HEMOCHROMATOSIS
REPORT OF FOUR CASES *

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Hemochromatosis is a chronic disease of males occurring during middle life. Abbott 1 has reported one authentic case in a woman. It is characterized by (1) a pigmentation of the skin that varies from yellow to ashen gray and involves by preference the exposed parts, the axillae, and the genitals; (2) cirrhosis of the liver with moderate enlargement; (3) slight enlargement of the spleen; (4) fibrosis of the pancreas and lymph nodes; (5) hyperglycemia with or without glycosuria.

It is not a common disease. There are records of but four cases of genuine hemochromatosis among 5,000 recent necropsies in Bellevue Hospital. Fuchter 2 found only three instances of this disease in the clinical records of the Johns Hopkins Hospital, covering 106,000 admissions.

Clinically, hemochromatosis may easily be confused with other diseases attended by pigmentation of the skin. The pigment may not be visible. It may be late in its occurrence. It is very frequently a postmortem revelation. During life the only certain method of diagnosis is the microscopic demonstration of iron reacting pigment in the skin.

Pathogenesis of the Disease.—The chief interest in this disease centers around the remarkable and widespread pigmentation that occurs. In fact, if we could lose sight of the presence of this pigment altogether, the pathology of the disease would narrow itself down to that of an ordinary cirrhosis of the liver, spleen and pancreas, accompanied by clinical evidence of diabetes in a greater proportion of cases than we are accustomed to find in simple interstitial lesions of the pancreas.

The origin of the pigment has been variously ascribed to: (1) increased iron ingestion; (2) increased iron absorption; (3) decreased iron output (a, inability of the intestines and kidneys to put out iron; b, inability of the iron containing cells anywhere in the body to part with their iron); (4) fragility of the iron conveyors (erythrocytes), and (5) specific derangement of the organs that have to do with iron metabolism (liver and spleen).

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Nature of the Pigment.—1. Hemosiderin: This pigment is distinguished by the fact that it contains iron. Its exact chemical formula is as yet undetermined. It is easily demonstrated by Perl’s method, appearing in the form of coarse Prussian blue granules. It is the more important pigment in hemochromatosis. The liver in a marked case of hemochromatosis is literally overrun with it, quantitative chemical determinations showing as much as one hundred times the normal amount of iron.

2. Hemofuchsin: This is an iron-free pigment that does not give Perl’s reaction. The formula is not known. It occurs as fine light brown granules. It is never present in great amounts, and, indeed, its very existence has been disputed by Abbott, Beattie and others, their contention being that, due to age, the iron is more firmly bound than in ordinary circumstances, and that by the use of hot reagents and a greater amount of time, the so-called hemofuchsin may be shown to contain iron. In carrying out this test, the frequency with which one encounters green and greenish blue reactions is supposed to add weight to this contention, especially in view of the fact that such green reactions can be turned into the typical Prussian blue reactions by using hot hydrochloric acid and giving the reaction sufficient time. We are inclined to believe that when the proper technic is observed, most, if not all, of the pigment can be shown to contain iron.

Distribution of the Pigment.—The organs in which pigment containing iron has been found are numerous. They include the liver, pancreas, lymph nodes, spleen, heart, suprarenals, thyroid, hypophysis, prostate and skin. Small amounts of such pigment occur also in the wall of the gastro-intestinal tract, in the testes, kidneys and bone marrow. The central nervous system and the lungs are comparatively free from it. The great mass of the iron pigment is found in the liver, pancreas and abdominal lymph nodes. Where the pigment occurs in such masses it is both extracellular and intracellular. Usually in those organs in which this extracellular pigment (overflow pigment) occurs we find scarring and connective tissue overgrowth. Since the two processes run pari passu, the indication is that they are related. Confirmatory of this is the fact that while great quantities of pigment are sometimes present in the heart, thyroid, suprarenals and hypophysis, it is entirely within the cells and is unaccompanied by fibrous change.

The site of election of this pigment is apparently the actively functioning cells of the parenchymatous organs. It occurs also in the endothelial cells of the blood vessels and ducts, in the heart muscle cells, and in Kupfer's cells in the liver. The connective tissue cells are also rich in hemosiderin in such organs as the liver and pancreas, but, as Sprunt points out, this is probably secondary to the disruption of the overlaiden cells of the parenchymatous organs. The presence of hemosiderin in the connective tissue cells is never seen in such organs as the thyroid, suprarenals and hypophysis, though there may be great quantities of pigment, there is, nevertheless, no evidence of extensive cell destruction.

The pigment which, in the hands of certain workers, has failed to stain blue with the potassium-nitroprussid-hydrochloric acid reaction, the so-called hemofuchsin, is never a very prominent feature of the microscopic picture. It is described as fine light brown granules occurring in smooth muscle cells and also in the connective tissue cells.

