CLINICAL REMARKS ON HYPERTROPHIC CIRRHOSIS OF THE LIVER WITH BRONZING OF THE SKIN: HÆMOCHROMATOSIS.*

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RATHER more than two years ago a man presented himself at the hospital complaining of a gradual darkening of the skin and an eruption on the legs. I do not remember to have seen him, and the diagnosis on his card was Addison's disease with an interrogation mark after it. He returned in May of this year with the bronzing of about the same intensity, but we found in addition that he had a greatly enlarged liver and an enlarged spleen, but no diabetes. Meantime, Dr. Opie, jun., had presented to our Medical Society a paper on Hæmo-chromatosis, and had considered fully the relation of this remarkable condition to hypertrophic cirrhosis and the *diabète bronzé*. I had become familiar in French literature with the latter condition, though I had never met with a case, and until hearing Dr. Opie's paper I was not aware of the significance of the general hæmochromatosis in connection with the disease. It called to mind also a remarkable instance of hypertrophic cirrhosis with bronzed skin which not long before had been under my care. As the literature of the subject is almost exclusively in French and German—Dr. Opie's paper will appear in the next number of the *Journal of Experimental Medicine*, vol. iv—I shall refer to a few of the landmarks in the progress of our knowledge. Hanot, whose name will always be associated with one form of cirrhotic liver, had noticed that in some cases the skin became bronzed, and he noticed further that diabetes was an occasional complication.¹ It is true that a bronzed cachexia in diabetes had been previously noted (Troisier, 1871), but Hanot's work began a long series of observations by the Paris physicians, through whose writings we have all become familiar with the subject. This author believed that the liver was the seat of origin of the pigment, but Letulle maintained that the liver cells stored but did not form the pigment, and he regards the cirrhosis as a secondary event. More recently Marie has suggested that the *diabète bronzé* is neither a pigmentary cirrhosis of the liver in diabetes nor a special bronzed cachexia, but a separate clinical and pathological entity—in fact, a new disease.

While the French observers had been studying the problem almost exclusively in connection with diabetes, in Germany it was approached from a different standpoint. In the *Haller Festschrift* (1877) Quincke had described a case of widespread pigmentation in anæmia. In 1889 von Recklinghausen described under the name hæmochromatosis a condition of pathological pigmentation, either local or general. To the local condition, which is met with in the heart and sometimes in the intestine, I need not here refer. The generalised pigmentation described by von Recklinghausen involved the skin, the liver, the spleen, the pancreas, and most of the glands of the body. In some of his cases of generalised hæmochromatosis there was cirrhosis of the liver, which von Recklinghausen suggested was the result of "eine hæmorrhagische Hepatitis." The German observers separated two forms of the pigment, one containing iron, hæmosiderin, and, a second, hæmofuscin, which does not give the iron reaction. In the general hæmochromatosis associated with cirrhosis of the liver, the pigment is the hæmosiderin and has an ochre yellow colour, which gives to the organs, affected a most remarkable and characteristic appearance.

In this country very little attention has been paid to the question. Saundby, in Allbutt's *System of Medicine*, vol. iii, in speaking of the liver, states that in diabetes it may be distinctly cirrhotic, and this form is sometimes associated with bronzing. Williamson, in his monograph on diabetes,

gives Hanot's clinical description, but, so far as I can gather, the condition has not received special study either in England or in the United States.

Two cases of this remarkable hæmochromatosis have been under my care within the past few years. Both are of special interest, from the fact that there was no associated diabetes, only the general hæmochromatosis with enlargement of the liver, and in one of them the condition was diagnosed during life.

CASE I. Clinical Summary.—Good General Health: Alcohol in Moderation: Progressive Bronzing of the Skin: For three years Numerous Attacks of Purpura and Urticaria on the Skin of the Legs: Enlargement of the Liver and Spleen: No Diabetes.—J. A. M., aged 43, a pilot, was admitted May 1st, 1899, complaining of a stitch in the right side over the liver.

Family History.—The father died at the age of 73 of paralysis; mother died at 25 in childbirth. His brothers and sisters are living and well.

Personal History.—When 7 years of age he had a severe illness, the nature of which he does not know. He had measles at 12, malarial fever at 14, with dumb chills and night sweats. With these exceptions he has been a very healthy man. He has been a pilot on the Chesapeake Bay. He has used alcohol ever since he can remember, but only takes a glass of whisky once or twice a week. He has never been a daily drinker, and never gets on sprees. I asked his wife particularly about his alcoholic habits, and she says he rarely touches whisky. He has smoked and chewed tobacco for many years. He had gonorrhœa ten or twelve years ago; he has not had syphilis. He has been a moderate eater. He has not lost in strength or in weight, and has not had to give up work.

