TREATMENT OF HEART FAILURE IN HAEMOCHROMATOSIS

BY

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The first major therapeutic advance in the treatment of haemochromatosis, the use of venesection, was introduced by Balfour *et al.* in 1942 and Finch in 1949, who realized that the excessive iron deposits which produced the disease could be mobilized by repeated bleeding; since then a number of case reports have appeared. The purpose of this paper is to report and discuss the effects of venesection in two cases of haemochromatosis with heart failure and the necropsy findings in one of them. So far as I am aware, only two reports of heart failure in haemochromatosis treated by venesection have been published and only one necropsy report describing a patient treated by venesection has appeared.

Case 1

A sign-painter aged 57 was admitted to St. David's Hospital, Cardiff, on November 10, 1952, for treatment of chronic eczematous dermatitis. During treatment grey pigmentation of his skin was noticed, and it was found that he had had loss of libido and increasing skin pigmentation for 10 years. Hair growth had been slow for some years and there had been attacks of colicky abdominal pains. There were no symptoms of cardiac failure and no abnormality of the cardiovascular system was noted. E.C.G. (Fig. 1) and chest x-ray film (Fig. 2) were normal. The liver was enlarged. Skin biopsy showed haemosiderin deposits around the sweat glands. A diagnosis of haemochromatosis was made.

He was admitted to the Cardiff Royal Infirmary on May 2, 1953, having become very breathless during the preceding fortnight. The relevant findings were: orthopnoea, a regular pulse rate of 68 a minute, and a blood pressure unchanged at 110/75, with ascites and bilateral pleural effusions. A chest x-ray film showed considerable increase in size of the cardiovascular outline; there was marked reduction of the E.C.G. voltage. The CR leads, recorded for the first time, showed T wave inversion in CR₄₋₇ (Fig. 1). Treatment with rest and digitalis was begun.

Between his second admission and his sixth on February 26, 1955, his condition deteriorated. He could walk only 10 yards (9 m.) in the ward before becoming exhausted, and at night required four pillows. At this stage clinical examination showed him to be a small man weighing 116 lb. (52.6 kg.) with pitting oedema over the sacrum and ankles. There was general bronzing of the skin, the colour being most marked over the extremities, face, and genitalia. The scalp hair was fine, soft, and lustreless. Hair was sparse on the face, absent in the axillae, and minimal in the pubic area. The testes were markedly atrophic.

The hard, smooth liver measured 5½ in. (14 cm.) in the midline and 5½ in. (14 cm.) below the costal margin in the anterior axillary line (Reidel's lobe). The spleen

tip was palpable, and ascites of moderate degree with bilateral pleural effusions was present. The pulse rate was 94 and its rhythm irregular owing to auricular flutter (Fig. 1). The blood pressure was unchanged and the jugular venous pressure was high. The cardiac impulse was feeble. The heart sounds were quiet and a triple rhythm was audible at times. Chest x-ray examination showed a generalized increase in the size of the cardiovascular shadow. The transverse diameter of the heart measured 17 cm. and the cardiothoracic ratio was 0.66. X-ray examination of the spine and forearms showed generalized bony rarefaction. The serum iron was 280 µg./100 ml. E.S.R. was 50 mm. in one hour—a marked increase. Glucose-tolerance test (blood sugar per 100 ml.): fasting, 89 mg.; half an hour after ingesting 50 g. it was 200 mg.; after 1 hour 250 mg.; after 1½ hours 289 mg.; after 2 hours 211 mg.; after 2½ hours 139 mg. After 2½ hours 0.3% of glucose was found in the urine. Repeated routine urinalysis revealed no glycosuria. Liver-function tests were as follows: serum total protein, 8 g./100 ml.; serum albumin, 4.1 g./100 ml.; serum alkaline phosphatase, 12.5 K.A. units/100 ml.; serum bilirubin, 0.8 mg./100 ml.; thymol turbidity, 5 units; thymol flocculation, 1+. Serum electrolytes, including calcium and phosphate, were normal.

