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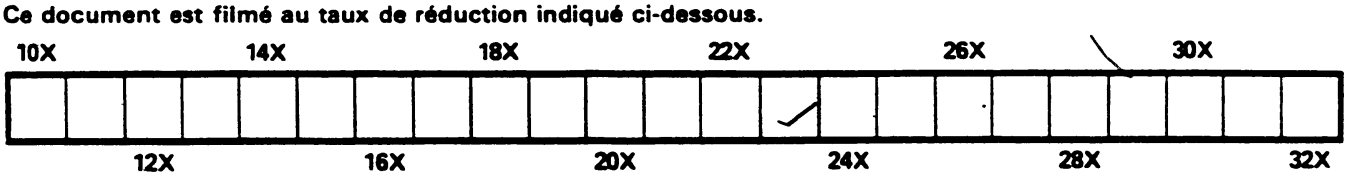

PIGMENTATION CIRRHOSIS OF THE LIVER IN A CASE OF HÆMOCHROMATOSIS.

By MAUDE E. ABBOTT, B.A., M.D.

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PIGMENTATION CIRRHOSIS OF THE LIVER IN A CASE OF HÆMOCHROMATOSIS.

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THE case which forms the subject of this paper was brought before the Montreal Branch of the British Medical Association in May 1898 by Professors Adami and Stewart, and a brief reference is made to it by the former in his article on "Cirrhosis" (1). For reasons which it is unnecessary to give here, a detailed description has been delayed until the present time.

I am indebted to Professors Adami and Stewart for permission to report this rare condition, the first of its kind observed on this continent, and indeed the first of its kind recorded as occurring in the female. The latter I have to thank for the clinical report, and the former for the post-mortem notes, for access to the material, and for direction in its study throughout.

The case was one of cirrhosis associated with so-called hæmochromatosis, the *cirrhose pigmentaire* of the French school. An advanced cirrhosis of the liver, and a moderate degree of chronic interstitial pancreatitis, were associated with an extensive deposit of iron-containing pigment in the tissues. There was a bluish-grey slaty tinge of the skin, and a rusty-brown discoloration of the internal organs. Sections of the liver and pancreas were loaded with golden-brown pigment, responding with a deep blue colour to Perl's test for iron, which was present also, though in a lesser degree in the spleen, suprarenals, and heart muscle.

The few cases analogous to this that are on record have, of late years, been the subject of much discussion among Continental writers. Indeed, the combined occurrence of hæmosiderosis and cirrhosis, and, what is more, the very frequent combination of hæmosiderosis, cirrhosis, and diabetes, which is the more common, forming the *diabète bronzé* of French writers, invites inquiry, for the etiology of the three conditions is alike obscure. Whether the one condition be dependent upon the other, or whether all are due to the action of one common cause, there may lie in their coexistence some clue to a pathogenesis that is as yet incompletely understood.

(Read before the Pathological Society of London Feb. 20th 1900.)

Among English observers, up to the time that our own case occurred, this subject had received little or no attention. Saundby (2) has a brief reference to one case of bronzed diabetes observed by him, while a case of a peculiar pigmentation of the skin described by Galloway (3) may be possibly another example of this condition. But further than this we have been unable to come across any reference, either in English or American literature. Recently, however, the literature has been enriched by an article of E. L. Opie (4), in which an able discussion of the subject is added to the report of a case occurring in the practice of Dr. T. Opie of Baltimore. In this, and in a recent article by Anschütz (5), the literature and the possible etiology are so fully discussed that it will be necessary for me to do little more than to add the few facts observed by us to those already upon record. It will be seen that a study of these facts leads up to conclusions a little different from those reached by Opie, in that we cannot feel assured that hæmochromatosis is to be regarded as a morbid entity.

Clinical History.

Mary G., æt. 50, unmarried; was first admitted to the Royal Victoria Hospital, under Dr. Stewart, in July 1897. Her present illness began two years previously with symptoms pointing to gastric irritation. Gastric pain and vomiting were complained of at intervals up to the time of her admission. For upwards of ten years she had been in the habit of taking an undiluted glass or two of gin daily. Some few months previous to her admission this gin had been replaced by beer. For years also she had been in the habit of drinking a mixture of vinegar and soda, two or three times daily. She had a tuberculous family history, although she herself showed no signs of tuberculosis.

On admission she was found to be poorly nourished, with yellowish conjunctivæ, while the face, neck, and hands presented a marked discoloration. The skin of these regions had a dark bluish or slaty colour. Similar changes but less marked in degree were present, generally over the skin of the unexposed parts of the body.

There was visible pulsation in the superficial arteries, and a fairly well marked degree of general arterio-sclerosis. At the apex and over the aortic area could be heard a soft blowing systolic murmur.

There were physical signs pointing to effusion into both pleural cavities, more marked on the right side. She was troubled with cough, accompanied by the expectoration of scanty brown sputum, which under the microscope showed epithelial cells, granular material, and a few brownish flakes.

