A CASE OF HÆMOCHROMATOSIS.—THE RELATION OF HÆMOCHROMATOSIS TO BRONZED DIABETES.

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Widely disseminated pigmentation of the organs of the body is a conspicuous phenomenon and at autopsy cannot readily be overlooked. The physiology of pigmentation is but little understood. Pathological pigmentation is involved in even greater obscurity. For this reason the following case has been considered worthy of study. It represents, I believe, an intermediate stage between two conditions which, though rare, have elicited much discussion, namely, hæmochromatosis of von Recklinghausen and the bronzed diabetes of Hanot and other French writers. The case to be described occurred in the practice of Dr. Thomas Opie.

Case.—Male; white; aged 55 years. The history which it has been possible to obtain is meagre. The individual, though never very robust, had enjoyed fairly good health. There was no history of alcoholic excess. He was married and had several children. His wife was healthy. For several months he had resided in Puerto Rico and until six or seven weeks before his death was able to continue his work of surveying. The onset of his final illness occurred with symptoms indicative of typhoid fever. When first seen two weeks later, he was evidently very ill. There was elevation of temperature and rose-spots were present upon the abdomen. Deep pigmentation of the skin attracted immediate attention, marked universal bronzing suggesting Addison's disease. Jaundice was not present. The urine at no time during the period of observation contained sugar. The first examination was made four weeks before death. Three days before death the urine was clear, of deep amber color and contained neither sugar nor albumin. The reactions of bile pigments were not obtained. The blood-serum caused the agglutination of the typhoid bacillus. Death occurred with increasing weakness.

Autopsy.—Performed 9 hours after death. The body, 170 cm. in

length, is that of a very thin, sparely built man. The skin over the entire body shows deep pigmentation of a bronzed metallic hue, most marked upon the back of the hands, about the nipples, and upon the penis, where just above the corona the skin has a deep brown color. The conjunctivæ are clear. The abdominal wall contains a small amount of deep yellow fat.

Peritoneal Cavity.—The parietal peritoneum, as well as that of the intestines, shows a varying degree of bluish discoloration. The appendix is fixed behind the cæcum by fibrous adhesions. The enlarged spleen is adherent to the diaphragm.

Thorax.—The lungs are free from adhesions and the pleural and pericardial cavities contain no excess of fluid.

Heart.—Weight 280 grm. The muscle, of a yellowish-brown color, is soft and flabby in texture. The intima of the coronary arteries is roughened by a few yellow, raised patches.

Lungs.—The left lung is everywhere crepitant. Upon the surface of the upper lobe of the right lung are seen several prominent areas, about 2 cm. across, over which the pleura is dulled. The tissue below is firmly consolidated, and on section has a grayish-red, finely granular surface. Several larger areas of similar consolidation are present in the lower lobe. The bronchi are intensely injected.

Liver.—Weight 2270 grm. The surface is of a deep reddish-brown color of peculiar character, resembling that of iron-rust. The surface of the left lobe, more markedly than that of the right, is superficially nodular and puckered, presenting in moderate degree the appearance of a hob-nail liver. On section islands of lighter brown parenchyma, representing one or several lobules, are surrounded by fibrous stroma of a deeper brown color. Sparsely scattered are opaque yellowish-white areas, often 1.5 mm. across. The gall bladder, distended by thin green bile, measures 12 cm. in length.

Spleen.—Weight 700 grm.—The organ is soft and on section the almost diffuent pulp has a deep red color. The Malpighian bodies are prominent.

Stomach.—The mucous membrane shows everywhere a deep greenish-black discoloration, evidently not due to post-mortem change. Along the lesser curvature there are a few areas of relatively normal yellowish-white appearance, but elsewhere the pigmentation is uniform.

Intestine.—The duodenum has a greenish-black discoloration almost equal in intensity to that of the stomach. This pigmentation is not uniform, and upon the areas of lightest color are seen deeply pigmented,

slightly raised nodules about 1 mm. in diameter. The jejunum is less markedly pigmented than the duodenum, while the ileum is of even lighter color, though still preserving a greenish-gray tint. Throughout the lower portion of the ileum, for the most part upon the Peyer's patches, are small round or slightly irregular ulcers with sharp edges and clean base, in which are occasionally seen exposed fibres of the circular muscle coat. Ulceration is most extensive immediately above the ileo-cæcal valve. The colon exhibits moderate greenish-gray discoloration. The distal 1.5 cm. of the appendix is obliterated.

Pancreas.—Weight 170 gm. The organ is of large size, measuring 16 cm. in length, and is very firm in consistence. On section the cut surface has a uniform deep chocolate-brown color. The capsule contains much fat, and extending inward from it are septa of adipose and fibrous tissue.

Adrenals.—Combined weight 10 gm. No abnormality is observable.

Kidneys.—Combined weight 470 gm. The capsule on removal leaves a smooth surface. The cortex of an average thickness of 7 mm. has a red cloudy appearance.

Bladder.—Mucous membrane is normal.

Testicles.—The cut surface has a light brown tint. The prostate and seminal vesicles are normal.

Lymphatic Glands.—In the retroperitoneal tissue near the hepatic vein, behind the stomach, above and below the pancreas, and on either side of the aorta as low down as its bifurcation, are enlarged, moderately firm lymphatic glands. On section they have a uniform, brilliant orange-yellow surface. In the gastro-hepatic omentum are enlarged glands of a similar nature.