Present Illness.—Three years ago he had the first attack of red blotches on the feet, and before this he had noticed that he had slight swelling of the ankles and feet, so that he had often to loosen his shoes and sit down. The spots turned purple and remained about three days. During the past three years he says he has had scores of these outbreaks of red blotches on the feet and ankles, sometimes on the legs. In February, 1897, he had a severe attack of pain on the right side, between the costal margin and the crest of the ileum, which lasted for about a week. On the day following the beginning of the illness his feet became swollen. He forgets whether he had the blotches.

In October, 1897, he had a second attack of pain in the right side, with high fever, and his right eye became inflamed and swollen. During this attack he had red welts on the legs as far as the groin. They turned purple and left areas of discoloration. During the past year and a-half these outbreaks of purpura and urticaria on the legs have been very much more frequent. His friends have noticed that his face has become darker in colour, and his hands, too, he thinks are very much darker.

Present Condition.—The patient was a sparely-built, healthy-looking man, weight 146 lbs. The skin of the face was slightly bronzed, not very intense, but his wife insists that his complexion has become very much darker during the past two years. There was no pigmentation of the mucous membranes of the lips or mouth. The general surface of the skin was slightly pigmented, that about the areolæ of the nipples and about the genitalia very much pigmented. The skin of the hands and wrists and of the legs as high as the knees was very deeply bronzed. The heart sounds were everywhere clear and strong. The pulse was regular in force and rhythm. The radial arteries were a little stiff, easily rolled under the finger. The abdomen looked natural, with the exception of a little fullness in the upper zone. On palpation the liver could be easily felt extending in the median line 8 cm. below the ensiform cartilage, between 6 and 7 cm. below the costal margin in the nipple line. The surface was everywhere smooth; the edge could be very distinctly felt. It was hard and firm and rounded. The absolute hepatic flatness in the nipple line began on the fifth rib, on the sixth rib in the mid-axillary line. On auscultation over the liver there was heard a distinct friction on deep inspiration. The gall bladder could not be felt. There was a fullness visible in the left hypochondrium, which altered on deep inspiration. On palpation this was found to correspond to a greatly-enlarged spleen, the border of which could be readily felt nearly 6 cm. from the costal margin. The axillary glands were enlarged. The patient had no fever. The urine was dark in colour, specific gravity 1014, reaction acid; no albumen, no casts, no sugar. There was no bile. Indican was present. There was a distinct reaction for iron. As the pigmentation, the enlarged liver and spleen, with recurring attacks of purpura, suggested the bronzed form of hypertrophic cirrhosis of the liver with which diabetes has been so often associated, the patient on May 5th, at 4 p.m., was given 75 grams of glucose, and the separate specimens of urine saved as voided until 8 a.m. on the 6th, and carefully tested for sugar. Each one of the four specimens was negative.

Blood.—The red blood corpuscles were above the normal number. There were no pigment granules seen either in the blood or in the leucocytes. The blood platelets were apparently diminished. The differential count of the leucocytes was as follows:

Polynuclears	...	...	131	...	63.9 per cent.
Small mononuclears	...	...	35	...	17.7 "
Large mononuclears	...	...	17	...	8.2 "
Transitionals	...	...	6	...	2.9 "
Eosinophiles	...	...	16	...	7.9 "

A portion of the skin of the leg was excised, and in it Dr. Opie determined the presence of the characteristic ochre-coloured pigment granules in the cells of the sweat glands.

CASE II. Clinical Summary.—History of Malaria and of Attacks of Continued Fever in the Tropics: No Alcoholic History: Enlargement of Upper Part of the Abdomen due to Hypertrophic Cirrhosis of the Liver: Progressive Pigmentation of Face and Hands; Enlargement of the Spleen: Suspected Tumour of Liver: Laparotomy: Large Red-brown Liver: Erythema Nodosum: Hæmorrhage from Stomach: No Diabetes: Death: Duration of Illness about Five Years.—G. M., aged 34, referred to me on January 18th, 1895, by Dr. MacMeans, of Monterrey, Mexico. The patient complained of an enlarged liver and a gradual alteration in the colour of his face.

Family History.—His mother died in childhood; his father died suddenly,

* Read in the Section of Medicine at the annual meeting of the British Medical Association, Portsmouth, 1899.

from what cause he did not know. He has had four brothers; one died of dropsy at the age of fifteen, the others are healthy and well.