Theories Explaining the Presence of Pigment.—Of purely theoretical interest is the idea which has been advanced that there may be an increase of ingested iron in the diet. Likewise, there is no proof of an increase in the known constant iron absorption which characterizes normal metabolism.

Turning to the question of whether there is a decreased iron output, we have first to consider a block in those excretory organs which are known to excrete iron. MacCallum has suggested that the fault may lie in the intestines, the specific cells of iron excretion having lost that function. The kidney might likewise share in the iron block. Histological evidence is against such a view, because if such a sievelike action were operative, the iron would be expected to accumulate at the point of obstruction. As a matter of fact, the kidney and intestines in hemochromatosis are relatively poor in iron. In a case of bronze diabetes, Garrod was unable to detect any iron in the urine, stools or bile.

Iron is known to be widely present under normal conditions in the tissues. It enters into the chemical equation of all nucleoproteins, which are essential constituents of all cells. All cells of the body normally, therefore, have a part in iron metabolism, though in some organs they participate more actively than in others. This may be spoken of as a part of their chromogenic function. This fact, taken in conjunction with the known pathologic anatomy, i.e., of a widespread distribution of iron pigment in the cells, gives the basis of the theory

advanced by Sprunt, Parker, Beattie, and others, that some unknown agent injures the cell in such a way as to interfere with or destroy its iron metabolizing or chromogenic function. The cells which formerly metabolized their iron in a normal manner now become depots for its deposit, the machinery for moving it having in some way been injured or destroyed. This is somewhat analogous to the familiar observation of fat accumulation in injured cells.

The erythrocytes are known conveyers of iron in their hemoglobin. The great majority of the earlier writers assumed that excessive destruction of red blood corpuscles was the source of the accumulated iron. This idea was advanced by Von Recklinghausen in his original description of the disease, and has since had the support of such authors as Osler, Abbott, Opie, Marie, Anschütz and others.

Doubt of the validity of this argument is aroused by the fact that there is no anemia associated with hemochromatosis; that the red blood corpuscles are normal in appearance, and to fragility tests, and that spectroscopic examination of the blood serum shows normal hemoglobin. At the same time, there is no reactive change on the part of the bone marrow, and there is no sterobilin and urobilin. Moreover, in severe and chronic anemias there is no comparable generalized pigmentation, as one would expect were the theory of Von Recklinghausen correct.

On the other hand, hemorrhage and purpura have been features in a number of cases. Roth contends that there is an active blood destruction, though in his opinion this does not satisfactorily account for the whole picture. He cites cases with the blood picture and clinical findings of pernicious anemia. The fact that the majority of the cases show no blood change he explains on the ground that there is an active compensatory erythrocythemia. Roth claims to have seen in the spleen and lymph glands small, irregular forms of red blood cells as well as young and immature cells. Rössle demonstrated the

phagocytosis of the red cells by parenchymatous cells. He explained the disease on the basis of injury to capillary walls with numerous minute scattered hemorrhages.

There is still another possibility, however. It is the consensus of opinion that dead red blood cells are disposed of in a definite way, that is to say, they are destroyed by the spleen and their useful elements, particularly the iron, is stored or resynthesized by the liver. In this connection it is significant that the great mass of the iron accumulation in hemochromatosis occurs in the liver. From this point of view it has been easy for many authors to assign the burden of the responsibility to disturbances of the hepatic function. The presence of pigment elsewhere they assume to be the result of transportation of pigment from the liver, although the method of transportation has not been demonstrated. This does not explain the relatively great quantity of iron in the pancreas and the spleen.

For our own part, we are inclined to agree with Roth, Abbott and others, that there is some toxic agent at work which simultaneously produces injury to the erythrocytes and to the cells of the parenchymatous organs. There is then more circulating iron than in normal conditions, making for its greater accumulation in injured cells.

The Relation of Cirrhosis.—The sequence of events in the liver merits careful consideration, since it is the scene of most extraordinary changes, notably in the form of massive and diffuse accumulations of iron pigment and accompanying connective tissue overgrowth. There are three possible explanations of the changes occurring in the liver:

1. That pigment is deposited and that there is a reaction to a foreign body in the form of connective tissue proliferation.
2. That the cirrhosis has so injured the cells that they become a ready depository for excess mobile iron.
3. In common with other cells of the body the liver cells have sustained toxic injury. In reacting to this, connective tissue is laid down precisely in the same manner as we are accustomed to conceive in cirrhosis of the ordinary type. Synchronously with this, is the deposition of iron representing the unperformed work of the injured cells of the liver in the metabolism of iron.