In view of the prognosis a systematic course of venesections was carried out. From March 6, 1955, to October 4, 1956, 500 ml. of blood a week was removed from the patient if the haemoglobin level had not fallen below 11.4 g./100 ml. (75%). At first the patient's haemopoietic response was not great enough to allow weekly venesections, but after four months this became possible. The first improvement was subjective. He felt better after 1 litre of blood was withdrawn, and in 10 weeks, when 2.5 litres of blood had been removed, he was able to walk a quarter of a mile (400 metres). Normal sinus rhythm reappeared

FIG. 1.—Electrocardiograms of Cases 1 and 2.

after 14 weeks, and venous congestion, pleural effusions, and ascites had disappeared. The heart size (Fig. 3) and liver size remained unchanged. After 11 months, when 18 litres of blood (9 g. of iron) had been removed, the heart size had returned to normal radiologically (Fig. 4), and exercise tolerance had increased to one mile (1.6 km.). He felt well, apart from recurrent precordial or abdominal discomfort.

Between June, 1956, and his last admission on October 10, 1956, there were increasing complaints of malaise, abdominal discomfort, and anorexia with weight loss. The urine became darker and the motions paler, while jaundice appeared at the beginning of October. At this stage he had had 33.5 litres of blood (17.75 g. of iron) removed by venesections over a period of 19 months.

On examination he was ill, the skin was lighter in colour, but pigmentation persisted and a light jaundice was superimposed. Hair distribution was unchanged, testes were unaltered clinically, and libido had not returned. In the cardiovascular system no abnormality apart from a short apical systolic murmur was found.

The liver was palpable 1 in. (2.5 cm.) below the costal margin in the mid-clavicular line, the gall-bladder was readily palpable, and the spleen tip could still be felt. The serum bilirubin was 2.8 mg./100 ml. Bilirubin was present in the urine and urobilinogen was increased. The electrocardiogram continued to show the increase in voltage noted in preceding months (Fig. 1).

At laparotomy on October 22 the gall-bladder was found to be grossly dilated and contained thin, clear bile. The pancreas was hard and enlarged. A cholecysto-jejunostomy was performed, but after operation his condition was poor and he deteriorated rapidly, passing into hepatic coma before death on the third post-operative day.

Necropsy Report

The heart weighed 320 g.; the colour was normal and both ventricular cavities were slightly dilated. There were no valvular lesions and the coronary arteries were only slightly atheromatous.

The liver, which weighed 1,980 g., was finely granular and a deep brown in colour. The fundus of the gall-bladder was anastomosed to the jejunum. A probe could not be passed along the common bile duct, but dissection revealed no stone. Chemical analysis showed that about 20 g. of iron was still present in the liver.

The pancreas was larger and firmer than normal. The spleen was enlarged (900 g.) and firm. The testes were small; the other endocrine organs were normal. There were small varicosities at the lower end of the oesophagus. A slaty-blue pigmentation of the mucous membrane of the stomach was less intense in the duodenum and absent in the rest of the gut.

Microscopy.—**Heart:**—The main feature was a diffuse fibrosis of the myocardium involving all chambers and the interventricular septum, with some fragmentation of the muscle fibres; no necrosis was seen. Only a scanty amount of haemosiderin was present, and most of this was seen in the fibrous tissue. The muscle cells, which were free from haemosiderin, contained a large amount of haemofuscin. **Liver:**—Diffuse hepatic fibrosis with well-marked biliary proliferation and haemosiderin, which was most pronounced at the periphery of the liver "lobules," was evident. There was less in the portal tracts and a small amount in the epithelial cells of the bile ducts. **Pancreas:**—Sections of the head showed fatty infiltration, with extensive fibrosis around the ducts and between the acini. Haemosiderin was marked in the acinar cells and to a less extent in the fibrous tissue. The islet tissue appeared to be reduced, and there were scanty haemosiderin deposits in the remaining islets. No tumour cells were seen. Testes showed atrophy of germinal epithelium.