Personal History.—Patient was born in the United States; was very healthy as a young man, with the exception of "chills and fever" at 10 and of small-pox at the age of 12. He has lived in Mexico for the past twelve years. He has travelled in the country a great deal but has enjoyed good health. He has never had yellow fever. Dr. MacMeans writes: "He has suffered from attacks of mild continued fever, very common in this locality, running a course of about fourteen days, and when uncomplicated by medication it is usually a very mild disease. I also might add it is commonly called malaria, but I am convinced that there is nothing malarious about it." Dr. MacMeans did not think that these attacks had any special connection with his present trouble. He has not had syphilis; of this he is quite certain. He has been a temperate man, taking wine and spirits only occasionally; he has used tobacco in moderation.

Present Illness.—For at least three years and a half the patient has noticed that he has been growing larger in the upper part of the abdomen. His general health has been very good, and he has been able to be at work. During this time he has had one or two febrile attacks such as described by Dr. MacMeans. A year and a half ago he was slightly jaundiced; has not had an attack since. There was no itching of the skin. He does not know when he began to change in colour but he thinks it was several years ago. The enlargement of the abdomen has been progressive, and lately he has had to have the waist band of his trousers let out. As stated he has been at work and has had a fairly good appetite and good digestion. Within the past year the enlargement has been very much more noticeable in the epigastric region, and Dr. MacMeans and others have regarded the condition as one of tumour of the liver.

Present Condition.—The patient was a medium-sized man, well nourished, lips and mucous membranes of a good colour. Tongue clean and red. The most noticeable feature about him was the peculiar bronzing of the skin, a somewhat leaden hue suggestive of argyria. On the face it was very deep, and at once attracted attention. It was uniform, but along the roots of the hair there was a line of about half an inch on which the skin was normal. The skin of the hands and wrists was also very pigmented. That of the general surface of the body was only a little increased. There was no pigmentation of the mucous membranes. The chest was well formed; there were no changes noticed in the heart and lungs.

Abdomen.—The whole upper zone looked enlarged, and a prominent mass filled the entire space between the costal borders. On palpation, this was found to be a firm solid mass which below reached to within exactly 2 inches of the navel. Here a rounded edge could be felt very readily, and it could be traced to the right, where it passed beneath the costal margin in the mid-axillary line. It could also be readily traced to the left. The edge was rounded and very hard and resistant. The general surface of the enlarged mass was smooth, but in places in the position of the right lobe it felt a little rough and irregular. The upper limit of hepatic flatness began in the mid-sternal line at the level of the fifth rib and extended to within 6 cm. of the navel. In the nipple line on the upper border of the sixth rib it extended a little below the costal margin. The edge of the spleen could be distinctly felt, and on deep inspiration came down 2 inches below the costal border. There were no changes in the blood; the urine was high-coloured, but contained neither bile pigments nor sugar. I was by no means certain as to the condition, but suspected a syphilitic liver, and ordered large doses of iodide of potassium.

I heard from the doctor again on November 21st. Mr. M. had been doing very well and keeping at work, though the mass was increasing in size.

The patient returned to see me on March 11th, 1896. The bronzing of the skin was more marked and more diffuse. He had been taking 30 gr. of iodide of potassium three times a day. The abdomen showed a very positive increase in the size of the mass in the epigastrium, which had lifted the tip of the ensiform cartilage, from which it extended exactly 1½ cm. The fingers could be placed under the edge of the liver readily from one costal border to the other. The surface was uniform, and there was a distinct prominence for the first few inches below the ensiform cartilage. It was very firm, but painless. There was no friction over it. The spleen had increased somewhat in size. When he stood up the mass made a prominent bulging in the epigastrium. The superficial veins were not enlarged. The conjunctivæ were not jaundiced. There was neither bile, albumen, nor sugar in the urine.

I was still very uncertain as to the nature of his trouble, and suggested an exploratory operation, to which he consented. This was performed by Dr. Halsted. The liver was enlarged, particularly the left lobe, which was very prominent. The capsule was not thickened. The surface was a little irregular, and the colour was of a deep brownish red. I was present at the operation, and noted the peculiar colour, but did not at the time realise its significance. The gall bladder was enlarged, and contained a light-coloured bile. There was no fluid in the peritoneum. The patient recovered rapidly from the effects of the operation, but two months later there was no change in his condition.

On December 22nd, 1896, Dr. Crouse, of Rockport, Texas, wrote as follows: "In his present condition the liver is five fingers' breadth from the navel. There is commencing dropsy of the feet and abdomen. He has had a very bad attack of erythema nodosum, involving both legs. Ten days ago, after a very wearisome boat trip, he had a hæmorrhage from the stomach, after which he passed tarry stools for three days. He died in May, 1897. His brother states that the abdomen increased in size, and that he lost flesh and strength."