A certain proportion of all uncomplicated cases of cirrhosis of the liver, if examined for iron-containing pigment, give Perl's reaction. We found four cases among the necropsy protocols of the 5,000 Bellevue Hospital records that were marked enough to suggest hemochromatosis, although the remaining organs were not pigmented. Abbott cites Kretz's twenty-six cases of cirrhosis of the liver with iron pigment present in fourteen of them. In our cases we have found fibrous changes associated with massive extracellular collections of pigment.
The relationship of hemochromatosis to diabetes mellitus constitutes a problem of interest and importance, particularly with reference to the changes in the pancreas. Thus, in the great majority of all cases of bronze diabetes which have appeared in the literature of medicine, pigmentary or other alterations in the islands of Langerhans were described as totally lacking. In diabetes mellitus, as ordinarily encountered, lesions in the pancreas occur in about 88 per cent. of cases, and consist of sclerotic or hyalin alterations in the islands of Langerhans, withdrawal of the secretion of these isolated groups of cells so interfering with carbohydrate metabolism as to permit the continuous excretion of glucose in the urine. In occasional cases, however, the only demonstrable change in the pancreas in diabetes mellitus consists of extensive connective tissue replacement, the islands remaining unaffected. In these circumstances the question arises as to whether the pancreas has anything at all to do with the production of the diabetic changes, or whether the diabetes is to be regarded as of extrapancreatic origin, the sclerotic changes in the pancreas constituting merely an incidental anatomic feature. This interpretation is of interest in connection with the experimental work of Scobolew, who demonstrated that ligation of the pancreatic duct was followed by atrophy and connective tissue replacement of the parenchyma, the islands of Langerhans remaining intact. If, however, the fibrous mass with its embedded islands is now removed, the animal promptly develops diabetes.

In hemochromatosis with diabetes, histologic changes in the islands of Langerhans, such as sclerosis or hyalin transformation, are practically unknown, and to implicate the pancreas as the cause of the diabetes necessitates assuming changes in the islands which are not demonstrable by ordinary histologic methods, since it is obvious that the mere presence of pigment in the interstitium, with or without connective tissue overgrowth, is insufficient to account for the metabolic disturbances in question. That insular changes of the sort indicated do exist has been shown by Symmers, who, in the islands of Langerhans of alcoholic subjects, demonstrated the presence of extensive fatty changes, using, however, special stains to bring them out, such as sudan III. In ordinary hematoxylin and eosin preparations the islands appear to be normal. Symmers, correlating these histologic changes in the islands of Langerhans in alcoholic subjects with the known fact that alcohol habitués are intolerant of sugar and excrete it in the urine when fed it in slightly excessive quantities, accounts for the intolerance on the basis of definite anatomic changes in the islands of Langerhans.

All things being considered, however, we believe it highly probable that the diabetic changes which are associated with hemochromatosis are dependent on changes outside the pancreas.

Summary of Cases Reported in the Literature.—At the time of this writing, eighty-one cases of hemochromatosis have been reported. Of these the records of seventy-five were available for study.

Liver: Information regarding this organ was found in fifty-three cases. The liver was generally enlarged. Clinically, it was described as slightly enlarged in 60 per cent., moderately in 10 per cent., and markedly in 4 per cent. No enlargement was made out in 20 per cent. of the cases examined. At necropsy, however, 95 per cent. were recorded as enlarged. Twenty-six cases with exact weights showed an average of 2,400 gm. Cirrhosis occurred in 96 per cent. and iron pigment in all cases. The color of the liver varied from brownish red to chocolate. Ascites occurred in eighteen cases. In the majority of cases the mass of iron pigment was found extracellular in the connective tissue. This was usually an amorphous collection. It also occurred in great quantities in the liver cells, which then tended to show signs of degeneration in their poor staining qualities and rather irregular and pyknotic nuclei. Intracellular pigment was always present in fine brown granules. This pigment could often be demonstrated beautifully in Kupfer cells, endothelial cells of capillaries, bile duct cells, and connective tissue cells. Occasionally a finer and lighter brown pigment which failed to respond to Perl’s test could be demonstrated in the vessel walls and the capsule. This corresponds to the so-called hemofuchsin.

Pancreas: Data concerning the pancreas were obtainable in sixty-five cases. Varying from golden brown to bronze in color, iron holding pigment was present in all cases. Of fifty-two cases with a record of the amount of connective tissue, forty-eight showed marked fibrosis. The islands of Langerhans were rarely affected. Eighty-five per cent. of the fifty-eight cases with records showed a moderate glycosuria (average of 5 per cent.).

Spleen: Clinical data concerning the size of the spleen were obtainable in forty-eight cases. In fifteen cases the spleen was referred to as slightly, twice as moderately, and twice as considerably, enlarged. In the remaining twenty-nine cases it was not felt.

At the time of the postmortem examination, from fifteen cases with available weights we find an average of 400 gm. Pigment on gross examination was only noted occasionally, but on microscopic study a small amount of pigment was usually to be seen. The spleen was usually firm, a few times it was soft.

