HAEMOCHROMATOSIS: A REPORT ON THREE CASES

BY

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Haemochromatosis is a disease of sufficient rarity for three new cases to warrant publication. Sheldon in his recent monograph has only been able to find in the literature 311 cases which he could accept as authenticated instances of the condition. The following three cases were all followed up to necropsy and the diagnosis verified by the typical post-mortem findings.

Case I

Male aged 27, tailor's trimmer. The patient was in apparent good health until the end of January, when he began to suffer from abdominal pain and distension. The pain was dull, intermittent, and not related to the taking of food. Shortly after this he began to complain of thirst and polyuria. A month after the onset of his symptoms he developed a brownish pigmentation of the skin, which grew steadily worse, and was remarked on by his friends. At this time, also, he noticed an increasing sleepiness, which became so marked that he actually fell asleep on his feet whilst at his work. Weakness and loss of weight became so marked that he could not continue at his work, and so he reported to his doctor, who sent him to hospital on April 8th, a little over two months after the first appearance of any symptoms.

On admission he was found to be well developed but undernourished. His height was 5 ft. 5 in., and weight 8 stone. There was a generalized greyish-brown pigmentation of the skin, most marked in the mammae and arms and hands. On physical examination nothing of note was found in any of the systems. There was no enlargement of liver or spleen. The blood Wassermann reaction was negative. A sugar-tolerance test with 50 grams of glucose gave a moderately severe diabetic curve, with considerable glycosuria.

Fasting level	...	...	...	...	...	195 mg. per cent.
$\frac{1}{2}$ hour	...	...	...	...	...	250 mg. "
1 hour	...	...	...	...	...	400 mg. "
$1\frac{1}{2}$ hours	...	...	...	...	...	375 mg. "
2 hours	...	...	...	...	...	350 mg. "

The previous health of the patient had always been good, the only illnesses having been measles and scarlet fever in childhood. The patient was teetotal. Under dietetic treatment the diabetes was satisfactorily controlled, the glycosuria clearing on a diet of 1,500 calories in two days, and a maintenance diet of 2,300 calories being attained without insulin. After four weeks he was discharged to continue treatment as an out-patient. However, he grew weaker and developed oedema of the ankles, and his glycosuria could not be controlled without insulin. His general condition deteriorated very rapidly, with the development of gross oedema and ascites, and he was accordingly readmitted to hospital, where he died with increasing anasarca. The glycosuria was controlled until the end, and ketosis did not develop. He died on August 15th—seven and a half months after the first appearance of any symptoms. At necropsy the typical findings of haemochromatosis were seen. Haemosiderin was found in the skin, myocardium, stomach, liver, spleen, kidneys, pancreas, and suprarenals. The liver weighed 1,550 grams, and was grossly cirrhotic. Microscopically it showed marked fibrosis and numerous islets of regenerating liver tissue. Haemosiderin was present in all the tissues, including the Kupffer cells. There was a slight degree of varicosity of the veins at the lower end of the oesophagus secondary to the portal obstruction. There was gross dilatation of the heart, but no organic valvular lesions or atheromatous changes in the vessels. The usual changes resulting from congestive heart failure were found in the other organs. The spleen weighed 490 grams, and showed an increase in fibrous tissue. Owing to post-mortem autolysis it was not possible to distinguish any islet tissue in the pancreas, which contained large quantities of haemosiderin.

Case II

Male aged 54, carpenter. For three years the patient had been troubled by breathlessness on exertion and swelling of the feet after exercise. During this period he had had occasional attacks of "tearing pain" situated behind the sternum and radiating down the inner side of the left arm. These attacks of pain were usually precipitated by effort. For the past eighteen months he had been troubled intermittently with thirst and polyuria and had lost 2 st. in weight. Pigmentation of the skin, chiefly affecting the face, hands, and forearms, had been noted for the same period as the diabetic symptoms. Diabetes was only diagnosed one week before admission to hospital. His previous health had been good and no illnesses could be recalled. At no time had the patient been a heavy drinker, but he had taken spirits fairly regularly in his younger days. The patient's mother suffered from diabetes.

On admission he was seen to be very sparely built and to look older than his years. He showed a dark, greyish-brown pigmentation of the skin, which was generalized but most marked in the face and hands. The chest was emphysematous, and he had chronic bronchitis. Owing to this it was not possible to map out the heart, whose sounds were faint but closed and unaccentuated in all areas. The pulse was regular—70 per minute—and the blood pressure only 105/75 mm. The liver was enlarged, and a firm edge could be felt one inch below the costal margin. The spleen was not enlarged on clinical examination. Blood Wassermann negative. During his seven weeks' stay in hospital until his death the diabetes was readily controlled by diet and insulin, and the urine was kept sugar- and acetone-free. He continued to have attacks of dyspnoea and palpitation even when at rest in bed. Attacks of paroxysmal tachycardia were frequent. Electrocardiograms showed a well-marked left-sided preponderance with right ventricular extrasystoles. One record showed supraventricular paroxysmal tachycardia. The oedema of the feet and legs and even the ascites seemed to increase and decrease quickly, depending upon the heart condition. He collapsed and died following the mild exertion of getting on to the bedpan.