She complained of a sense of weight in the epigastrium and frequently vomited after meals. A test breakfast given showed the presence of hydrochloric and lactic acids, but not of butyric acid. The abdomen was fuller than normal, and in the epigastrium was a firm hard mass, having a rough and convex surface with well-defined borders. The movements of this mass during respiration were synchronous with those of the liver. The gall bladder could not be palpated. The spleen was found considerably enlarged, reaching to within $2\frac{1}{2}$ in. of the anterior-superior spine.

A few weeks after admission she was transferred to the surgical department of the hospital for treatment of a suppurative otitis media and mastoid abscess. Upon her return to the medical side her general nutrition was found to be considerably improved, there being a definite gain in weight and strength.

Pigmentation of the skin, however, was distinctly deeper in colour, although it varied somewhat from day to day. It was so marked that the patient was familiarly known throughout the hospital as "Blue Mary." It was of a deep ashy colour, deepest, as on admission, upon the exposed parts. Eventually some cyanosis of the lips, ears, and finger-nails showed themselves, together with a slight degree of subcutaneous œdema of the lower limbs. On several occasions the chest was aspirated and a few ounces of blood-stained serum removed. During her residence in the hospital, epistaxis, though moderate in degree, was frequently complained of, and for some days previous to death much blood-stained fluid drained from the mouth.

The urine at no time presented abnormal characters, save on a few occasions there was a trace of albumin; *sugar, although frequently tested for, was never found to be present.* On 15th April 1898, the patient became suddenly worse, passing into a semi-stuporose state and refusing nourishment. She died on the following day. Previous to this sudden and fatal attack her condition had varied little for two months, the discoloration of the skin had remained about the same, although varying in deepness of tint from day to day. The diagnosis made during life varied between malignant disease of the liver itself, or of the head of the pancreas becoming adherent to the liver, and again of hepatic cirrhosis.

Pathological Report.

The following is a brief abstract from the report of the autopsy which was made eighteen hours after death :—

The body was that of a well-nourished woman of middle age, the face and exposed parts of the body were of a curious ashen-grey to bluish colour, other parts were tinged bluish-grey but to a less extent. The skin of the face was rough, that of the palms and hands singularly smooth and almost silky.

On opening the abdomen a characteristic pungent subacid odour, exhaled by the body in general, was given off very strongly. There was a complete absence of ascites. There were several bands of richly vascular omental adhesions to the parietes in the right anterior portion of the abdomen. The stomach was large, greatly distended, and of a slaty colour. The portions of the organs which were in contact with the stomach—the inner surface of the spleen, the under surface of the left lobe of the liver, and the pancreas, showed an intense blue-black pigmentation, evidently post-mortem. The coils of the small intestines were full and of the same slaty-blue colour presented by the stomach. The edge of the liver passed to about 1·5 cm. below the ensiform cartilage, the right lobe being almost entirely covered by the ribs, the relatively large left lobe forming the main visible portion, and forming further the tumour visible during life; the visible surface was distinctly of the hobnailed type.

Upon removing the organs the stomach was found large, rather thin-walled, and contained abundant black blood and gas; the mucosa was stained black; there were no enlarged submucous veins of the stomach. The first few feet of the jejunum were greatly distended with bluish fluid blood. The lower portion of the small intestine was relatively empty but blood-stained, but within a few feet of the valve was more solid coagulated blood, and this continued, filling the colon, right down to the rectum; evidently, the cause of death was excessive hæmorrhage.

On examining the œsophagus, it showed a plexus of dilated and varicose submucous veins, forming, here and there, well-marked projections of the mucosa. At a point not quite an inch above the cardiac orifice, and roughly along the posterior median line of the œsophageal tube, pressure upon one of the projecting varicosites led to free oozing of blood from a little punctate depression of an ulcer. Here evidently was the seat of hæmorrhage.

The liver was of normal weight (1550 grms., or about 51 oz.), but on the

whole was rather smaller in dimensions than normal, the right lobe being relatively more shrunken than the left. There were extensive adhesions, in the shape of well-formed vascular fibrous strands between the right lobe and the diaphragm; no evidence of gummata. On section the organ was dense and firm, presenting, everywhere, small lobular islands of dirty yellowish colour, surrounded by bluish-grey glistening fibrous tissue present in great abundance. The reverse of the usual colour relationships between the interstitial tissue and the parenchyma was a prominent feature.

The spleen was relatively enormous, weight 720 grms., and in dimensions 23·5 × 13·5 × 4 cms. There were numerous adhesions to the diaphragm and surrounding organs, which broke down easily. The organ was flabby, and on section was pale and pulpy.

The pancreas was long, thin, and moderately congested. The suprarenals were of dark colour with softened medulla.

The kidneys presented a condition of mixed nephritis, and were relatively large and somewhat congested.

The bladder and vagina were normal; the uterus was atrophied, presenting numerous adhesions, of old standing, to the rectum and the right ovary. There was evidence of chronic endometritis, and some small mucous intramural and subserous fibroids were present. The right ovary was atrophied and adherent to the middle of the posterior wall of the uterus. The left ovary was shrunken and adherent to a coil of the sigmoid flexure. The Fallopian tubes were singularly long.