Case 2

The patient, a colliery engine driver, was aged 58 when first admitted to the Cardiff Royal Infirmary on October 24, 1954, for investigation of a left hemianopia which had developed overnight, and which seemed to be of embolic origin. Loss of libido and increasing pigmentation had been present for 10 years and increasing breathlessness for 12 months. His general condition was good. A diffuse bronze pigmentation of the body, more pronounced on the extremities, face, and genitalia, varied in intensity from day to day. Facial, axillary, and pubic hair were present but sparse. Jugular venous congestion was present but there was no oedema. The relevant cardiovascular findings were: auricular fibrillation, pulse rate 82 and of good volume, and B.P. 150/100. The cardiac impulse was not thrusting in quality. A pansystolic murmur was audible at the apex, while the heart sounds were soft. No third heart sound was audible. Some crepitations were heard at the lung bases. The smooth, firm, non-tender liver was enlarged 4 in. (10 cm.) below the xiphisternum and 4 in. (10 cm.) below the costal margin in the mid-clavicular line. A complete left homonymous hemianopia was found together with general areflexia.

The E.C.G. (Fig. 1) showed auricular fibrillation, together with digitalis effects, and the chest x-ray picture revealed an overall cardiac enlargement with a transverse diameter of 16.2 cm. and a cardiothoracic ratio of 0.61. Evidence of minimal pneumoconiosis was present. Screening revealed an enlargement of both right and left ventricles with diminished ventricular pulsation. X-ray examination of the spine and long bones showed moderate loss of bone density and rarefaction. There were no appreciable articular changes. Total serum protein, 8 g./100 ml.; serum albumin, 3.4 g./

FIG. 2.—Case 1. Radiograph taken before heart failure. FIG. 3.—Case 1. Radiograph during heart failure. FIG. 4.—Case 1. Radiograph after venesection.

100 ml.; alkaline phosphatase, 14 K.A. units; thymol turbidity, 7 units; thymol flocculation, 0. Glucose-tolerance test (in mg./100 ml.): fasting level, 140; half an hour after ingesting 50 g. it was 233; after 1 hour 287; after 1½ hours 243; after 2 hours 211; after 2½ hours 195. After 2½ hours 2% of sugar was present in the urine. Under normal conditions, however, the urine was glucose-free. The serum iron was 250 µg./100 ml. Skin biopsy showed the presence of haemosiderin in some of the sweat glands in the basal layer. Sternal marrow showed a marked increase of stainable iron.

The patient's condition was diagnosed as idiopathic haemochromatosis, and it was decided to treat him with digitalis and by venesection. As in the first patient, 500 ml. of blood was withdrawn at frequent intervals provided the haemoglobin levels had not fallen below 11.4 g./100 ml. From March 11, 1955, to August 6, 1956, a total amount of 37.5 litres of blood was withdrawn (18.5 g. of iron). After five months his venous congestion had disappeared, and after nine months he returned to light work underground. However, his exercise tolerance had not altered greatly. After 17 months his iron reserves were exhausted and he developed an anaemia which persisted for several weeks. His serum iron had fallen some time before. After exhaustion of his iron stores follow-up continued, and on November 28, 1958, examination revealed that he could walk up a mild gradient for ¼ mile (1.2 km.), but he was dyspnoeic after climbing 18 steps. Pigmentation was less and hair growth and impotence were unchanged. His liver was normal in size. Auricular fibrillation was still present. B.P. 155/100. An apical mid-systolic murmur was heard. Chest x-ray examination showed no change in the cardiac outline and size. Screening revealed a grade 3 left ventricular enlargement, a grade 2 right ventricular enlargement, and no systolic expansion of the left auricle; the cardiac pulsation was improved.

Discussion

The first patient gave a classical history of haemochromatosis with pigmentation, weakness, loss of libido, and severe congestive heart failure. Removal of the iron stores improved his general condition, his glucose tolerance, his liver, and the electrocardiogram. Most impressive of all was the rapid improvement in cardiac function, with restoration of normal cardiac size radiologically, in spite of the fact that he had more than 20 g. of iron still stored in his tissues when he died.