Lymph Nodes: The most marked changes were seen in the abdominal nodes. The fact that such nodes are in the line of lymph
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drainage from the liver and pancreas has been used as an argument in favor of the idea that there is an active transportation of pigment. Thirty-five of forty-four cases describe massive collections of iron pigment; in some cases this was very extensive, replacing the structure of the organ. There was usually marked evidence of fibrosis. Grossly, the glands were enlarged, shading from a brown to a chocolate color, and usually firm. There are instances, however, in which the glands were extremely soft, in some cases actually diffuent.

Skin: The microscopic studies of the skin are disappointing because there is a wide disparity between the striking clinical appearance and the postmortem findings. Iron pigment in the skin was usually scant and found only in the sweat glands. It occurred in about one-half of the cases.

Heart: In only twenty-two cases among the seventy-five available for study was the heart described. One-half of these showed hemosiderin within the muscle. This was situated intracellularly at the nuclear poles. In one case only did the connective tissue contain iron pigment. Fibrosis of the organ was reported once, and was not of marked degree.

Kidney: Of twenty-three cases described in the literature, sixteen showed iron pigment, always in small quantities, within the epithelial cells of the tubules. Only once (Strater's case 12), was pigment described in the glomerular tuft. Five cases showed another light brown pigment which we believe was iron pigment not properly demonstrated by Perl's stain.

Gastro-intestinal Tract: Histologic data were available in nineteen cases. Six cases showed iron pigment in the small intestines situated intracellularly in the depths of the glands. Twelve cases showed an iron free pigment in the muscularis mucosa. The duodenum and the first part of the jejunum seemed to be the most favorable site for pigment deposit. The stomach seemed to be a less favorable site than the intestine.

Suprarenals: The condition of the suprarenals was mentioned in thirteen cases. Ten showed the presence of iron pigment consistently found in the cortex.

Lungs: The lung seems to be one of the organs which is relatively free of iron deposit. Eleven cases gave histologic data. In only two was iron pigment observed and then in very small amounts.

Thyroid: Nine cases of the eleven describing this gland showed the presence of moderate amounts of iron pigment. Here, as is usually

the case in organs rich in parenchyma, the deposit was in fine granules, situated intracellularly, within the epithelial cells lining the acini. The connective tissue was always reported free of iron pigment.

Prostate: The epithelium of the gland cells contained iron pigment in eight of nine cases reported. The connective tissue contained iron pigment in two cases, while in two others, an iron free pigment was described. Sprunt reports a case in which the seminal vesicles and vas deferens were rich in iron pigments.

Testes: In eight cases only the testicles were studied for pigment. In two an iron containing pigment was found in the endothelium lining the small blood vessels and capillaries. In six cases an extracellular iron free pigment was seen in the seminal canals.

Parathyroids: In only two cases have we found the parathyroid described. Both of these contained iron pigment, moderately once, in the other case in huge amounts. The pigment was intracellular in both.

Bone Marrow: The bone marrow was examined in eight cases. It was usually hyperplastic, and in seven cases iron pigment was present both intracellularly and extracellularly. One case showed no pigment.

Brain: Cerebral hemorrhage was present in two of the seventy-five cases reviewed. Histologic examination in these cases revealed no iron pigment.

Hypophysis: Two cases have been studied as to the presence of pigment in the hypophysis. In both it was observed in the parenchymatous cells and in one in the connective tissue.

REPORT OF CASES

CASE 1.—Male, aged 50 years, expressman. In the hospital three days. Duration of the disease twenty-one days.

Past History.—Never sick in his life. Denies venereal disease. Drinks from four to five beers a day and whiskey in small quantity.

Present Illness.—Three weeks ago injured right side in a fall from a wagon. Was unconscious at the time. From that time on was in the hospital complaining of pain in the right side and shoulder. He passed no blood in the urine or stools. His bowels were regular and his appetite fair.

Physical Examination.—His skin was dark brown in color and was thought to have a case of "vagabonds' disease." His heart was negative. There were signs of hypostatic congestion at the pulmonary bases which increased until the time of his death. The abdomen was enlarged with gas. The liver and spleen were not felt. He died after three days in the hospital.

Urine.—Sp. gr., 1.020; cloudy; acid; no albumin. Casts, red blood cells, leukocytes and sugar present.

Chemical Blood Examination.—Carbon dioxid tension normal. Sugar, 471 mg./100. Temperature: From 100 to 106 F.; pulse from 80 to 40; respiration, from 24 to 52.

Clinical Diagnosis.—Diabetes. Hemochromatosis. Perinephritic abscess.