HISTOLOGY.[1]

The liver.—Under a low power (Reichert No. 3) two pathological changes are most strikingly apparent: an extensive annular cirrhosis with atrophy of the liver cells, and a heavy golden-brown pigmentation of both parenchyma and fibrous tissue.

Connective tissue. — Wide bands of fibrous tissue traverse the section irregularly, sometimes leaving two or three lobules intact, more often invading the parenchyma, penetrating some lobules, and obliterating or altering the shape of others. So enormous is the cirrhotic change, that sometimes the whole field of the microscope is occupied by an area in which no hepatic tissue is visible. The central vein lies sometimes free in the lobule, sometimes it is the centre of a localised area of fibrosis, and, most often, is involved in the wide stretches of cirrhotic tissue that occur. At points where diverging bands of tissue meet, or again where new tissue is invading the parenchyma, heavy clumps and masses of dark brown pigment occur. The fibrous tissue is, in parts of old standing, poor in cells; in other parts, generally in the neighbourhood of the degenerating hepatic tissue, or where it itself is most heavily pigmented, it is very cellular. It is very vascular, the numerous thin-walled vessels filled with blood giving it in some places an almost angiomatous appearance; moderate numbers of new bile canaliculi occur.

Hepatic parenchyma.—Little lobular arrangement remains. The liver cells are often atrophied, especially those that are deeply pigmented, or those lying in the neighbourhood of the cirrhotic bands. No sign of compensatory hypertrophy is seen. Almost all the cells show a greater or less degree of pigmentation, which gives them under this power a diffuse golden-brown colour, much lighter than that of the heavy brown masses lying in the connective tissue. Those cells lying at the periphery are generally most heavily pigmented, but sometimes the change extends quite definitely to the very centre of the lobule. In some parts of the section there was slight fatty degeneration.

With a higher power (Reichert No. 7A) the form and arrangement of the

[1] Sections stained with eosin-hæmatoxylin and by Van Gieson's method.

pigment is very interesting. It is of two kinds—very fine granules, and coarse highly refractive particles, which are generally rounded and often resemble red blood corpuscles both in form and size. In the fibrous tissue these particles are aggregated into heavy clumps and masses. In the older, less cellular regions of the cirrhotic tissue, pigmentation is scanty, the granules being generally small and arranged along the course of the fibres. In the newer, more cellular part, where the pigment is abundant, it is quite irregular both in form and arrangement; fine granules, coarse particles, and heavy masses lying between the cells and fibres, or apparently free upon the surface. The pigment does not appear to lie within the *connective tissue* cells. Highly pigmented *liver cells* are seen enclosed in the connective tissue. They are sometimes completely transformed into a mass of pigment granules, and are recognisable only as the remains of liver cells, from their form and the nucleus which, though staining badly, can still be made out.

The heavy homogeneous pigment masses in the connective tissue also often resemble liver cells in form, and some peculiar spindle-shaped cells occur which, from their segmented arrangement upon each other, suggest an origin from the parenchyma. These collections of cells bear a general resemblance to fibroblasts, but the transverse segmentation is distinct from anything ever seen in cells of connective tissue origin. I would suggest that collections of cells of this nature led (or misled?) Hamilton (6) to conclude that the liver cells can function as fibroblasts in the cirrhosed liver.

The endothelium of the capillaries and of portal vessels is often pigmented. The epithelium of the new bile canaliculi is generally free from pigment. This is the opposite to what has been observed in most cases reported, and of the condition we have ourselves seen in the livers of two cases reported by Kretz (7), which we have had the opportunity of examining.[1]

In the liver cells the pigment, when in moderate amount, is finely granular, and is arranged along the side of the cells bordering upon the bile capillary and around the nucleus. When the cell is loaded, the granules are coarser, sometimes angular in form, and there is no regular arrangement. When pigmentation has gone on to destruction of the cell quite large particles occur, generally rounded. The variations in size and appearance indicate a gradual clumping of the finer granules into larger more refractive masses. Here and there, through the parenchyma, occur islands of such broken-down cells, represented by coarse golden-brown granules, among which young connective tissue cells are developing. In most instances of extreme pigmentary degeneration, unless the cell be completely broken down, the nucleus still stains well. In the endothelium of the capillaries and in the leucocytes granules were observed, none were seen free in the blood stream.

When the liver was tested microchemically for iron by Perl's test, the whole section assumed a deep blue colour. Microscopically, all pigment granules had taken on a Prussian blue colour; the heavy clumps in the connective tissue are almost black, while the finer particles in the liver cells are a brilliant blue or sometimes a bluish green.

Pancreas.—Here again, as in the liver, there is overgrowth of connective tissue and extensive pigmentation. Trabeculæ penetrate the parenchyma, sending finer prolongations inward, which surround the acini or groups of acini. The new tissue seems to be of slower growth than that in the liver, for it is much less cellular, it is also less vascular. Clumps and masses of pigment lie in it, identical in form and appearance with those in the cirrhotic areas in the liver. Within the fibrous tissue islands of one or more degenerat-

[1] I have to thank Dr. Augenette Parry of New York for her kindness in having forwarded to me this material, which she obtained through the courtesy of Dr. Kretz and Prof. Albrecht of Vienna.

ing acini often occur, many cells of which have lost their form and have become simply a mass of pigment granules.