Cultures.—From the heart's blood the typhoid bacillus was obtained in pure culture. The same organism was obtained from the liver, gall bladder, and kidney. The *Bacillus lactis aërogenes* was found in the lung and kidney. The colon bacillus was grown from the pancreas. A culture from the spleen remained sterile.

Anatomical Diagnosis.—Typhoid fever; ulcers in the ileum; acute splenic tumor; cloudy degeneration of the kidneys; broncho-pneumonia. Hæmochromatosis: pigmentation of the liver, pancreas, heart, stomach, intestine, peritoneum, lymphatic glands, skin and testicles. Cirrhosis of the liver. Chronic interstitial pancreatitis.

HISTOLOGICAL EXAMINATION.—The organs which show the most marked pigmentation are the liver, pancreas, heart and gastro-intestinal canal.

Liver.—Advanced cirrhosis is indicated by the presence of wide bands of fibrous tissue, occupying one-half to one-third of the area of the cut surface and separating the parenchyma into islands which represent one or several liver lobules. These septa, which are densely fibrous and in general poor in cells, surround both the portal spaces and the sublobular veins. There is but little invasion of the periphery of the lobule by fibrous strands, but surrounding the central vein a mass of tissue penetrates the lobule and sends out irregular, radiating projections along the capillaries between the columns of liver cells. The most conspicuous feature of the histological picture is the immense amount of yellowish-brown pigment present, both in the parenchyma and in the interstitial tissue. In the liver cells the pigment is found in varying quantities. When in moderate amount, it is situated in that part of the cell most distant from the capillaries, consequently occupying the central part of the columns of liver cells. The pigment is deposited in the form of brilliant, brownish-yellow, relatively coarse granules, round or polygonal in outline, and of slightly variable size. The endothelial cells of the capillaries and Küpffer's cells contain granules of similar character. The accumulation of pigment in the newly formed fibrous tissue is even greater than that within the parenchyma. Here it exists in part as fine granules within spindle-shaped cells, of which some are apparently fibrous tissue cells, while others represent the endothelial lining of capillaries or lymphatics. The greater quantity of the pigment is, however, not contained in cells. While this extracellular pigment is of the same yellowish-brown color as that abundant in the cell, the individual particles vary greatly in size, globules being often found whose diameter is two or three times that of a red corpuscle. These pigment particles are as a rule collected into small clumps and between the clumps are at times small round cells.

The hepatic cells which contain a moderate amount of pigment are in general normal in appearance. In specimens stained with methylene-blue the cell protoplasm is found to contain in great abundance granules of varying size and shape taking a deep blue stain. Usually they are angular, but often are rod-shaped and resemble bacilli. A few cells containing fat droplets are occasionally seen at the periphery of the lobule. When, with increased accumulation of pigment, granules occupy all portions of the cell body, basal as well as central, changes in the cell are demonstrable. The nucleus often presents evidence of degeneration. It is smaller, irregular in outline, with less nuclear material present, so that it remains as a pale shrivelled body, visible in some cases only

with careful focusing of the microscope. Other masses of pigment granules maintaining the outline of liver cells contain no nucleus. Representing apparently the final stage of cell disintegration, a mass of pigment granules is found free in the tissue. No longer presenting the outline of a cell, it corresponds in size with the pigment accumulations found in those cells which are most intensely impregnated. Conspicuous in stained sections are groups of pigment masses, which, for the most part maintaining cell outlines, represent often ten or twenty cells and stand out as pigment islands in sharp contrast to the well-stained liver cells adjacent.

In those cells whose protoplasm is almost wholly replaced by pigment much irregularity in the size of the granules is observable. Globules often the size of red corpuscles are found. With further evidence of cell degeneration the size of the globules increases, so that, when final disintegration takes place, there is liberated a mass of granules and globules resembling those found in great abundance in the fibrous tissue. Along the central vein and following the strands of tissue radiating from it are seen masses of pigment whose location indicates that they are transported, presumably along lymphatic spaces, from the interior of the lobule toward the central vein. Abundant accumulation of pigment exists in all parts of the interlobular tissue, both along the course of the sublobular veins and in the tissue about the portal spaces.

The adventitia and media of the hepatic artery and portal vein contain but little of the brownish-yellow pigment. The endothelial cells of the portal vein, however, contain a moderate amount, and within the lumen are seen large flat oval cells containing pigment granules. It seems probable that the majority of these at least are endothelial cells, which after death, possibly in the process of hardening or cutting, have been dislodged from their normal position. The brownish-yellow pigment is not present in the endothelium of the hepatic arteries and in their lumen no pigment-containing cells are seen. Pigment is more abundant in the wall of the sublobular veins. Their endothelial cells contain it in abundance and within their lumen are pigmented cells resembling those found in the portal vein.

Newly formed bile-ducts are numerous in the interstitial tissue. Occasionally in the tissue about the central vein one sees several such structures represented by parallel rows of cubical cells. These ducts contain the brownish-yellow granules in moderate amount. The epithelial cells of the larger ducts contain similar pigment.

The brownish-yellow pigment, whose location has been described, gives

the microchemical reactions characteristic of iron. Treated with potassium ferrocyanide and hydrochloric acid it takes a green color. Aqueous solution of hæmatoxylin gives it a deep black. The reaction with potassium ferrocyanide and hydrochloric acid varies with the time of exposure and with the strength of the reagents. If sections are immersed for an hour to an hour and a half in equal parts of a two per cent solution of potassium ferrocyanide and hydrochloric acid, one part to a hundred parts of water, all the granules within the liver cells assume a green color.