The second patient showed a different response to treatment, for exhaustion of his iron reserves as judged by the development of an iron-deficiency anaemia and a fall in serum iron level (Finch and Finch, 1955) produced only slight improvement. That the heart failure was due to haemochromatosis was assumed, for thorough investigation failed to reveal an alternative explanation, but the only positive support was the slight improvement in exercise tolerance and the disappearance of venous congestion following venesection. There was little doubt of the presence of haemochromatosis, for the classical features were present and venesection revealed that at least 18.5 g. of iron had been stored in his tissues.

It is believed that the basic defect in haemochromatosis is absorption of excessive amounts of iron; if this assumption is correct, the prevention of abnormal absorption or the removal of the excessive deposits is a logical form of treatment. Venesection when first introduced (Balfour *et al.*, 1942; Finch, 1949) appeared to be an excellent method of removing the iron deposits from the body and reversing the disease process.

Although much has been written since then (Davis and Laurens, 1950; Davis and Arrowsmith, 1952, 1953; Blackburn *et al.*, 1953; Warthin *et al.*, 1953; Bradford

et al., 1953; Houston, 1953; Peterson and Ettinger, 1953; Howard *et al.*, 1954; Fineberg, 1954; Davey *et al.*, 1954; Davis, 1955; Finch and Finch, 1955; Drew, 1955; Christensen, 1955; Kleckner *et al.*, 1955; Myerson and Carroll, 1955; Pirart and Carpent, 1955; von Kappeler, 1956; Vaisrub and Karlinsky, 1956; Althausen and Sborov, 1956; McAllen *et al.*, 1957) on the use of venesection in haemochromatosis, few cases have been described in sufficient detail to make precise comparisons. Of 34 cases, 29 have improved, subjectively or objectively, in that pigmentation has diminished, liver enlargement has receded, or insulin requirements have been less. In three cases (Warthin *et al.*, 1953; Myerson and Carroll, 1955; McAllen *et al.*, 1957) libido has returned. Venesection, however, does not cause the cirrhosis to disappear (Peterson and Ettinger, 1953), although the liver size is reduced, nor does it prevent a hepatoma developing (Bradford *et al.*, 1953; Davis, 1955). Similarly, diabetes has developed nine months after venesection has started (Christensen, 1955), and, in our case, a "benign" fibrosis of the pancreas causing bile-duct obstruction occurred after 15 months' treatment.

Of cases of heart failure in haemochromatosis treated by venesection only two other than ours have been published. One case (Christensen, 1955) was found at necropsy to be due to constrictive pericarditis, so that the lack of response was not surprising. The other case (McAllen *et al.*, 1957) had had signs of increasing cardiac decompensation for 12 months before admission to hospital. Improvement on venesection was rapid enough to allow him to return to work after two months, but radiologically his heart remained unchanged in size for over two years. Our two cases responded to a differing degree. The first patient made a remarkable improvement with eventual return of heart size to normal, while the other one showed a definite but only partial response.

Other reports (Bradford *et al.*, 1953; Davis, 1955; and McAllen *et al.*, 1957) refer to E.C.G. changes, but only three cases have been reported in detail. In one case low T waves reverted to normal, and in another the T waves improved but later became flattened again; the third case showed no change. An interesting pattern was noted in our Case 1. The standard E.C.G. leads were at first normal. After the rapid development of cardiac failure the E.C.G. became abnormal with lower voltage QRS complexes and flattened T waves. Auricular flutter occurred later, and its disappearance was one of the first responses to venesection, but the E.C.G. did not revert to its initial form even months after the cardiac silhouette became normal, nor after 17.75 g. of iron had been removed. In Case 2 the E.C.G. was abnormal before and after treatment without any improvement.

This variation in results following treatment needs to be explained, for the above brief review of published case reports shows that removal of iron deposits does not always revert or arrest this disease process.

The question of why a feeling of well-being occurs so soon after venesection has started also needs interpretation. As yet no answer has been found, but the work of Rackér and Krimsky (1948) and Krimsky and Rackér (1949), for example, shows that small amounts of ferrous iron cause inactivation of enzymes, including those dealing with glucose metabolism such as glyceraldehyde phosphate dehydrogenase. Mobilization

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

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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

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