Necropsy Report.—The body is that of an emaciated male. The conjunctivae are icteric. Skin of face, neck, forearms and hands bronzed. Fifty c.c.
of pericardial fluid. The right lower lobe is the scene of a bronchopneumonia. There are basal adhesions. The liver weighs 2,715 gm. It is brownish red in color and coarsely nodular. Lobules are indistinct. The pancreas is long and thin and brownish red in color. Spleen weighs 920 gm., is dark red in color and grumous. The suprarenals show an enlarged brownish red medulla. The right kidney is larger than the left. The testes are normal. The intestines are normal, except for the duodenum and jejunum. Here the mucous membrane is colored brown. There is fluid in the abdomen. Anatomic Diagnosis: Cirrhosis of liver and diabétet bronzé; chronic splenomegaly; hemochromatosis; chronic hyperplastic gastritis; suppurative nephritis and perinephritis (right), and suppurative prostatitis and periprostatitis; moderate pial edema; terminal sepsis.

Microscopic Examination.—Liver: There is a moderate degree of cirrhosis. Coarse strands of connective tissue interrupt somewhat the normal architecture of the organ, but there is not the advanced overgrowth noted in some cases. The formed connective tissue is fairly cellular and contains many capillaries and budding and regenerating bile ducts. The liver cells are fairly well preserved. Their nuclei are only slightly smaller than normal and a bit irregular.

Pigment is present in all of the liver cells, but the majority of it is found in massive collections in the connective tissue septums. In the liver cells, the pigment is more or less diffuse, occurring in the form of discrete brown granules, which are not numerous. However, Kupfer cells scattered among them are fairly bursting with quantities of the pigmented granules. Some of the connective tissue pigment can be made out as lying in the cells, some is apparently in the lymph channels; very little, if any, appears in the new formed bile ducts. The greater part of the pigment, as was said, is aggregated together into the extracellular amorphous collections. Practically all of the pigment gives the reaction for iron.

Heart: With Perl's method quantities of greenish blue pigment is brought out in the heart muscle cells. Much of it is an exaggeration of the bipolar arrangement. There is also some amorphous pigment outside of the cells. In the connective tissue and fat there is a small amount of hemofuscin. The inner coats of the coronaries show the same pigment. There is a slight fibrosis of the myocardium.

Pancreas: There is a fair amount of perilobular fibrosis here. The pigment is chiefly aggregated in this position and is mostly extracellular. There is also pigment in the cells of the acini and in the cells lining the ducts. The islands of Langerhans are very few in number and small. With Perl's test most of the pigment stains dark green. That in the gland cells tends to retain its yellow brown color.

Kidney: Cloudy swelling; multiple small abscesses. In a very few of the cells of the convoluted tubules scattered blue reacting granules can be seen.

Spleen: A small amount of pigment diffusely scattered can be observed. It reacts positively for iron, and lies in the mononuclear cells for the most part. The connective tissue fibers of the capsule are encrusted with iron salts.

Suprarenals: The glomerular zone shows a massive intracellular collection of iron reacting pigment. There is only the slightest amount of pigment in the reticular zone. The pigmentation is entirely confined to the cells.

Skin: There is a small amount of yellow pigment in the cells of the papillary layer and also in the connective tissue of the walls of the veins. No reaction for iron is obtainable.

Intestines: A beautiful contrast is seen in this section between the blue iron containing pigment in the basal cells of the ducts and the fine yellow granules in the muscularis mucosa, which do not give the iron reaction.

Prostate: Normal.

Testes: Show no pigment and are apparently normal.

Case 2.—Male, aged 49 years, clerk; in the hospital seven days. Duration of the disease six months.
Past History.—Diseases of childhood. No illness for ten years. Has dizzy spells. Venereal disease denied. Drinks a little beer but no whiskey.

Present Illness.—For six months he has had thirst and polyurias. During this time his private physician has found sugar in his urine. He dieted and lost thirty-five pounds. A roentgen-ray examination of the liver six months ago was said to show carcinoma of that organ. For two months his abdomen has been getting larger.

Physical Examination.—The face is a dusky hue. Collateral circulation established over the body. Heart is negative. Lungs show congestion at the bases. The abdomen is large and contains fluid. The liver can be felt 21 cm. below the costal margin. It has a roughened border. There are no enlarged lymph nodes. He grew gradually worse, complaining very little and died seven days later.

Urine: Sp. gr., 1.035; cloudy; acid; no albumin present; no casts. Leukocytes and sugar present.

Wasserman: Negative.

Chemical Blood Examination.—Carbon dioxide, 86. Sugar, 300 mg. per 100 c.c.

Clinical Diagnosis.—Diabetes; carcinoma of the liver.

Temperature: From 97 to 98 F.; pulse, from 78 to 120; respiration, from 20 to 26. Blood pressure, 130/85.