The clinical features of the 24 cases of the so-called bronzed diabetes have been carefully analysed by Anschütz.² No case has occurred in a female, and in a discussion at the Société Médicale des Hôpitaux (1897) Letulle stated that of the 30 known cases all were in men. Pigmentation was present in 14 of the 24 cases. The melanoderma may be the first symptom noted, and may precede the diabetes for several years. It is sometimes of a peculiar leaden tint, and in Hanot's original description he speaks of "une teinte plombée." The diabetes,

the symptom which has attracted special attention, is of the ordinary form; the amount of sugar is often considerable. In 6 cases the diabetes ceased under observation. Only a few instances have been reported—5 of the 30—(Letulle) without diabetes. The general opinion is that the diabetes is secondary to a disease of the pancreas, which in 18 cases has been found deeply pigmented and cirrhotic.

The pathology of the process is still very obscure. The present state of our knowledge is perhaps best expressed by the conclusion in Opie's paper already referred to:

"1. There exists a distinct morbid entity, hæmochromatosis, characterised by the widespread deposition of an iron-containing pigment in certain cells, and an associated formation of iron-free pigments in a variety of localities in which pigment is found in moderate amount under physiological conditions.

"2. With the pigment accumulation there is degeneration and death of the containing cells and consequent interstitial inflammation, notably of the liver and pancreas, which become the seat of inflammatory changes accompanied by hypertrophy of the organ.

"3. When chronic interstitial pancreatitis has reached a certain grade of intensity diabetes ensues and is the terminal event in the disease."

To one additional point I may refer. In Case 1 the hæmorrhages into the skin of the legs, which occurred so frequently, might be regarded as the cause of the general hæmochromatosis. Though experimentally Hunter and others have caused accumulation of large quantities of iron-containing pigment, particularly in the spleen, I believe no widespread hæmochromatosis has ever been produced.

I happen to have had under observation within the past two years a case of hypertrophic cirrhosis in a hard-working farmer who had been a very temperate man, and whose trouble began in 1895 with jaundice associated with urticaria and extensive subcutaneous ecchymoses and purpura. Dr. Tompkins, of Charleston, W. V., noted at that time a large, hard tumour-like mass in the epigastrium. I saw him first on December 23rd, 1897. He then had jaundice, a large, smooth liver, and an enlarged spleen. He had had during the two years innumerable attacks of purpura, and when I saw him there was a fresh crop, with large irregular wheals. In 1898 I saw him again and heard of him repeatedly. The special feature was the recurring attacks of purpura, very much of the same character as those noted in Case 1. Towards the end of the year he became more jaundiced and dropsical. He died in coma early in January of the present year. The point of special interest is that the liver, which was much enlarged and very cirrhotic, presented a totally different appearance from that of the liver in hæmochromatosis. There was none of the ochre-yellow pigment, and it could be seen at a glance that the condition was entirely different from that presented by the remarkable sections which I here demonstrate, and which were kindly loaned to me by Dr. Opie.

REFERENCES.

- ¹ Hanot and Chauffard, *Revue de Médecine*, 1882. ² Deul. *Arch. f. klin. Med.*, Bd. lxii.

ROYAL SOCIETY OF EDINBURGH.—At the annual general statutory meeting held on Monday, November 27th, the following office-bearers were elected for the ensuing session: *President*: The Right Hon. Lord Kelvin, G.C.V.O., F.R.S. *Vice-Presidents*: Professor J. G. McKendrick, M.D., LL.D., F.R.S.; Professor Chrystal, LL.D.; Sir Arthur Mitchell, K.C.B., LL.D.; Sir William Turner, M.B., F.R.S.; Professor Copeland, Astronomer-Royal for Scotland; the Rev. Professor Duns, D.D. *General Secretary*: Professor P. G. Tait. *Secretaries to Ordinary Meetings*: Professor Crum Brown, F.R.S., and Sir John Murray, K.C.B., LL.D., F.R.S. *Treasurer*: Philip R. D. MacLagan, F.F.A. *Curator of Library and Museum*: Alex. Buchan, M.A., LL.D., F.R.S. *Councillors*: Sir J. Batty Tuke, M.D., D.Sc.; A. Beatson Bell, Advocate; Professor Shield Nicholson, M.A., D.Sc.; Dr. John Gibson; the Hon. Lord M'Laren, LL.D.; C. G. Knott, D.Sc.; Dr. Alex. Bruce, M.A., F.R.C.P.E.; James A. Wenley; the Rev. Professor Flint, D.D.; James Burgess, C.I.E., LL.D.; R. M. Ferguson, Ph.D., LL.D.; Robert Irvine. *Honorary Representative on George Heriot's Trust*: Sir John Murray, K.C.B., LL.D., F.R.S.