There is present a second less conspicuous variety of pigment differing from that already described both in situation and in morphology. In certain cells in the media and adventitia of both veins and arteries are deposited fine, pale yellow granules of almost uniform size. Some of the cells containing this pigment are elongated and spindle-shaped with rod-like nuclei, while others are large, irregular in shape, and provided with irregular processes. The first are apparently smooth muscle cells, the second connective-tissue cells. The latter are abundant in the walls of the ducts, in the tissue about nerves, in the intervening tissue of the portal space and as a conspicuous layer in the liver capsule a short distance below the serosa. The pigment in these cells does not give the microchemical reactions characteristic of iron, being unchanged by potassium ferrocyanide and hydrochloric acid. In sections stained with methylene-blue these granules take a blue, often bluish-black color, and become very conspicuous. This fact was observed by Buss (8).

Areas of focal necrosis referable to typhoid fever are present. They may represent either a small number of necrotic cells or a considerable portion of a lobule.

Pancreas.—Chronic interstitial inflammation is present. Bands of fibrous tissue separate the lobules which often stand out as isolated islands of parenchyma. Although the most marked increase of fibrous tissue is interlobular, there is here and there an invasion of fibrous strands between the acini. Pigment giving the reactions of iron is deposited in great quantity within the secreting cells and is located, when moderate in amount, in that portion of the cell directed toward the lumen of the acinus—with greater accumulation all parts of the cell body are occupied and, as in the liver cells, globules of large size are then seen. Such a cell may have a palely staining nucleus of irregular outline or a nucleus may not be demonstrable. In the interstitial tissue the pigment is for the most part in groups of granules and large globules, varying much in size. These are apparently masses of pigment set free by the disinte-

gration of cells. About such pigment round cells are often numerous. Pigment is frequently abundant in the cells composing the intertubular cell-groups or islands of Langerhans. These structures are present in moderate number. They have not as a rule their usual position within the lobule, being surrounded by fibrous tissue, which may contain much pigment. At times there is an increase of fibrous tissue along the capillaries penetrating them. Here and there in sections are seen areas which present a peculiar appearance. The cells of one or several lobules or a part of a lobule have lost the alveolar arrangement characteristic of the pancreatic parenchyma. At first sight it may be supposed that this disturbance of the usual structure is artificial in origin, produced possibly in cutting the section, but it has been observed in tissues hardened by a variety of methods and cut after embedding in both paraffin and celloidin. Moreover, the cells of such areas differ from those of the surrounding gland tissue. They are smaller, polygonal in shape. Their nucleus is often smaller and contains more chromatic substance than those adjacent. A conspicuous feature is the abundance of cells containing two nuclei and at times three or even four are seen in the same cell. Mitotic figures have not been observed. The significance of these areas is doubtful; it is possible that they are the seat of cell proliferation and may bear some relation to the increased size of the organ.

Finely granular iron-free pigment, like that found in the walls of the hepatic blood-vessel, is present also within cells of the same character in the walls of the veins and arteries of the pancreas. Pigment of identical characteristics is found in the walls of the larger ducts.

Heart.—Well-marked fragmentation and segmentation of the myocardium is present. Brownish-yellow pigment is deposited in great quantity within the muscle fibres. It has the location of that which is present with brown atrophy of the organ and, when moderate in amount, is accumulated in the neighborhood of the nucleus. All the pigment present does not give the reactions of iron, and in specimens treated with ferrocyanide of potassium or with aqueous hæmotoxylin a considerable amount of unchanged pigment remains. In sections of heart muscle treated with methylene-blue none of the pigment within the muscle cells takes the blue color observed when the iron-free pigment of the walls of the hepatic blood-vessels is so treated. This pigment is apparently that which is found normally in the muscle fibre and is increased in the condition of brown atrophy. The pigment, remaining unchanged after treatment with reagents which demonstrate iron, is greater in amount than that normally present in the muscle fibres. In the

interstitial tissue are seen here and there groups of globules of iron-containing pigment similar to those found free in the tissues elsewhere. The walls of the blood-vessels contain iron-free pigment staining with methylene-blue.

Gastro-Intestinal Tract.—The pigmentation of the stomach and intestine differs from that of the organs previously considered. Here the pale yellow, iron-free pigment predominates and gives microscopic discoloration to the organ. Brownish-yellow, iron-containing pigment is fairly abundant in the epithelial cells of the cardiac glands and is present in very small amount in the cells of the pyloric glands, while an occasional clump of granules is seen free in the tissue. The iron-free granules are in cells which have usually the character of smooth muscle fibres, although a few are apparently connective-tissue corpuscles situated between the muscle fibres or in the submucosa. The distribution of the pigmented cells varies in different parts of the gastro-intestinal tract. Throughout the stomach the muscularis mucosæ is pigmented. In the cardiac portion the circular and longitudinal layers are not so affected, while in the pyloric region there is in the circular muscle layer a conspicuous zone of pigmentation immediately below the submucous tissue. The walls of the arteries and veins of the submucosa contain pigment of the same nature. Throughout the small intestine iron-free granules are found in the cells of the muscularis mucosæ. A small amount of pigment is present in the circular muscle layer, but does not form the zone present in the pyloric portion of the stomach. In all parts of the small intestine pigment is most abundant in the cells of the longitudinal layer. The vessels of the submucosa contain numerous pigmented cells. Less pigment is present in the ileum than in the jejunum, while in the colon it is found in still smaller quantity, though it has the same location as elsewhere. The epithelium of the Brunner's glands of the duodenum are conspicuously impregnated with iron-containing pigment, the protoplasm of the cells being almost completely replaced by pigment granules.