The epithelial cells are irregularly often heavily pigmented, and there is extensive necrosis. Examined under an immersion lens of high magnification, where the fine granules, both in the hepatic and pancreatic cells, are relatively scattered and separate, they are seen to be arranged with remarkable persistence in pairs, and thus closely resemble, if they are not identical with, the diplococcoid forms in the liver and other cells to which Professor Adami has called attention.

Retroperitoneal lymph glands.—The only lymph glands examined were from the neighbourhood of the pancreas; the fibrous septa were distinctly widened, but did not seem to penetrate into the lymphoid masses lying in their meshes. Part of the gland was comparatively free from pigment; here and there a few round particles lay between the cells, and sometimes a row of fine granules surrounded the nucleus as though enclosed within the cell protoplasm. A large area of the gland was, on the other hand, completely transformed into coarse granules of golden-brown pigment, between which lay isolated lymphoid cells. In these areas there seemed to be no increase of connective tissue. At points where the pigmentation was heaviest there were areas of necrosis—hyaline regions staining with hæmatoxylin-eosin, a pale pinkish violet, in which lay a curious network of highly refractive homogeneous fibrils. This network was of a pale yellow colour, in unstained specimens, and did not stain with hæmatoxylin and eosin. With Van Gieson the fibrils took a dark greyish, almost black, colour, they gave a deep Prussian blue with Perl's test, the blue colour developing here much more rapidly than in the other pigmented areas of the section. The iron reaction appeared after ten minutes in a 1 per cent. solution of *cold* hydrochloric acid.

These curious fibrils resemble nothing ever observed by us before; their general appearance strongly suggests a capillary network which has undergone hyaline degeneration, and has taken up iron pigment in a soluble form.

Spleen.—The trabeculæ do not appear to be increased. By Van Gieson's method a limited fibrosis is apparent near the surface of the organ, fine threads of fibrous tissue traversing the parenchyma. Pigmentation is scanty, some very fine granules being scattered through the tissue. These do not react to Perl's test, although the whole section takes on a pale diffuse blue colour. The only true Prussian blue reaction that occurs is in the adventitia of the large vessels in which the coarsely granular form of pigment lies.

Heart muscle.—Van Gieson's method shows a very early fibrosis, fine strands of connective tissue running here and there between the fibres. There is limited pigmentation, golden-brown, finely granular pigment being arranged around the poles of nuclei as in brown atrophy. The reaction to Perl's test is irregular; in some cells the granules react freely, in others the colour remains unchanged; the whole section takes on a diffuse blue tinge.

Suprarenals.—There was extensive necrosis of the medulla (probably post-mortem) and a brownish pigmentation, which gave no iron reaction. There were scattered areas of small-celled infiltration in the medulla and dense iron pigmentation of the epithelium of some of the cortical acini.

Kidney.—Some congestion and a mixed nephritis exist. There is no fibrosis and no iron pigmentation, except in the epithelium of a few isolated tubules in the cortex.

Lungs.—With the exception of a few leucocytes lying free in the alveoli, which took a diffuse blue tinge, no iron was apparent.

Skin.—In spite of the peculiar bluish-grey, slaty tinge described, there was surprisingly little microscopical evidence of pigment. All that could be observed were a few golden-brown granules in some large, irregularly shaped cells, situated in the connective tissues of the dermis, a little below the Malpighian layer; there was no reaction to Perl's test. The discrepancy

between the macroscopic and microscopic appearance of the skin is noted by other students of this disease, and it has been suggested that the discoloration is simply due to a peculiar form of cachexia.

Alimentary tract.—Unfortunately, the only part of the alimentary tract reserved for microscopical examination was the lower part of the œsophagus and the cardiac end of the stomach. The wall of the latter turned a diffuse blue with Perl's test; the muscle cells of the muscularis mucosæ contained granules of golden-brown pigment, not reacting to this test. The lymphoid follicles in the subserous layer of the stomach were transformed into dense masses of golden-brown pigment, in which lay areas of necrosis, showing the same highly refractive fibrillary network observed in the retroperitoneal glands.

As indicated by the post-mortem blackening of the organs in the immediate neighbourhood of the stomach, early putrefactive changes had occurred with diffusion of hæmoglobin from the blood abundantly present in the viscus. The diffuse reaction of the whole stomach wall is thus to be regarded but as an evidence of this diffusion.

The histological study of this case revealed the following points:—

1. More or less fibrosis of all organs, except the kidney, was associated with a greater or less degree of hæmosiderosis.

2. In both liver and pancreas the heavy pigmentation of the connective tissue had its source, in part at least, in the broken-down pigmented cells of the parenchyma.

3. A fairly advanced chronic interstitial pancreatitis existed without the clinical picture of diabetes so common in cases of advanced hæmochromatosis.

A word with regard to the microchemical reaction:—

Sections of the organs were tested with ammonium sulphide and with potassium ferrocyanide, with affirmative results. In the closer study of the case, however, Perl's test only was used. In its employment several difficulties were encountered.

