one of them later came to necropsy, and on microscopy the thyroid showed definite though mild hyperplasia together with many haemosiderin granules in the acinar cells. In explanation of these findings those authors suggested that these granules might act as minute foreign bodies and stimulate the secreting cells to increased activity.

In the following case of haemochromatosis the presenting features were those of thyrotoxicosis.

Case Report

In January, 1957, a 35-year-old sergeant noticed for the first time that his ankles were swelling at the end of the day, and that a brown pigmentation was present over the front of his legs. During the next three months he became increasingly nervous, sweated easily, and despite a good appetite lost over a stone (6.4 kg.) in weight. Later he became aware of an irregular thumping of his heart, and shortly before his admission to Queen Alexandra Military Hospital on March 15 he experienced several attacks of paroxysmal nocturnal dyspnoea. He gave a history of recurrent attacks of malaria between 1943 and 1950. There was no relevant family history.

On admission he was obviously thyrotoxic, with a hot sweaty skin, marked exophthalmos, and a fine tremor of the outstretched hands. The thyroid was diffusely enlarged, with a systolic bruit over the right lobe. Pretibial myxoedema was present and in addition there was an uneven brown pigmentation of the skin over the front of the legs and dorsum of the feet. The pulse was rapid and irregular and the blood pressure 160/80 mm. Hg. The jugular venous pressure was normal and there were no murmurs. A tender liver edge was palpable two fingerbreadths below the

*Now at the Department of Medicine, Postgraduate Medical School, London, W.12.

costal margin and a large spleen extended to four finger-breadths. There was no shifting dullness. The testes were of normal size, and pubic and axillary hair was present.

Investigations.—Haemoglobin, 15 g. per 100 ml.; white-cell count, 3,500 per c.mm., with a normal differential count; serum cholesterol, 130 mg. per 100 ml.; serum proteins, 6 g. per 100 ml. (albumin 3.2 g., globulin 2.8 g.); electrophoretic pattern normal (γ-globulin 1.28 g.). Liver-function tests: serum bilirubin 1 mg. per 100 ml., thymol turbidity 5 units, alkaline phosphatase 7.5 units, bromsulphthalein test 1% retention at 45 minutes. Barium swallow—no oesophageal varices seen. There was slight glycosuria. Glucose-tolerance test showed a "lag" type curve with a fasting blood-sugar level of 105 mg. per 100 ml. rising to a peak of 238 mg. and falling to a level of 96 mg. at two hours. The electrocardiogram confirmed the presence of auricular fibrillation, and the basal metabolic rate was +28%.

Progress and Treatment

The initial diagnosis was thyrotoxicosis and thyrotoxic heart disease, the hepato-splenomegaly being attributed to a latent cirrhosis, although there was no history of alcoholism or hepatitis. Two days after admission treatment was started with methylthiouracil, 100 mg. t.d.s., and L-thyroxine, 0.1 mg. daily. During the next few weeks his general condition improved, but at the beginning of April he complained of persistent right-sided abdominal pain and increasing abdominal distension. The size of the liver and spleen was unchanged, but the abdominal girth had increased by 3 in. (7.5 cm.) and definite shifting dullness was present. Liver-function tests on April 18 showed an increase in thymol turbidity to 10 units, with normal serum bilirubin (0.4 mg. per 100 ml.) and alkaline phosphatase (9.5 units) levels.

At this stage carbimazole ("neo-mercazole"), 10 mg. t.d.s., was substituted for thiouracil as it was thought that this might be responsible for the deterioration in hepatic function. During the next week he improved, and on May 9 there was a spontaneous reversion to sinus rhythm. His abdominal girth decreased and the signs of ascites disappeared. Liver-function tests on May 20, however, showed a thymol turbidity of 12 units, with a striking increase in γ-globulin to 2.55 g. per 100 ml. which over the next month increased to a maximum of 2.82 g. per 100 ml. A further complication arose on May 27, when he developed an unexplained purpuric eruption over both legs. A skin biopsy from this area showed granules of haemosiderin scattered through the corium, especially around the sweat glands, but a further biopsy from the trunk was normal. The rash cleared and he steadily improved, the dose of carbimazole being gradually increased to 55 mg. daily.

By the beginning of August he was clinically euthyroid and after a course of Lugol's iodine a partial thyroidectomy was performed, three-quarters of each lobe being removed. Histological examination of the gland showed the picture of a partially treated toxic goitre with large colloid-filled acini in some areas but in other parts considerable glandular activity with sheets of acinar cells and colloid resorption.