At post-mortem the typical appearances of haemochromatosis were seen. Haemosiderin was found in all the tissues and organs—particularly in the liver, spleen, pancreas, and myocardium. The liver was enlarged and weighed 2,950 grams; the organ was of a pronounced chocolate colour and markedly cirrhotic. Microscopically haemosiderin was found to be deposited everywhere in the liver, even in the lining cells of the branches of the portal vein. The pancreas showed a chronic interstitial pancreatitis, and the islets were reduced in number and contained iron-containing pigment. The heart was markedly enlarged owing to dilatation of all the chambers. The myocardium was thin and contained much haemosiderin. The valves showed no abnormalities, and there was no evidence of coronary disease. There was only slight atheromatous change in the aorta, but the few plaques present contained haemosiderin. The spleen was enlarged and weighed 570 grams.

Case III

Female, aged 34, shop assistant. About nine months before admission to hospital the patient noticed an increasing lassitude, and her skin began to grow darker in colour. This was first noticed in the parts exposed to the sun, and steadily increased in intensity and became generalized. There were periods when the colour appeared to fade slightly for a week or so at a time, and at these times the lassitude was not so well marked. Six months before coming to hospital swelling of the feet, legs, and abdomen was first noticed. With rest in bed this improved, but there was a recurrence on getting up, and on the reappearance of the ascites she suffered from dyspnoea and palpitation. These symptoms continued, with relapses and remissions, until admission. Her appetite remained fairly good, but she found that small meals were most suitable on account of a feeling of distension and flatulence. Her previous health had been good apart from measles as a child and rheumatic fever seven years previously. She had had amenorrhoea since the age of 21. There was nothing to note in the family history, and the patient was a teetotaler.

On admission she was found to be a well-developed adult with oedema of the lower limbs and some ascites. There was a well-marked, generalized pigmentation of a brownish-grey colour, most marked on the exposed surfaces. The pigmentation was complicated by the presence of cyanosis. There was no pigmentation of the mucous membranes. The liver was enlarged four fingers below the costal margin and was slightly tender. The spleen was palpable at the costal margin. There were effusions in both pleural cavities. The heart was grossly enlarged, the apex beat being in the sixth left interspace outside the mid-clavicular line, and the right border one and a half inches beyond the edge of the sternum. The sounds were soft and the rate slow and irregular, the patient having been treated by digitalis before admission. On admission the blood pressure was 110/70 mm. Electrocardiograms taken at intervals throughout her stay in hospital showed slight variations. There was always a low potential, which grew more marked with occasional short remissions. The conduction was slowed, with a prolongation of the P.R. interval, and there were ventricular extrasystoles, these changes being attributed to the digitalis. There was always a right-sided preponderance. A sugar-tolerance test gave a non-diabetic curve, and there was never any glycosuria.

Fasting level	...	...	...	...	100 mg. per cent.
$\frac{1}{2}$ hour	...	...	...	...	129 mg. "
1 hour	...	...	...	...	161 mg. "
2 hours	...	...	...	...	145 mg. "
3 hours	...	...	...	...	118 mg. "

The other blood chemical findings were: urea N, 18 mg. per cent.; cholesterol, 165 mg. per cent.; albumin, 3 grams per cent.; globulin, 2.82 grams per cent. The patient was treated by tapping the pleural effusions and ascites on many occasions. She was also given digitalis and salyrgan, but steadily went downhill and died in six weeks with increasing oedema. A diagnosis of Addison's disease was made, and treatment with cortical hormone was tried. This was, however, without effect, the blood pressure falling steadily until the systolic level was below 70 mm. and not estimable.

At post-mortem the characteristic appearances of haemochromatosis were discovered and haemosiderin was found deposited in the skin, liver, pancreas, spleen, kidneys, suprarenals, and heart. The liver was greatly enlarged, firm in consistence, and of a rusty brown colour. On section it showed a fine cirrhosis. The whole of the gastrointestinal tract was grossly congested, but no varicosity of veins was noted. The pancreas was small and cirrhotic. On section it showed a patchy appearance of chocolate-coloured areas embedded in white fibrous tissue. The spleen was enlarged and firm in consistence. The suprarenals were small, but showed no abnormalities apart from the presence of haemosiderin: they weighed—left, 2.9 grams; right, 4.6 grams. (Normal 4.5; 7.5 grams.) The heart was enormously dilated, and the myocardium thinned out and of a rusty brown colour. It appeared to contain more haemosiderin than the other organs. There was no evidence of any valvular disease, and the coronary arteries and aorta were free from degenerative changes.