The routine method at first employed was as follows:—Potassium ferrocyanide, 2 per cent. solution, three minutes; hydrochloric acid, 1 per cent. watery solution, two to five minutes; wash with distilled water. The bulk of the material was hardened in Müller's fluid, to which 2 per cent. formalin had been added, and was preserved in methylated spirits. On taking up the study of the case, when the material was some two months old, the writer found that whereas the iron reaction had been prompt in the fresh specimens examined shortly after the autopsy, no typical reaction now occurred, the granules turning a greenish yellow, or at most a green colour, many not reacting at all. The only part of the tissue where the Prussian blue colour developed, after ten minutes in cold hydrochloric acid, was the remarkable hyaline network seen in certain of the necrotic areas of the lymph glands.

It was at first thought that the formalin in the fixing fluid had liberated the iron or else had thrown it into closer combination. That the iron was not liberated, but that the reaction was only

delayed, was proved by the fact that sections left in hydrochloric acid solution, two to twenty-four hours, gave a typical Prussian blue colour, while, when the test was performed with hot hydrochloric acid, the reaction was almost instantaneous. Pieces of liver were placed for four days in 4 per cent. formalin, cut and tested with control parallel sections of the Müller-formalin material. The sections kept in formalin gave a typical reaction in two minutes with cold hydrochloric acid. Thus the action of the formalin was to throw the iron into looser combination and make it react more readily. Bits of tissue, hardened from the first in alcohol, reacted readily—Müller's fluid seems thus to have been the cause of the delayed iron reaction. Quincke (8), in his work on hæmosiderosis, made a similar note, to the effect that Müller's fluid interferes with the iron reaction.

It is noteworthy that the iron-containing pigment reacts very unevenly to Perl's test; many granules showing at most only a light yellowish green at the end of twenty minutes in cold HCl, and assume at once a deep blue colour on being placed in the hot acid. In the lymphatic gland, after five minutes in cold HCl, only the curious homogeneous network (above described) reacted, while on treatment with hot HCl all the golden-brown granular pigment turned a deep Prussian blue.

The obvious conclusion is, that in our case all the granules, both the darker brown and the paler yellow,—in the liver, the lymphatic glands, and the pancreas,—*i.e.* both the hæmosiderin and what we regarded as the hæmofuscin of other observers, are iron-containing, the essential difference being that in the one the iron is in looser, in the other somewhat firmer, combination, only being rendered free by the action of hot HCl; on the other hand, even hot HCl, as employed by me, did not cause the reaction to develop in the "hæmofuscin" granules of the muscle cells. The ordinary muscle pigment is clearly distinct from the pigments characteristic of hæmochromatosis.

A point of interest in this case is the occurrence of a chronic interstitial pancreatitis without any diabetes. Diabetes has been so commonly associated with cases of advanced hæmochromatosis that *diabète bronzé* has been regarded by many observers, especially in France, as a distinct morbid entity. The first cases reported under this name were published by Hanot and Chauffard (9) in 1882. The diabetes would seem to be secondary, dependent upon disease of the pancreas, which has been found affected in every instance in which microscopical examination has been made. Anschütz has collected twenty-four cases of *diabète bronzé* from the literature. In eighteen cases there had been microscopical examination: there was chronic interstitial pancreatitis fifteen times, and three times a heavy deposit of iron pigment in the glandular epithelium.

In our case, however, as in several others in the literature (as, for instance, in one of Hintze's [11]) and in Opie's), there was pancreatitis without diabetes; in other words, a condition anatomically of the same order as *diabète bronzé* existed without the clinical features of the disease. We are inclined to believe with Opie that the disease of the pancreas may not have been sufficiently advanced to give rise to symptoms, enough of the gland remaining healthy still to perform its functions. Or the diabetes may have been latent while the patient was under observation. Marie [12]) notes a tendency in these cases for the diabetes to disappear under treatment, or in the later cachectic stages of the disease, and in six of the cases collected by Anschütz this occurred. At all events cases such as these seem to form a connecting link between the cirrhose pigmentaire, pure and simple, and the *diabète bronzé* of the French school, and would seem to indicate that these two conditions are not separate morbid entities, but stages in the course of one general disease.

The majority of cases of advanced generalised hæmochromatosis, with or without diabetes, seem to have been observed in France, and, as has been said, have been described by French writers as cases of bronzed diabetes or pigmentation cirrhosis. In Germany, on the other hand, where the cases have been fewer, the subject seems from the first to have been viewed from a wider standpoint, to which the later French writers are inclining. All cases in which there is an abnormal deposit of blood pigment in the tissues have been classed together as different stages in the same pathological process, to which in 1889 von Recklinghausen [13]) gave the name of "hæmochromatosis." The most important studies along these lines are those of Quincke (1880), von Recklinghausen (1889), Hintze (1895), and Kretz (1896).

Among ten miscellaneous cases, in most of which the iron pigment is confined to the liver cells and to the spleen, Quincke includes a case of general hæmochromatosis in diabetes. von Recklinghausen included, under the term hæmochromatosis, cases of pigmentation cirrhosis and *diabète bronzé*, with others in which the pigmentation was limited to the intestinal wall alone. Hintze gives six cases, in two of which there was general hæmochromatosis without diabetes, in one pigmentation confined chiefly to the liver and spleen, in one affecting only the pancreas and retroperitoneal glands, and in two involving the intestinal wall alone.