On return from sick leave a month later he was clearly toxic again, with a rapid pulse and hot sweaty skin. The B.M.R. was +31%. He was restarted on carbimazole, 10 mg. t.d.s., with rapid disappearance of the signs of toxicity. The hepato-splenomegaly and abnormal liver-function findings were unchanged, the liver remaining very tender to palpation. On October 9 a liver biopsy showed a portal cirrhosis with large amounts of iron-staining pigment in the periportal areas and in the parenchymal liver cells (Fig. 1). The serum iron level was then estimated and found to be high (228 μg. per 100 ml.) and the iron-binding capacity fully saturated. Finally, staining of the resected thyroid for iron showed large numbers of haemosiderin granules, mainly in the acinar cells lining the colloid spaces (Fig. 2).

With the diagnosis of haemochromatosis firmly established the patient was started on a long-term programme of repeated venesections. A pint (570 ml.) of blood was withdrawn daily for the first 10 days, weekly for a month, and then subsequently once a fortnight. There was an initial fall in haemoglobin to 9 g. per 100 ml.; it then rose again despite continued venesections and has remained between 13 and 14 g. per 100 ml. Six weeks after starting the venesections the electrophoretic pattern of his serum proteins had returned to normal (γ-globulin 1.36 g. per 100 ml.) although flocculation tests were still strongly positive.

When seen in July, 1958, eight months after venesections were started, he was well and had returned to work. The liver was no longer palpable and the pigmentation of the legs much less pronounced. The flocculation tests were normal, the thymol turbidity being 2 units.

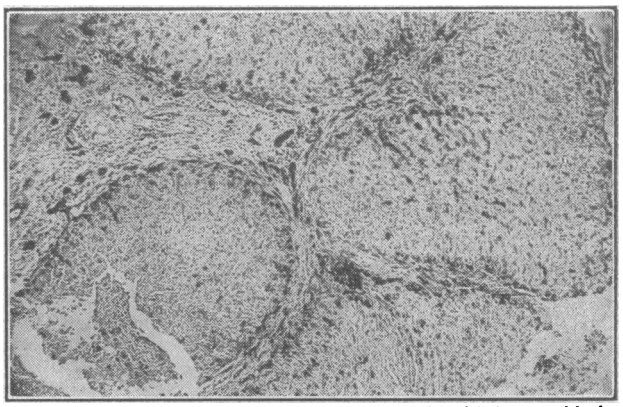

FIG. 1.—Liver biopsy showed a portal cirrhosis with haemosiderin granules in the liver cells and in the periportal areas.

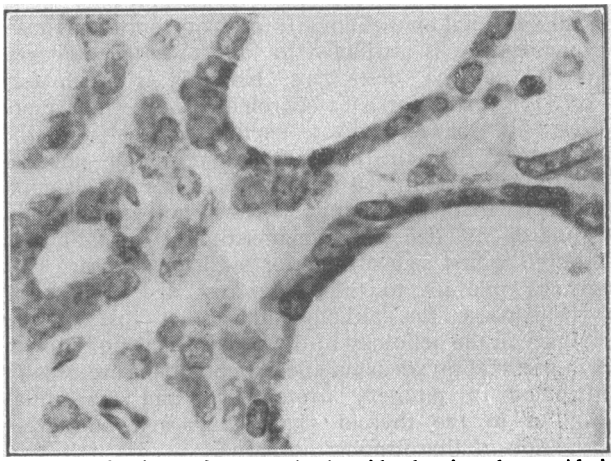

FIG. 2.—Section of resected thyroid showing haemosiderin granules in the acinar cells lining the colloid spaces. (Perles stain.)

Discussion

There can be no doubt about the diagnosis of haemochromatosis in this case. The liver biopsy showed the classical pigmentary cirrhosis, and the combination of a raised serum iron level with a fully saturated iron-binding capacity is diagnostic (Houston and Thompson, 1952, 1953). The pigmentation was unusual in being confined to the legs, there being no abnormal pigmentation of the face, forearms, or genitalia, which are the sites usually affected in haemochromatosis (Sheldon, 1935). Owing to the presence of purpura no reliance could be placed upon the finding of haemosiderin deposits in the biopsy specimen of the skin taken from the leg, although it is interesting to note that these deposits were situated in the deeper layers of the skin around the sweat glands, which is the characteristic site for iron deposition in haemochromatosis. It has been

said that deposits of haemosiderin resulting from such vascular disturbances become unduly prominent in haemochromatosis as the excessive body iron limits their reabsorption (Finch and Finch, 1955). One of the striking clinical features was the complaint of persistent right-sided upper abdominal pain with marked tenderness of the liver on palpation. Abdominal pain is in fact common in haemochromatosis, occurring in 37% of the patients in one series (Marble and Bailey, 1951), and is thought to be due to distension of the liver capsule by intrahepatic iron deposits.