Lymphatic Glands.—Several lymph glands were examined. One of these was situated beside the inferior vena cava where it receives the hepatic vein. Lymphatic tissue is almost wholly replaced by masses of brownish-yellow pigment giving the reactions of iron, so that the organ is practically a mass of pigment surrounded by a thickened capsule and penetrated by thickened fibrous septa. Among the pigment granules are scattered lymphoid cells, small groups remaining here and there. The pigment lying within the meshes of the reticulum is almost wholly

extracellular, being in the form of particles which vary greatly in size and resemble the extracellular pigment in the interstitial tissue of the liver, pancreas and heart. It is apparently carried to these lymphatic glands along lymphatic channels in the same way that coal pigment is carried from the lung to the bronchial glands. An occasional fixed tissue cell containing brownish-yellow granules is observed. In the smooth muscle and connective-tissue cells of the blood-vessels and in connective-tissue corpuscles of the capsule iron-free granules are found.

Spleen.—The great engorgement of the blood-vessels and consequent tumefaction explain the fact that in spite of an abundant pigment deposit there is not the macroscopic pigmentation observed in other organs. Iron-containing granules are present in the branched reticular cells of the pulp and in the endothelial cells of the capillaries. Indeed the capillaries on cross-section often form conspicuous rings of pigment-containing cells. In less quantity round and oval pulp cells contain brownish-yellow granules. In the Malpighian bodies pigment is almost entirely absent, and when found occurs in clumps of irregular extracellular globules, resembling those so abundant in the lymphatic glands. Iron-free pigment is not abundant, but is found occasionally in the elongated connective-tissue cells of the trabeculæ.

Adrenal.—Pigmentation is almost wholly limited to the so-called glomerular zone, which forms a sharply defined corona of brownish-yellow color immediately below the capsule. When moderate in amount, the pigment, which gives the characteristic reactions of iron, is situated in that portion of the cell most distant from the capillaries, but as a rule it is present in such quantity that all portions of the cell body are occupied. Degenerative cell changes similar to those observed in the liver and pancreas are associated with the accumulation of pigment. The capsule in places is very slightly thickened and cellular, and contains globules of pigment, apparently set free by the disintegration of parenchyma cells. In the cell columns there is here and there a deposit of pigment granules.

Kidney.—Pigment is present in very small quantity and is limited to an occasional tubule or glomerulus. Here and there the epithelial cells of a convoluted tubule contain pigment granules in great quantity and differ from those of neighboring tubules in being of smaller size and more cubical. The glomeruli often contain pigment granules located apparently in the epithelial cells and occasionally there is a similar deposit in the loop of Henle. The blood-vessels differ from those of the organs more impregnated with iron in containing almost no iron-free pigment. An occasional cell thus pigmented can be seen, but search is required for its demonstration.

Lung.—Pigment is scant. Occasionally within the alveolar septa are found yellowish-brown granules resembling the iron-containing granules in other situations. At times they completely fill an oval cell with an oval nucleus, while again they are extracellular. In many instances it is evident that these cells or free masses lie within the lumen of capillaries. Pigment-containing cells of a similar nature are seen in the larger vessels and it is not inconceivable that in part at least they are endothelial cells of the liver or other organ, which, injured by pigment accumulation, have been dislodged from their position. Within the lumen of the larger vessels pigment granules are occasionally seen in round mononuclear cells very slightly larger than polymorphonuclear leucocytes. Iron-free pigment is not found in the walls of the blood-vessels.

Skin.—In the lowermost cells of the Malpighian layer there is a well-marked increase of the normal pigmentation. The granules here found do not give the reactions of iron nor do they stain with methylene-blue. In the cells of the sweat glands are occasionally found iron-containing granules in small number and between the tubules are connective-tissue cells containing similar pigment. Iron-free pigment is found in very small amount in the walls of blood-vessels of the subcutaneous tissue. Neither pigment granules nor pigment-containing cells are found within the lumen of the blood-vessels.

Testicle.—The cells of the seminiferous tubules contain no pigment. Along the vessels in the angular interstices between the tubules are conspicuous groups of polygonal and oval cells completely filled with yellow granules, apparently the so-called interstitial cells, which normally contain a small amount of pigment. The endothelial cells of the vessels also contain conspicuous granules. The pigment of the interstitial cells remains unchanged after treatment with potassium ferrocyanide and hydrochloric acid, while that of the adjacent endothelium gives the characteristic reaction of iron.

Under the designation “*hæmochromatosis*” von Recklinghausen (1) in 1889 described a condition of pigmentation affecting various organs. Brown pigment, which he thinks is derived from the hæmoglobin of the blood, is deposited within certain tissues and gives to them macroscopic pigmentation. Cases of intense widespread pigmentation had previously been described by Quincke (2), Tillmanns (3) and Hindenlang (4). Cases of similar pigmentation, associated

with diabetes and cirrhosis of the liver, had been described by Hanot and other French writers.