Discussion

The two male cases were diagnosed during life, and illustrate most of the usual features of the disease. The female patient, however, was only found to be a case of haemochromatosis at post-mortem, the diagnosis during life having been Addison's disease. Many observers have previously stressed this general resemblance to Addison's disease, and some reasons for the mistake in diagnosis may be offered. Only sixteen cases of haemochromatosis have previously been described as occurring in females, and in them the prominent features have been the later age incidence, the reduced size of the liver, and the history of alcoholism. The present case shows none of these features; at 34 the patient is the third youngest female to be reported, and she was teetotal, whilst the liver was greatly enlarged. Glycosuria was also absent and the blood sugar curve was normal. As the synonym "bronzed diabetes" indicates, glycosuria is usually a prominent feature of the disease, being found in 78 per

cent. of the cases. The absence of glycosuria, the pigmentation, low blood pressure, and old rheumatic history gave rise to the diagnosis of Addison's disease complicated by heart failure secondary to rheumatic heart disease. At necropsy, however, the suprarenals, though smaller than normal, were not obviously pathological, and no evidence of valvular heart disease was found. All the symptoms could be attributed to the deposition of pigment impairing the functional efficiency of the different organs. The low blood pressure and myocardial failure were caused by the excessive deposition of haemosiderin in the heart and suprarenals. The pigmentation was of a brownish-grey colour. In Addison's disease the colour is stated to be typically brownish, in contradistinction to the bronze or bluish-grey colour of haemochromatosis. This distinction is, however, not so obvious as some textbooks would suggest. The presence or absence of pigmentation of the buccal mucosa is also of little help in diagnosis, as in both diseases it may be present in this situation, though commoner in Addison's disease. This patient showed the phenomenon of variation in the intensity of the pigmentation. Such a fluctuation in intensity has been recorded in seven previous cases. The fluctuation was associated with variations in the feeling of lassitude, and suggests that the suprarenals were involved in the production of the pigmentation. A decrease in the intensity of the coloration has been noted in other cases following on the adequate treatment of the diabetes with insulin. R. D. Lawrence has suggested that this type of pigment change may depend on a varying content of glycogen and water of the epidermal cells through which the pigment grains are seen. Neither of the present two male cases showed such a change under insulin treatment, which was successful in keeping the urine sugar- and acetone-free.

The second male case resembled the female in certain respects. The symptoms were all along chiefly referable to the circulatory system, and these symptoms continued until death to overshadow any signs or symptoms due to liver or pancreatic damage. This is somewhat unusual, as 80 per cent. of cases of haemochromatosis begin with either diabetes, pigmentation, or symptoms secondary to the cirrhosis of the liver. As in the female a very low blood pressure was found, and, as is usually the case, arteriosclerosis was absent. Gross cardiac failure as found in these two cases is not a common feature, although a few electrocardiographic abnormalities have been previously described. For the most part, however, the extensive deposits of pigment produce surprisingly little clinical evidence of their presence.

In the past diabetic coma was by far the most common cause of death. Sheldon suggests that with the use of insulin it is probable that the majority will now die from the effects of the cirrhosis of the liver, in spite of the fact that about 30 per cent. of the diabetic cases turn out to be insulin-resistant, and that an undue liability to hypoglycaemic shock is often found. In the present series Case I died of cirrhosis, but would probably have died in coma in pre-insulin days. Case II could probably have been controlled without insulin, and definitely died as the result of myocardial degeneration, as did Case III, which showed no sign of upset in carbohydrate metabolism. Death could thus be attributed to myocardial failure in two out of the three cases. Sheldon found that a miscellaneous group, including intercurrent conditions and myocardial failure, accounted for only about 10 per cent. of the total deaths. The common causes of death were coma, cirrhosis, pneumonia, and tuberculosis, the first two accounting for over 70 per cent. of all deaths.

Owing to the slow and insidious onset of the disease it is difficult to calculate the length of time over which

symptoms last. It has, however, been found that about eighteen months usually elapse between the first calling in of medical advice and death. In the first male case, therefore, the disease ran an unusually rapid course, death occurring only five months after he first called in his doctor and seven and a half months after being in apparently perfect health.