Kretz in his valuable monograph on hæmosiderin and cirrhosis, in a study of some eighty-eight livers, obtained the following results:— In twenty-six cases of cirrhosis of the liver there was hæmosiderosis fourteen times, in two instances these were cases of *diabète bronzé*; in four other cases—typhoid, pneumonia, chronic tuberculosis with hæmorrhagic pleuritis, and chronic peritonitis with marasmus—there was a moderate deposit of iron pigment in the liver cells not extending to the connective tissue.

In the microscopical study of sections of the liver and pancreas from the material before me—our own and the two cases recorded by Kretz—we have noted repeatedly the heavily pigmented hepatic cells, breaking down to form masses of coarse granular pigment in the fibrous tissue, which at such points is very cellular, evidently of new formation. This appearance would indicate that the formation of pigment is, in part at least, antecedent to the cirrhotic change. Other observers, Opie, Anschutz, Hintze, and Kretz, and indeed all whose work I have followed carefully, have noticed this appearance and drawn this conclusion.

If, then, the pigmentation be primary, it seems rational in studying the etiology of this condition to follow along German lines, and seek to ascertain the pathological conditions under which pigment, giving the iron reaction, is deposited in the parenchymatous cells.

Following the example of Peters, Hunter, and Kretz, I have examined microchemically the organs from a large number of cases. The following results are interesting:—

Among sixteen cases of cirrhosis, there was hæmosiderosis six times. Here the liver only was examined, as the material was obtained from a number of cirrhotic livers collected for another purpose. In three of these cases pigmentation was marked, the iron being present, not only as fine granules in the liver cells, but lying also in coarser masses in the connective tissue, as in our case of general hæmochromatosis. In the remaining three cases it was confined to the liver cells, lying as fine granules along the margin of the bile capillaries.

Among eight cases of typhoid examined there was hæmosiderosis twice; in one it was very slight, simply giving a greenish tinge to the section; in the second, in which there was a clinical history of intestinal hæmorrhage, it was marked, occurring as fine granules in the liver cells. The connective tissue was free.

Forty-one cases were chosen from the post-mortem material at the Royal Victoria Hospital of the past eighteen months, because there was a note in the report that golden-brown pigmentation of the liver cells existed. The liver, spleen, pancreas, and sometimes the heart muscle were examined. Cases of pernicious anæmia, where hæmosiderosis of the liver cells is an almost constant condition, were excluded. In these forty-one cases there was hæmosiderosis four times; both liver and spleen gave a marked reaction, but the *pancreas was free from pigment in all cases.* In the liver the pigment lay in finely granular form in the cells, sometimes in the capillaries and the capillary endothelium, never in the connective tissue. In the spleen there was a diffuse staining and also a coarsely granular pigmentation of the parenchyma. The trabeculæ were generally free. In a fifth case there was iron pigment in the capillary walls and contents, none in the liver cells or spleen. The following is a short account of these cases:—

CASE 1 (Path. No. 41, 1898).—Male, æt. 43. Scirrhous carcinoma of pancreas; secondary carcinoma of left lung, pericardium, and œsophagus; pericarditis adhesiva; old empyema of left lung, *forming an abscess cavity*, which had been operated on and drained; *venous congestion of the intestinal wall*; firm old adhesions between ascending and transverse colon, omentum, and wall of the gall bladder.

MICROSCOPICAL EXAMINATION.—*Liver.*—Some small-celled infiltration along the portal sheaths, small cells scattered irregularly between the liver cells; pigmentation and fatty degeneration of the liver cells. With Perl's test the section assumes a diffuse blue colour, fine iron pigment granules lie in the cells, generally centrally in the acini along the margins of the bile capillaries. *No iron in the portal tissue.*

Spleen.—Some congestion and hyperplasia of the follicles. Coarse lumps and granules of iron-containing pigment giving an intense reaction to Perl are scattered through the parenchyma. Trabeculæ free from pigment.

Pancreas.—No pigmentation.

CASE 2 (Path. No. 1, 1899).—Old man. Pneumonia senilis; *large sloughing ulcer covering the whole surface of left leg*; skin over the surface of the right leg pigmented; inguinal glands enlarged; left sero-fibrinous pleurisy; *duodenitis*; brown atrophy of heart.

MICROSCOPICAL EXAMINATION.—*Liver.*—Heavy golden-brown pigmentation in the cells; no marked increase of portal tissue, but areas of small-celled infiltration are scattered throughout the parenchyma, generally coinciding with the more heavily pigmented areas. Some newly formed bile ducts lie in the portal sheaths. Liver cells at the periphery of the lobules are most heavily pigmented, all the granules react strongly to Perl. In the blood vessels are some small round bodies the size of a red blood corpuscle which react deeply. *The connective tissue is free from iron.*

Spleen.—Marked congestion; some atrophy of parenchyma with increase in size of trabeculæ. With Perl there is a diffuse, somewhat blotchy blue staining of the parenchyma in which coarse granules and masses of iron pigment lie. Trabeculæ free.