Necropsy Report.—The body is that of an emaciated male adult. The face and neck are bluish. Heart muscle is brownish in color, flabby and the wall is thin. The lungs show small tumor nodules on the pleural surface. The liver is very large, weighing 5,085 gm. It is brownish red in color and finely granular. On section it shows multiple tumor nodules throughout. The bile is tarry green in color. The pancreas is larger than normal and there are tumor nodules throughout it. It is reddish brown in color, and the connective tissue appears to be increased. The spleen is normal in size and brownish in color. The connective tissue is apparently not increased. The follicles cannot be seen. The lymph nodes at the hilum of the liver as well as those lying retroperitoneally present a peculiar appearance. They are reddish brown in color and almost diffluent. The kidneys are normal, except for a slight brownish color. The suprarenals show a dark brown cortex. The esophagus, stomach and large intestine are normal. From the pylorus to the iliocelecal valve the mucous membrane of the intestine is greenish black in color. The thymus is small and bluish red in color. The brain is normal.

Anatomic Diagnosis: Brown atrophy of heart; multiple pleural metastases in lung; primary carcinoma of the liver; hemochromatosis of spleen, suprarenals, kidney, pancreas, retroperitoneal nodes, duodenum, jejunum, ileum, liver; secondary carcinoma of peritoneum with ascites; few metastases in pancreas; multiple pigmented atrophic tibial scars.

Microscopic Examination.—Liver: The liver is the site of a primary carcinoma. There is in addition a marked cirrhosis. Iron staining pigment is seen in considerable amounts in most of the remaining parenchymatous cells, also in many of the cells of the new growth. There is a moderate amount of iron staining pigment in the connective tissue both intracellular and extracellular and a small amount of fine yellow pigment in the connective tissue which does not give the iron reaction. The duct cells and endothelium of the blood vessels and sinuses contain practically no pigment.

Pancreas: There is a considerable increase in the amount of interlobular connective tissue. The islands of Langerhans are normal in number and size but some of the cells contain iron pigment. The blue staining iron pigment is seen chiefly in the cells of the acini and the duct cells in fine granules.

In the connective tissue both intracellularly and extracellularly there are amorphous deposits of various sizes appearing as a green pigment with the hematoxylin and eosin stain, and of a faint yellowish-brown tinge with the iron stain.
Lymph gland: Huge masses of green pigment taking the iron stain almost entirely replace the pulp. Few lymphocytes remain. The connective tissue septums show only a slight yellowish shimmer with the hematoxylin and eosin stain. With the iron stain all of the connective tissue septums are colored a beautiful Prussian blue, suggesting a diffuse incrustation of iron. The vessel walls are literally pipes of iron.

Skin: The hematoxylin and eosin section demonstrates a moderate amount of fine, light brown granular pigment in the cells of the sweat glands. With the iron stain there are a few fine blue intracellular granules and a moderate connective tissue incrustation. There is no pigment in the epidermis or other structures.

Testes: In a few localized areas there is a blue staining iron pigment in fine granules. This is extracellular and is situated chiefly in the tunica vaginalis and the connective tissue between the seminiferous tubules. Between the seminiferous tubules there are many large mononuclear leukocytes which contain a considerable quantity of light yellow pigment, sometimes in granules, sometimes diffusely distributed. This does not take the iron stain. Elsewhere the section is normal.

Epiglottis: The section is normal, except for quantities of fine granular pigment lying in the cells. There is also a small amount of granular blue pigment in some of the cartilage cells.

Large Intestine: A slight scattering of blue granular pigment on the surface of the glands of the mucous membrane is undoubtedly an artefact. There is a slight yellow pigmentation in a few of the muscle cells. Otherwise the sections are normal.

Prostate: The cells of the acini contain a moderate amount of granular iron pigment. In marked contrast to this are yellow granules of pigment seen within the spindle cells of the interstitial tissue which do not stain with Perl's method.

Thyroid: The acini contain a small amount of colloid and are about normal in size and number. The epithelial cells are loaded with huge amounts of blue staining pigment. In some places iron pigment is seen extracellularly in the connective tissue. There is no other kind of pigment present.

Lungs: The lungs contain many erythrocytes and phagocytizing epithelial cells laden with broken down erythrocytes. However, with the iron stain there is no evidence of the presence of hemosiderin. The disintegrated erythrocytes appear as a granular dark brown amorphous material.

Choroid Plexus: Most of the cells contain a large amount of finely granular blue staining iron pigment. This is quite uniform.

Suprarenals: The suprarenals contain no iron pigment. The glomerular zone contains a moderate amount of intracellular, coarse brown amorphous pigment which does not take the iron stain.

Kidney: The kidney section shows the epithelium of the tubules and the glomeruli very much swollen. There is no pigment present with any of the methods of staining used.

Optic Nerve and Retina: There is brown pigment in the basal cells of the retina, probably melanin. With the iron stain there is no blue pigment except for a slight incrustation of the connective tissue.

Case 3.—Male, aged 56 years; in the hospital one month; doesn't know how long he has been ill.

Past History.—Venereal disease denied. Drinks only a little beer. Pneumonia three years ago.

Present Illness.—Patient is stupid and complains of pain in the knees and difficulty in walking. He sleeps well, has no headache, and his appetite is good.