The anatomical picture of generalized pigmentation drawn by v. Recklinghausen is very clearly defined. Most of the glands of the body have a deep brown color and within their secreting cells are found reddish-yellow or ochre-colored granules. In the liver this pigment is present in the parenchyma cells and in Küpffer's cells. Microchemical reactions prove that it contains iron. A second kind of pigment, distinguishable from the first by the occurrence in finer granules of pure yellow color, is found in the smooth muscle cells of the stomach and intestines, of the blood- and lymph-vessels, rarely in those of the urinary bladder, ureters, and vas deferens. It also exists in the connective-tissue cells of certain localities, for example, Glisson's capsule, the splenic trabeculæ, and the sheaths of blood-vessels. This pigment does not give the reactions characteristic of iron. v. Recklinghausen calls the iron-containing pigment "hæmosiderin," the iron-free pigment "hæmofuscin." The use of these names does not necessarily imply that we have any means of identifying these substances as definite chemical compounds or that we can recognize them when they occur in other situations.

Von Recklinghausen thinks that the hæmofuscin as well as the iron-containing hæmosiderin is derived from the hæmoglobin. In his cases of generalized pigmentation there was an associated cirrhosis of the liver.

Von Recklinghausen studied twelve cases which he regards as examples of local and general hæmochromatosis. Hæmochromatosis he apparently defines as a condition of pathological pigmentation due to the deposition of pigment derived from the blood. Such a definition includes a variety of dissimilar forms of pigment deposit; brown atrophy of the heart, for example, fulfills its conditions, since, as is believed, the ultimate origin of the pigment there found is the hæmoglobin of the blood. Nevertheless it evidently has but little in common with the general hæmochromatoses already described. There is however, a local condition which has been associated with hæmochromatosis by several observers. I refer to pigmentation of the intestine

caused by deposition of fine yellow granules in the smooth muscle cells. Goebel (5) has made a careful study of this form of pigmentation. In adults a moderate degree is almost constant. The amount of pigment present bears a relationship to the age of the individual, so that with increasing age there is an increased pigment deposition. Other influences, however, may play an important part in producing the condition. With wasting diseases, for example tuberculosis and carcinomatosis, there may be an accumulation equal to that present in advanced age. In sixteen of one hundred bodies studied by Goebel the pigment deposit was of sufficient magnitude to cause macroscopic discoloration, characterized by him as rust brown. Hintze (6) has described two cases of similar intestinal pigmentation.

The pigment present in these cases does not give the reactions of iron and agrees in morphology and location with the hæmofuscin of v. Recklinghausen. Hence both Goebel and Hintze conclude that this intense intestinal pigmentation represents the first stage of hæmochromatosis. Hæmosiderin is, however, not present and it is the hæmosiderin, whose wide distribution forms the most characteristic feature of general hæmochromatosis. Indeed, the iron-free pigment has apparently been overlooked in a number of cases of generalized pigmentation, whose description otherwise agrees with the picture drawn by v. Recklinghausen. It is, moreover, as will be shown, with the presence of this iron-containing pigment that are found marked pathological changes in the containing cells. The accumulation of pigment within the smooth muscle cells of the intestine is apparently an accentuation of a physiological process, much more closely related to the brown atrophy of the heart than to general hæmochromatosis. v. Recklinghausen's description represents a condition, presenting no close similarity to any form of local pigmentation with which we are familiar.

The important features of this description are: (1) The presence in the epithelial cells of various glands, notably the liver and pancreas, of an iron-containing pigment. (2) The presence of an iron-free pigment in smooth muscle cells of the gastro-intestinal tract and of the blood- and lymph-vessels and in certain connective-tissue cells. (3)

The association of cirrhosis of the liver with the pigmentation. To this condition, apparently a distinct pathological entity, the term hæmochromatosis should be limited, even though v. Recklinghausen, its originator, applied it to conditions of local pigmentation as well.

Prior to v. Recklinghausen's publication several observers had studied cases of widespread pigmentation. Quincke (2) in 1877 observed with anæmia a deposition of iron in various organs notably in the liver and spleen and in one instance found macroscopic pigmentation of the liver and pancreas as a result of the iron deposition. Tillmanns (3) described brown pigmentation of the liver, of the abdominal lymphatic glands, and in less degree of the spleen and pancreas, in a man who two months before death had sustained a fracture of the pelvis and, the observer thought, a contusion of the liver. Hindenlang (4) observed in association with morbus maculosus Werlhofii pigmentation of the glands of the body, particularly the liver, which was slightly cirrhotic, and the pancreas, and in these organs found a pigment corresponding morphologically and in situation to that which v. Recklinghausen subsequently described as hæmosiderin. The presence of an iron-free pigment was not mentioned, but, being much less conspicuous than the hæmosiderin, it may readily have been overlooked, the gastro-intestinal tract not having received histological examination. Hintze (6) has described six cases which he regards as examples of hæmochromatosis. Several of them had previously been mentioned by Lubarsch (7). Only three agree in detail with the description which v. Recklinghausen has given. Two are the cases of extreme intestinal pigmentation before mentioned and in a third, the case of an individual, who five years before death had undergone an operation for removal of a cyst of the pancreas, the deposition of iron-containing pigment was limited to the pancreas and neighboring lymphatic glands. The pancreas was the seat of a chronic interstitial inflammation with cyst formation and the pigment was present only in the fibrous tissue while the epithelial cells contained none. Although the intestine presented the variety of pigmentation described by Goebel the condition cannot be regarded as hæmochromatosis and was probably the result of local hæmorrhage in or about the diseased pancreas. Buss (8) has described a typical case of hæmochromatosis associated with cirrhosis of the liver and diabetes mellitus.