The case presented several unusual features. The spleen was much enlarged, although this may have been related to the recurrent attacks of malaria in the past. Glycosuria was present, but it was clearly due to the "lag" type of impaired glucose tolerance which is often seen in thyrotoxicosis and attributed to rapid intestinal absorption of glucose. Finally, there was no evidence of hypogonadism, which is one of the more constant features of haemochromatosis. It has been suggested that hypogonadism with testicular atrophy in this condition is due to damage to the anterior lobe of the pituitary by deposits of haemosiderin, which may be particularly marked in the basophil cells (Sheldon, 1935; Althausen *et al.*, 1951).

Another explanation is that primary testicular failure occurs as the result of deposition of iron in the testis; but this is never very marked, and the deposits are found in the walls of the blood vessels and only rarely in the germinal epithelium. In ordinary portal cirrhosis hypogonadism is attributed to failure of the damaged liver to inactive oestrogens, but this is much less likely to be true for haemochromatosis, in which there is less disturbance of liver function, at least until the later stages. If the pituitary origin of the gonadal failure is accepted, then its absence in this case is good evidence that the pituitary was not significantly damaged, as deficient gonadotrophin formation is usually the first sign of anterior pituitary failure. This may be relevant to the subsequent development of thyrotoxicosis, for, although the exact role of the pituitary in the aetiology of thyrotoxicosis is not known, both pretibial myxoedema and exophthalmos are usually attributed to pituitary overactivity, and the initial stimulus to the thyroid gland may well be excess formation of thyrotrophic hormone.

Whether the haemochromatosis was responsible in any way for the development of thyrotoxicosis is not known, but, even if unrelated, the presence of impaired hepatic function due to deposition of iron in the liver may well have aggravated the thyroid toxicity. Thyroxine is excreted by the liver into the bile mainly in the form of a glucuronide (Myant, 1956), and increased serum protein-bound iodine levels have been reported in acute hepatitis (Kydd and Man, 1951), so that it is not surprising that liver disease is said to aggravate thyrotoxicosis.

Since Paul in 1865 described a case of cirrhosis of the liver in a woman dying of thyrotoxicosis there have been numerous reports concerning abnormal hepatic function and pathological changes in the liver in thyrotoxicosis (Cameron and Karunaratne, 1935; Allison, 1949; Movitt *et al.*, 1953). Experimentally, liver glycogen is depleted by feeding thyroid to animals and both toxic and dietary liver injury are potentiated. Himsworth (1947) suggested that liver damage in this disorder was due to a relative deficiency of such factors as cystine, methionine, and tocopherol, and, in support of this, Allison (1949) found a relationship between the degree of impairment of liver function and the degree of weight loss in thyrotoxicosis prior to treatment. It has also been shown (Myers *et al.*, 1950) that the hepatic blood flow in thyrotoxicosis is little if at all increased despite the increased cardiac output, and as the oxygen requirements of the liver are increased it is very likely that the centrilobular areas which receive their blood supply last may suffer from anoxia, with resulting necrosis. Whatever the mechanism of liver damage in thyrotoxicosis, it seems reasonable to assume that the onset of thyrotoxicosis would be a further insult to a liver already damaged by haemochromatosis. This may well have been the explanation of the deterioration in hepatic function which occurred after admission to hospital before the thyroid toxicity was controlled, although the possibility that this was a toxic reaction to thiouracil cannot be excluded.

The treatment of haemochromatosis by repeated venesections is now well established (Finch *et al.*, 1950; Davis and Arrowsmith, 1952; McAllen *et al.*, 1957) although the long-term results are not known. Certainly there has been a marked clinical improvement in this patient, with decrease in size of the liver and improvement in hepatic function. It is hoped that by reducing the iron stores to normal further progress of the disease will be prevented.

Summary

Attention is drawn to the surprising rarity of disturbance of thyroid function in haemochromatosis, and a case is described which presented with thyrotoxicosis. It is suggested that a vicious circle occurred in which the thyrotoxicosis caused further damage to a liver already the site of extensive iron deposition and fibrosis. This impairment of hepatic function in its turn aggravated the thyroid toxicity, possibly as a result of a failure of detoxication of thyroid hormone.

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