Physical Examination.—His skin is a dusky bronze color. Heart and lungs are negative. The abdomen is normal and neither the liver nor the spleen can be felt. The left knee joint is tender. While in the hospital his nose
bled for twenty-four hours continuously. He reports that six months and one month ago, respectively, the same thing happened. While in the hospital, the pigmentation gradually increased and involved the mucous membrane of the mouth. He became dyspneic and drowsy before death.

Urine: Sp. gr. 1.015; clear; acid; no albumin or casts; sugar negative. Was given 30 gm. of glucose without producing glycosuria.

Blood: Erythrocytes, 3,800,000; Hb., 70 per cent.; leukocytes, 10,200; polymorphonuclears, 68 per cent.; slight anisocytosis and poikilocytosis.

Blood Sugar: From 214 to 421 mg. per 100 c.c.

Temperature: From 97 to 99 F.; pulse, from 60 to 90; respiration, from 18 to 24. Blood Pressure: 165/80.

Clinical Diagnosis.—Addison's disease.

Necropsy Report.—The body is that of an adult male of large frame. The sclerae are icteric. The gums are bluish in color. The skin is somewhat dark in color and there are a few brown spots on the abdomen. The heart is brownish yellow in color and shows on section a moderate amount of scarring. The pericardium contains a moderate amount of hemorrhagic fluid. The lungs are normal. The liver weighs 2,100 gm. It is brownish red in color. The surface is smooth with slight lobulations. The pancreas is large and brick red in color. The lobulations are normal in configuration. The spleen weighs 255 gm. It is brick red in color and gummy. The bronchial and abdominal lymph nodes are enlarged, brownish in color, and very soft. The kidneys are asymmetrical. They are otherwise normal. The suprarenals are normal. The testes are normal. The glans penis is greenish yellow in color. The esophagus and small intestine are normal. The stomach and colon are dark green on the inner surface. The cartilages of the ribs are green on section. The bone marrow is red and active looking. The synovial membranes of the knee joints are yellowish brown in color.

Anatomical Diagnosis: Hemochromatosis; emphysema and acute and chronic bronchitis; acute pulmonary congestion and edema; hemopericardium; slight chronic interstitial myocarditis; slight chronic aortitis; chronic perisplenitis, splenic tumor with pigmentation; small right kidney (arterio sclerotic); large left kidney; moderate acute parenchymatous hepatitis; large pigmented pancreas; pseudomelanosis of large intestine; carious teeth, pyorrhea and gingivitis; pigmented synovial membrane in knee with arthritis.

Microscopic Examination.—Liver: Bands of connective tissue interlace to form coarse lobulations. The scarring, however, is not extremely marked. The liver cells, on the other hand, stain poorly. They are small and show somewhat pyknotic nuclei. They uniformly contain quantities of dark brown granules. In this case, as in the previous one, the greatest deposits are in the connective tissue. Here it appears as masses of various size lying outside of the cells. The connective tissue cells contain very little. The duct cells are noticeably free. The distribution of the pigment is such that the greatest quantity lies at the periphery of the lobules. Studied for iron the reaction is a dark bluish green color, which is undoubtedly positive. In the walls of the vessels a few fine yellow granules which do not react for iron can be seen.

Pancreas: There is a moderate interlobular and interacinar fibrosis. The acini as well as the islands of Langerhans appear normal. Almost all of the pigment is interacinar, the connective tissue being relatively free. The pigment everywhere appears as pure blue granules, with the iron stain. The cells of the acini, islands and duct cells, contain the largest amount of pigment.

Lymph Nodes: The lymph nodes are almost entirely replaced by brown pigmented cells. Thick trabeculae of connective tissue can be seen everywhere. The germinal centers in the small nodes contain the pigment, while at the periphery of the lobule, the normal lymphoid arrangement is present. In the nodes with little pigment, the endothelial cells of the sinuses seem to be involved chiefly, but in the large nodes with extensive change, all the cells
become pigmented. The connective tissue stains a pale lavender with the hematoxylin and eosin stain and with the iron stain all the pigment presents a blue color.

Heart: The muscle is markedly thickened.

Spleen: The splenic architecture is maintained with little increase of connective tissue. Arranged fairly regularly about the trabeculae are numerous large mononuclear cells full of brown granular pigment. These large cells are seen also within the pulp, some clumped and some in strands. With the iron stain blue granular pigment is seen in all of the cells of the pulp and in the large mononuclear cells just described. The fibrous elements show a moderate incrustation.

Stomach: The structure is normal, save for a small amount of finely granular blue pigment, situated intracellularly in the epithelium at the base of the glands. It is fairly well distributed in this location throughout the section.

Lungs: The section shows a marked congestion and a slight scarring of the tissue. The interalveolar tissue contains large mononuclear and polymorphonuclear cells which contain anthracotic pigment. There are also numerous large mononuclear cells which contain fine blue granules when stained by Perl's method.