Letulle records two cases and Richardière one in which associated with hypertrophic cirrhosis, accompanied by very abundant hæmosiderin pigmentation, there was similar pigmentation of the pancreas and of other organs. In these cases pigmentation of the skin was apparently absent.

A condition, associated with hæmochromatosis by v. Recklinghausen, has been studied particularly by French writers. In 1882 Hanot and Chauffard (11) described two cases of diabetes mellitus associated clinically with hypertrophic cirrhosis of the liver and bronze-like pigmentation of the skin. At the autopsy upon the first of these cases was found cirrhosis of the liver, characterized by the presence of wide bands of connective tissue. In the liver cells, as well as in the interlobular bands, were brown pigment granules in great quantities. In the second case, more carefully studied, the liver and pancreas presented a brown pigmentation and were the seat of advanced chronic interstitial inflammation, both parenchyma cells and interstitial tissue containing masses of pigment granules. The stomach and duodenum were of a bluish-black color and pigment in small granules was found below the serosa. Letulle (12) several years later reported two cases of a similar nature. In a second communication Hanot in conjunction with Schachmann (13) recorded a fifth case and reviewed those previously published. He believed that the observations previously made established the existence of a new form of cirrhosis, *cirrhose pigmentaire diabétique*, and of a new clinical condition, *diabète bronzé*.

The designation “diabète bronzé” has been in general accepted, but not without protest. Bronzing of the skin is not a constant phenomenon and has been found absent in one case of Letulle, in the case of Hanot and Schachmann and in a case recorded by Brault and Galliard (14).

In the recorded cases of so-called bronzed diabetes,* as far as they are reported with sufficient detail, the symptoms and pathological findings are very constant. Clinically, the picture is one of a rapidly fatal diabetes mellitus associated with cirrhosis of the liver, usually of the hypertrophic variety. Bronzing of the skin is as stated not constant, but has been present in the majority of the cases. At autopsy has been found a deep pigmentation of the liver and pancreas associated with cirrhosis and in cases carefully examined macroscopically

* The published cases of bronzed diabetes, numbering twenty-four, have been carefully collected by Anschütz, and certain data are presented in tabular form in his comprehensive review of the subject which has appeared in the *Deutsches Archiv für klinische Medizin*, 1899, lxii, p. 411, subsequent to the preparation of this paper. For this reason a table of cases prepared by myself has been omitted.

and histologically interstitial pancreatitis. An ochre-colored pigment giving the microchemical reactions of iron is present in the parenchyma cells of the liver, pancreas and other glands, in the muscle fibres of the heart, in the interstitial tissue of these organs and in the lymphatic glands.

The facts relating to the incidence of the disease are of interest. No recorded instance of hæmochromatosis or of bronzed diabetes has occurred in the female. The age of the individuals affected with bronzed diabetes has varied between 33 and 62 years, the greatest number occurring in the fourth and fifth decades. The cases of simple hæmochromatosis fall within these limits. It has been believed that the disease is more common in France than elsewhere and this is to a certain extent indicated by the fact that of twenty-four cases seventeen have been observed in that country. Simple hæmochromatosis has been, however, described more frequently by German writers.

The pathogenesis of the condition has been the subject of varied speculation. Hanot and Chauffard and subsequently Hanot and Schachmann have maintained that the primary etiological factor is the diabetes mellitus, that the diabetic alteration of the blood in conjunction with endarteritis, which they have found constant in their cases, causes a disturbance in the nutrition of the liver cells, an alteration of the pigment metabolism and a deposition of pigment within the cell body. The excess of pigment so formed is reabsorbed by the capillaries and diffused possibly in the form of emboli over the entire organism. Letulle (12) finding the same process of pigment deposition in other organs, for example the heart, that takes place in the liver, comes to the conclusion that the pigment is formed in the cells in which it is found from the hæmoglobin of the blood. He regards the diabetes as primary and thinks that degeneration of hæmoglobin wherever it exists occurs under the influence of the hyperglycæmia. Brault and Galliard (14) also give prominence to diabetes as the important factor in the production of pigmentation. The hæmoglobin of the diabetic is, they think, so altered that it is incapable of the normal transformation into bile pigment and is deposited in the liver

cell. Furthermore, it accumulates in the blood and wherever pigment is elaborated and utilized.

Hernandez (16) thinks that dissolution of hæmoglobin takes place under the influence of a general malady, diabetes, and pigment is deposited in the glandular cells altering their nutrition and finally causing their destruction. The pigment is not eliminated, but passes into the lymphatics, and causes in their walls an irritation, manifested by an increase of the connective tissue of the organ. Mossé (17) believes that under the influence of the hyperglycæmia pigment granules are formed within the blood-vessels at the expense of the altered or dissolved hæmoglobin. The pigment accumulation in the liver is in proportion to the specialization of the liver cells to a chromogenic function and to the large volume of blood which traverses the organ. The coexistence of hyperglycæmia and melanæmia contributes in very great part to the production of cirrhosis. De Massary and Potier (19) support the conception that a diabetic alteration of the blood is the essential etiological factor in the production of the pigmentation. Rendu and de Massary (20) advance the hypothesis that the pigment is deposited in the various cells of the body as the result of an abnormal action exerted by the cell upon the hæmoglobin of the blood, the alteration of metabolism being the manifestation of a general cachexia caused by diabetes associated with cirrhosis of the liver.