CASE 3 (Path. No. 3, 1899).—Male, æt. 57. Operation five days antemortem for irreducible hernia of ten days' standing; death from intestinal obstruction. *Post-mortem.*—Double pneumonia; inflammatory infiltration and hæmorrhagic condition of great omentum, forming a mass to which the small intestine was attached, causing a kink which formed the point of obstruction. The whole of the *intestine* here *showed marked inflammatory change* and the mucosa was covered with a necrotic pseudo-membrane.

MICROSCOPICAL EXAMINATION.—*Liver.*—Fatty degeneration and finely granular pigmentation of the liver cells, which are much atrophied and misshapen and often broken down. No attempt at the formation of new connective tissue. Some congestion, the capillaries being often distended. Pigment in the liver cells reacts to Perl.

Spleen.—Congestion some fibrosis; well-marked siderosis of parenchyma.

CASE 4 (Path. No. 8, 1899).—Male, æt. 76. Compression myelitis due to pressure from a large cancerous mass in the pelvis. Adeno-carcinoma of prostate and retroperitoneal glands. *Large sloughing bedsore over sacrum*, of about one month's duration.

MICROSCOPICAL EXAMINATION.—*Liver.*—Extreme fatty degeneration, almost the whole tissue being in parts transformed into a mass of fat globules, the remaining liver-cells are often heavily pigmented. Some increase of connective tissue in portal sheaths. In this case the golden-brown pigment in the cells does not react to Perl. Numerous dark granules lie in the leucocytes, in the capillaries, and on the lining endothelium of the capillaries, and stain a diffuse blue.

Neither spleen nor pancreas contain iron.

CASE 5 (Path. No. 20, 1899).—Female, æt. 69. Pneumonia; *intestinal hæmorrhage on day of death.*

MICROSCOPICAL EXAMINATION.—*Liver.*—Fatty degeneration of the liver cells, which are often swollen. There is finely granular iron pigment in the liver cells, arranged along the walls of the bile capillaries, also diffuse staining of the capillary endothelium as in the last case. Many leucocytes in the capillaries contain iron granules.

Spleen.—The parenchyma takes a diffuse blue tinge with Perl, and coarsely granular iron-containing pigment is scattered through it.

Pancreas.—No pigmentation.

There was in all these cases a history of localised blood disintegration, either hæmorrhage or chronic suppuration, and in all cases a history of some intestinal disturbance.

Blood disintegration, either from localised extravasations into the body tissues, or from breaking down of red corpuscles within the blood stream—as in pernicious anæmia and extreme cachexia—seems to be very frequent in cases of hæmochromatosis. In Hintze's three cases there was a history of subcutaneous hæmorrhage, hæmorrhagic pericarditis, and hæmorrhagic peritonitis. Hindenlang (14) (1880) gives a case of advanced hæmochromatosis with cirrhosis occurring in a course of purpura. In our own case, though there was no obvious anæmia (no blood count was made), it is interesting to recall the tendency towards hæmorrhage evinced by the frequent epistaxis. On the other hand, such a history is not constant, and blood disintegration may exist both as an extravasation and in advanced cachexias without hæmosiderosis of the liver cells. Zaleski gives a case of purpura in which there was no hæmosiderosis. I have myself examined several cases in which hæmorrhages had taken place into the tissues, among others a case of purpura, with a negative result.

Auscher and Lapique (15) injected blood into the peritoneal cavity of animals, and obtained iron pigmentation of the spleen, but not of the liver cells.

Hæmorrhage alone is thus clearly not the cause of hæmochromatosis, there must be something behind or accompanying it—a something which becomes active, either under repeated interstitial hæmorrhages or destructive changes occurring in the circulating blood. And, further, it may be that some disturbance of the specific cells of the liver and other organs is also required to favour the deposit within them of the iron-containing pigment. It is possible, indeed we know, that under ordinary conditions the blood pigment is eliminated in a soluble form, leaving no trace of its presence within the cells.

The remarkable frequency with which hæmosiderosis occurs in cases of cirrhosis, and when affecting the pancreas its frequent association with advanced disease of this organ, shows that this possibility must be kept in mind. Thus Kretz found hæmosiderosis in fourteen of the twenty-six, and we ourselves in six out of sixteen, cirrhotic livers. On the other hand, the tissue changes in cirrhosis, and the interstitial pan-

créatitis may themselves be due to the action of one common and primary cause, and there may be one common factor causing blood destruction,—the liability to hæmorrhage and to morbid disturbances in the liver, pancreas, lymphatic glands, etc.; we cannot, I think, wholly pass over this possibility.