Kidneys: A marked glomerulotubular nephritis is present. No pigment can be seen.

Suprarenals: There is present a fine granular pigment situated intracellularly in the glomerular zone of the cortex. This takes the iron stain. There is no evidence of fibrosis and no pigment is present elsewhere.

Prostate: All the structure of the prostate appears normal. In the blood vessel walls there is a finely granular iron staining pigment situated intracellularly in the connective tissue. No pigment is seen elsewhere.

Bone Marrow: The bone marrow is hyperplastic. Many of the large myelocytes are seen to contain a moderate amount of iron pigment in fine granules. There is none seen elsewhere.

Testes: Structure is normal. No pigment is present.

Aorta: No pigment is present.

Case 4.—Male, aged 56 years; in the hospital two months. The whole duration of the present illness is eighty days.

Past History.—Typhoid fever, fifteen years ago. Neisser infection, several times. Denies syphilis. Drinks seven or eight beers a day and whiskey occasionally.

Present Illness.—Has had no appetite for two weeks. Legs have been weak and he has had pain in the back.

Physical Examination.—The skin is icteric. There is cyanosis of the face, edema of the conjunctivae, legs and back. The heart shows mitral insufficiency and dilatation. Fluid in both chests. The abdomen is enlarged and contains fluid. The liver and spleen are not felt. The right knee, spine and pelvis are tender, and have been so for two weeks. Both chest and abdomen were tapped successfully.

Urine: Sp. gr., 1.025; clear; acid; albumin, sugar and bile negative. Erythrocytes present.

Blood: Erythrocytes, 3,000,000; Hb., 75 per cent.; leukocytes, 9,000. Spectroscopic examination of the blood normal.

Temperature, from 98 to 101 F.; pulse, 72; blood pressure, 105.

Clinical Diagnosis.—None.

Necropsy Report.—Emaciated male adult. Skin and conjunctivae icteric. Face and neck brownish. Heart muscle is brown and pale. There is a lobular pneumonia at the right base. There are also basal adhesions. The liver is small. It is greenish brown in color. It is finely and coarsely granular. The pancreas is large and flabby. It is coffee colored. The peripancreatic and
retroperitoneal nodes are anthracotic and cheesy. Kidneys, adrenals, testes normal. Thyroid shows no alteration. Bile stained clear fluid in the abdomen. 

Elevated yellow foci over the entire peritoneum.

Anatomic Diagnosis: Atrophic cirrhosis of the liver; ascites, icterus, chronic granular peritonitis; chronic hyperplastic perisplenicis; brownish pigmentation of pancreas and retroperitoneal lymph nodes; chronic adhesive pleurisy, emphysema and chronic bronchitis; tuberculous lymphadenitis of peripancreatic and retroperitoneal lymph nodes; lobular pneumonia; multiple erosions of gastric mucosa; scoliosis, osteoporosis general and fragilitas ossium; esophageal varices with melena.

Microscopic Examination.—Liver: There is a moderate grade of cirrhosis. The capillaries throughout the liver are tremendously dilated. The liver cells are swollen and stain badly and there is a rather widespread round cell infiltration which is particularly marked under the capsule. With hot hydrochloric acid and potassium ferrocyanid most of the pigment gives the iron reaction. This case is remarkable on account of the fact that practically all of the pigment occurs intracellularly. It is found in both liver and connective tissue cells. Striking also is the amount of pigment that is to be found in the endothelial cells of the capillaries and also in the lining cells of the bile ducts. The findings in the liver in this case suggest a rather more acute termination than occurred in the others.

Thyroid: The acini are filled with colloid. The gland cells are crowded with iron holding pigment. There is no evidence of injury to the parenchymatous cells. The connective tissue is normal in amount and is the scene of no pigment deposit.

Lymph Nodes: The mesenteric nodes show the presence of a chronic tuberculosis. There are quantities of brown pigment, chiefly extracellular. Some pigment, however, is to be seen in the large mononuclear cells. Studied by Perl’s method, most of the pigment gives the dark green color, and lies in coarse amorphous clumps. That which is still granular and within the cells stains blue.

Spleen: There is a marked thickening of the capsular connective tissue. Most of the pigment is found in this location by preference assuming a position near the side of the gland pulp. It also is to be found in the trabeculae. There is relatively a small quantity in the pulp cells. All of this pigment is hemosiderin.

Intestines: Nothing of note is to be observed, except the very small amount of pigment that occurs in the basal cells of the glands and in the muscularis mucosa. None of this reacts positively for iron.

Testes: In the connective tissue and in the endothelial cells there is pigment. In the supporting cells between the seminiferous tubules there is a small amount of fine yellow pigment. No iron reaction is obtainable.

Kidney: There is a mild chronic nephritis. The cells of the convoluted tubules are the site of an inconspicuous pigment collection. Perl’s test fails to show the presence of iron.