A second smaller group of writers think that the pigmentation is produced by a primary disease of the blood, that as a result of some fundamental cause there is an alteration of the blood and subsequent formation of pigment from the altered hæmoglobin. The relation of the concomitant diabetes and cirrhosis then remain to be explained. Buss suggests that the glycæmia may be the result of an incomplete oxidation of oxidizable carbon, resulting, in turn, from a diminished oxygen-carrying power of the altered hæmoglobin. P. Marie (18) thinks that there follows the action of some primitive cause a dissolution of the hæmoglobin, which is transformed by the protoplasm of various cells of the body into pigment, deposited in them. The pigment in turn causes a degeneration and destruction of the cells in which it is accumulated and consequently chronic interstitial inflam-

mation of various organs, notably the liver. The bronzed diabetes is neither clinically nor pathologically the classic diabetes, but is a distinct morbid entity, as is according to his belief pancreatic diabetes, and if, he says, it should be necessary to compare the condition with any other he would turn his attention to pancreatic diabetes. Acard (21), Dutournier (22), and Jeanselme (23) reiterate the conception of Marie and suggest that perhaps the diabetes is only an accessory phenomenon which appears with a certain degree of chronic interstitial pancreatitis. Anschütz has convinced himself that the diabetes finds its cause in chronic interstitial pancreatitis which like the cirrhosis of the liver, he believes, is a manifestation of an underlying condition.

The French writers who have described cases of "diabète bronzé" do not identify the pigmentation with the hæmochromatosis of v. Recklinghausen. In the very early cases no examination of the chemical nature of the pigment was made. Hernandez demonstrated that the brownish-yellow granules found by him in the epithelial cells of the liver, pancreas and kidney, in the muscle cells of the heart, in the connective tissue of these organs and in the lymphatic glands gave the microchemical reactions known to be characteristic of iron. In this and in subsequent cases the brownish-yellow pigment agrees in morphology and in location with the hæmosiderin of v. Recklinghausen. No mention is made by the majority of the French writers of an iron-free pigment present in smooth muscle cells and in certain connective-tissue cells. It is the absence of hæmofuscin alone which raises doubt as to the identity of the pigmentation of bronzed diabetes with hæmochromatosis. The hæmofuscin, occurring in fine pale-yellow granules within cells, is much less conspicuous than the more coarsely granular hæmosiderin, and may very readily be overlooked in specimens treated with reagents which demonstrate iron. Auscher and Lapicque (24) studied the pigment present in the case reported by Marie. In addition to widely distributed ochre-colored pigment which became black on treatment with ammonium sulphide, they found on the intestinal wall a second variety of pigment which was according to them of black color and dissolved in ammonium sulphide. Quantitative determination of the iron of the intestinal wall demonstrated

a small percentage while that of the liver was extremely large. The pigment observed by Auscher and Lopicque and subsequently found by Acard and Dutournier, though described as black in color, is apparently the iron-free hæmofuscin.

Buss, in an inaugural dissertation, as mentioned, reports a case of diabetes associated with cirrhosis of the liver and of the pancreas and with general hæmochromatosis. He finds the iron-containing and the iron-free pigment in locations corresponding to those mentioned by v. Recklinghausen. On the one hand there is no reason to doubt that the pigmentation in this case is identical with that of hæmochromatosis and on the other hand the case presents the clinical and pathological picture to which Hanot has given the name "diabète bronzé."

The case described by the writer holds a position intermediate between hæmochromatosis and the so-called bronzed diabetes. Associated with hæmochromatosis there is bronzing of the skin, cirrhosis of the liver of advanced grade, and chronic interstitial pancreatitis. Diabetes was, however, not present. It is evident then that the generalized pigmentation of bronzed diabetes is the hæmochromatosis of v. Recklinghausen.

When considering the etiological factors concerned in the deposition of great quantities of pigment in the liver and other organs we direct our attention to the blood, since it cannot be doubted that this iron-containing material is derived more or less directly from the hæmoglobin. It is well known that in pernicious anæmia with active blood destruction there is a deposition of iron within the liver and other organs, but pigmentation of the character under consideration is at least in the great majority of cases not found. A considerable proportion of the cases, both of simple hæmochromatosis and of hæmochromatosis associated with diabetes, have been accompanied by conditions which involve active destruction of the red blood corpuscles. Hindenlang's case of general pigmentation, almost certainly one of hæmochromatosis, was associated with morbus maculosus Werlhofii. In four other cases purpuric eruptions have been observed. In several there have been local hæmorrhagic conditions as, for example, hæmorrhagic pericarditis or peritonitis in cases of Hintze. In the

case of Buss there was found at autopsy hæmorrhagic pleurisy and peritonitis and hæmorrhagic pachymeningitis. Other forms of local hæmorrhage have been noted. The conditions cited present considerable variety, and in many cases were late manifestations in the disease. In many cases, moreover, local hæmorrhages were not demonstrable. It is then unnecessary to assume that the hæmoglobin forming the pigment arises from the destruction of red corpuscles of extravasated blood. It seems possible that, associated with some primitive alteration of the blood, there is a tendency to local hæmorrhage, the hæmorrhages being merely secondary manifestations of the same disease of the blood which, associated with intravascular destruction of red corpuscles, precedes the pigment deposition.