What has especially struck me, as it also impressed Hintze, is that common to all these cases we have evidence of more or less chronic intestinal disturbance. Indeed, as Hintze points out, the earliest stage of recognisable hæmochromatosis is that in which the walls of the small intestine alone are involved. We are forced also to recognise that in ordinary portal cirrhosis we have a similar history of chronic intestinal disturbance. Boix ([17]) has gone further, and has caused advanced cirrhosis in animals by feeding them with large quantities of the more deleterious products of intestinal digestion, and again by inoculating them with toxines developed from the bacteria inhabiting the intestinal tract. *There is then a certain amount of possibility, that the cause of hæmochromatosis is to be found in association with intestinal disturbance.*

In Cases Nos. 1, 2, 3, and 5 (Case 4, where the iron was only in the capillaries, may be omitted from consideration), and in the case of typhoid above mentioned, we found that the distribution of iron pigment differs from the case of general hæmochromatosis, which forms the subject of this paper, in the following points:—

1. In the liver, the pigment is found in the hepatic cell, where it lies in rows of fine granules along the margins of the bile capillaries; the connective tissue is free.

2. While there is pigmentation of both liver and spleen, the pancreas is quite iron free.

An identical distribution of iron pigment occurs in many cases in the literature, where there has been a history of local hæmorrhage.

The question arises, Is this a difference of degree only? or, is it essential? In other words, is hæmochromatosis a distinct morbid entity? Or is it simply a more advanced stage in the same pathological process at work in the cases of more localised iron pigmentation cited above?

The pigmentation of the connective tissue does seem to be a further step in the same process. In these slighter cases the pigment granules lie along the margin of the bile capillary, apparently being continuously excreted. In pigmentation cirrhosis, while the same appearance exists in the healthier cells, there are large areas of extensive pigmentation where the cell becomes overloaded, breaks down, and forms a mass of coarse pigment lying free in the newly formed connective tissue. The liver cell seems to have become unequal to its task of throwing off the insoluble granules which have been deposited in it, and succumbs at last to the accumulation of unrejected pigment which loads it down. Again, in the cases of cirrhosis, where there was hæmosiderosis of the liver cell without general hæmochromatosis, the

connective tissue is often pigmented, as in ten out of Kretz's fourteen cases, and in three out of our six.

On the other hand, the different distribution of iron in the organs seems at first sight to indicate that an essentially different process is at work. Not only in the one set of cases is the spleen pigmented, while the pancreas remains free; but in the other (pigmentation cirrhosis), the pancreas, with the other glandular organs, is loaded with pigment, while the spleen is relatively free. A possible explanation may be that the degenerating liver cells have lost much of their power of excretion, and, ceasing to act as a natural barrier, allow the blood pigment to pass on to the other organs. But this can hardly hold, for the lung is free from iron while pigmentation of the spleen is relatively slight. Neither those organs within the sphere of the portal circulation, nor those lying in a relation of contiguity to the liver, share evenly in the pigmentation, but certain elements which lie far removed from each other—for instance, the pancreas, thyroid, salivary glands, hypophysis cerebri, and heart muscle. These are all organs in which iron-free pigment is commonly formed. There would seem to be some degeneration of the parenchymatous cells of these organs, by which they become unable to throw off the altered blood pigment deposited in them.

The observations of Hunter would seem to us to possibly throw light upon the difference in these two sets of cases. Those observations in the first place show that there is a difference, in the extent to which the different organs become the seat of the removal of the hæmoglobin and modified blood pigment, according to the primary seat of the blood destruction. Where this is in the systemic circulation, it would seem that the kidney and the spleen are more active; where, on the other hand, we are dealing with a blood destruction in the portal circulation, there more especially is the liver affected. This, however, is not nearly all; thus Hunter points out there may be very extensive blood destruction, and the spleen itself, when its pulp is examined immediately after death, may show abundant evidence of the same, and yet microchemical tests may reveal no excess of pigment reacting to Perl's test.

This would seem also to be true in connection with the liver; even after extensive transfusion there may be little or no pigmentation of the organ; in other words, hæmoglobin, and it may be certain of its derivatives, do not react to the ordinary test for iron. Some further change is necessary in order to produce hæmochromatosis. While further, as Hunter again indicated, and as we have also pointed out in connection with pernicious anæmia, some definite and specific morbid condition of the cells of the liver (and of other organs) is very probably the factor in the development of the condition. It may, therefore, be that in these two different classes of cases, we are dealing, not so much with a different process as with a process originating in different areas, and

accompanied by morbid conditions, telling now more especially upon one set of organs, now more especially upon another.

From the comparison of these cases, and a study of the literature, the following conclusions are suggested:—

1. In general hæmochromatosis some primitive agency, as yet unknown, is at work leading to (*a*) an increased destruction of hæmoglobin taking place either in localised hæmorrhages, or within the blood stream, or perhaps sometimes within the parenchymatous cells themselves; (*b*) a degeneration of the cells of certain organs by which they become unable to throw off the granular pigment deposited in them, and, becoming loaded, finally disintegrate.

2. The cirrhosis would seem to be of the nature of a chronic interstitial inflammation, secondary upon the presence in the tissues of pigment set free after the destruction of the parenchymatous cell.

These are practically the conclusions to which Kretz came in his study along the same lines.

Hæmosiderosis of the liver cell was observed in our cases (as in many in the literature), to be associated with a history of intestinal disturbance, and at times (in three instances) of prolonged suppuration.

These facts suggest that the primitive agency, leading alike to blood destruction and to cell degeneration, may be bacterial in its nature.

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