Summary

1. Three cases of haemochromatosis are described in all of which the diagnosis was checked by post-mortem examination.

2. A female case was diagnosed as Addison's disease during life, and the difficulties in diagnosis are discussed.

I wish to express my thanks to Professor D. M. Lyon for permission to publish these cases, which were under his charge.

REFERENCE

¹ Sheldon, J. H.: *Haemochromatosis*. Oxford University Press, 1935.

THE DRAINAGE OF THE MAXILLARY SINUS

A NEW TECHNIQUE

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Sinus surgery has in recent years become very much more conservative than it used to be, and surgeons are now fully alive to the dangers of extensive interventions. This is particularly true with regard to the ethmoidal and frontal sinuses. The radical operation on the maxillary sinus (Caldwell-Luc or its modifications), however, is still very often performed. That it is not entirely devoid of complications is only too well known. It is not disputed that there are cases of gross disease of the mucosa lining the antrum where the radical operation is necessary. But the opinion is certainly prevalent that the indications for the radical operation could be, and should be, greatly reduced. Why then do many otologists have recourse to the Caldwell-Luc operation rather than the simpler intranasal antrostomy? The explanation in my opinion is that with the present technique the intranasal antrostomy often gives an uncertain result, even in the hands of the expert, and that rather than risk an unsuccessful operation the radical procedure is undertaken in preference.

Postulates in Treatment

In the majority of cases of antral disease all that is required is:

1. A sufficiently large opening, placed well forward, and level with the floor of the meatus, to enable the surgeon to remove polypi, and to allow the discharge to escape freely by gravity and the ciliary action which, as has been proved by Proetz, still persists even in the most gravely infected sinuses.

2. The restoration of the normal ventilation inside the sinus, which often becomes defective due to blockage of the normal ostium. The above desiderata are fully obtained by the intranasal antrostomy. The mucous lining, unless grossly diseased and polypoid, usually recovers after this operation.

The removal of as much bone of the antro-nasal partition as is possible has been advised, in order to give an adequate permanent opening into the antrum, the contention being the larger the opening the larger will be the communication between the antrum and the nose.

This is a fallacy. It is not sufficient to make a big opening in the bone to obtain a satisfactory communication with the antrum, nor does a big opening in the bone assure it.

The antro-nasal partition does not consist of bone only; it is actually made up of five layers—namely, mucosa, periosteum, bone, periosteum, mucosa. It is clearly not sufficient to make an adequate opening in the bony layer alone, for this does not necessarily correspond with the opening in the other layers of the partition. What actually happens is this. When piercing the bone during the intranasal antrostomy the nasal and antral mucosae are torn and indented; the bone-cutting instrument which is then used removes the bone, but not necessarily the muco-periosteum lining the bone on either side. The torn membranes are inclined to escape the bite of the forceps. Ultimately, at the completion of the operation, we have a large opening in the bone with tags of mucosa overlaying it like a curtain on either side. These tags have a real tendency to unite with each other on either side of the bone and across the opening with those on the other side. It is clear that this process is progressive, and will diminish materially the size of the antro-nasal communication. If the mucosal tags on either side of the bone do not correspond in position and size, the contraction of the original opening will be even more rapid, with the result that what appeared to be a very satisfactory foramen at the operation may become so small as not to allow the passage of an antrum cannula at the end of the second week.

That antro-nasal openings have a tendency to close up is familiar to the expert and the beginner alike. The above is in my opinion the explanation for this tendency. The success of an intranasal antrostomy depends on an adequate opening being made in all layers forming the antro-nasal wall. It is for this reason that I have for the last eighteen months practised a somewhat modified technique when performing this operation.

Technique of Operation

The operation is done under local, evipan, or chloroform anaesthesia. As the galvano-cautery burner is used during the operation ether must be avoided. The nose is packed with a 10 per cent. solution of cocaine and adrenaline one hour before, and the area below the inferior turbinate receives an extra application of cocaine and adrenaline immediately before the operation. The inferior turbinate is not interfered with, unless overhanging and obstructing the meatus, and then no more than is absolutely necessary is removed of its anterior end. The first step aims at making an opening in the nasal mucosa which should be well forward and level with the floor of the meatus. For this purpose I employ the galvano-cautery, using a flat and specially bent burner (see Figure).

Enough mucosa is destroyed to make it correspond with the future size of the communication with the antrum. An opening is next made in the bony layer of the partition; this is first pierced with a frontal sinus rasp fairly far back beneath the inferior turbinate; or a chisel may be used for this purpose. The opening is then enlarged with bone-cutting forceps, particularly forward towards the extreme anterior limit of the inner wall and towards the lower part of the antro-meatal wall. Only enough bone, however, is removed to permit the insertion of an instrument for the removal of