In a case of Jeanselme examination of the blood demonstrated the presence of a moderate grade of anæmia, but otherwise no marked pathological change of the blood was noted. Coagulation was not retarded.

Attempts have been made to reproduce experimentally the pigmentation found in human beings. Two methods have been employed: (1) The conditions of local hæmorrhage are produced, for example, by injecting blood into the peritoneum. (2) Hæmoglobin is set free within the circulating blood by the use of toxic substances which cause destruction of the red-blood corpuscles. Auscher and Lapique (25) and Meunier (26) have attempted by these means to reproduce the pigmentation of the internal organs found in bronzed diabetes. Auscher and Lapique by injecting blood into the peritoneum caused accumulation of an iron-containing pigment in considerable quantity in the spleen but in very small quantity in the liver. In cases of hæmochromatosis, however, the liver is the prominent seat of pigment accumulation.

It has long been known that toluylendiamin causes a destruction of the red-blood corpuscles, large doses producing in dogs hæmoglobinauria. By the use of this substance numerous experimenters have caused the deposition of an iron-containing pigment in the liver and other organs. Meunier, attempting to reproduce in dogs the pigmentation of bronzed diabetes, succeeded by the repeated injection of

small doses in obtaining an iron-containing pigment in moderate amount in the liver, lymphatic glands, spleen, and bone marrow. The immense iron accumulation of hæmochromatosis, however, has not been reproduced so that experiments have thrown but little light upon the pathogenesis of the condition.

The origin of the second form of pigment described by v. Recklinghausen, hæmofuscin, has been discussed at length by several writers who have studied hæmochromatosis. The data at hand are, however, very meagre. If the hæmofuscin were derived from the hæmosiderin, the two would be found side by side in the same cell and v. Recklinghausen, therefore, thinks that the hæmofuscin is formed independently from the hæmoglobin or some soluble derivative present in the lymph. Lubarsch and Hintze believe the hæmofuscin to be elaborated from the hæmoglobin as the result of a specific activity of the smooth muscle cells. Lubarsch injected defibrinated blood between the serosa and muscularis of the intestine of rabbits and obtained in the smooth muscle cells yellow granules of an iron-free pigment, formed, he thinks, by the action of the cells upon the liberated hæmoglobin.

It has been pointed out that a pigment apparently identical with the hæmofuscin of v. Recklinghausen is present in adults in the smooth muscle cells of the intestine under conditions which may be regarded as physiological, and according to Goebel increases with advancing age. In the sixteen cases of well-marked intestinal pigmentation without hæmochromatosis studied by him this pigment was not limited to the muscle of the intestine, but was found sparsely distributed in the smooth muscle cells of the blood-vessels of the intestine, kidney, liver, and lung, in the smooth muscle of the bronchi, urinary bladder, and prostate. He observed similar pigment in the spindle-shaped cells of the splenic trabeculæ and in connective-tissue cells of the liver, submaxillary gland, and mesentery. It seems evident then that the hæmofuscin found abundantly with hæmochromatosis occurs under conditions which may probably be regarded as physiological. Undoubtedly this pigment may occur unaccompanied by a generalized deposition of the iron-containing hæmosiderin.

Certain other iron-free pigments existing in moderate quantity un-

der physiological conditions have been in the case herewith described found increased. The iron-free pigment present in the heart muscle is greater in amount than that found under normal conditions. The interstitial cells of the testicle, normally containing pigment in moderate quantity, are loaded with pigment granules which do not give the reaction of iron. The pigmentation of the skin which has given name to the disease is caused by the presence in the deepest cells of the Malpighian layer of an iron-free pigment apparently not differing from that found under normal conditions.

It seems probable then that the same conditions which cause the deposition of an iron-containing pigment in various cells of the body favor the chromogenic metabolism of those cells which under normal conditions are capable of forming pigment. It may be pointed out, moreover, that hæmofuscin is present in considerable quantity in the walls of the vessels of the liver, pancreas, and lymph glands which contain hæmosiderin in great quantity; while in the vessels of organs like the kidney and lungs, in which is deposited very little iron-containing pigment, it is almost absent.

As already indicated a majority of those who have studied cases of bronzed diabetes regard the diabetes as the essential etiological factor. V. Recklinghausen so explained his case of hæmochromatosis associated with diabetes. Without sufficient basis apparently an active blood destruction is assumed to be the result of the diabetic condition. In the ordinary form of diabetes, however, an accumulation of iron does not take place in the liver or other organs, as shown particularly in cases studied by Zaleski * and Kretz.† A case of diabetes associated with cirrhosis of the liver without pigmentation is recorded by Hanot and Schachmann. Similar cases in which pigmentation was not, at least, a conspicuous feature are mentioned by Hansemann and other writers upon diabetes. There is, moreover, as will be pointed out reason to believe that the diabetes is secondary to the hæmochromatosis.

* Virchow's *Archiv*, 1886, civ, 91.

† *Beitr. zur klin. Med. u. Chir.*, Hft. 15, Wien, 1896; *Centralbl. f. allg. Path. u. path. Anat.*, 1897, viii, 620.

In the cases of bronzed diabetes the two prominent features in addition to the generalized pigmentation are diabetes and cirrhosis of the liver, and it is to this second factor that a number of writers have directed their attention in attempting to explain the pigmentation. It is to be recalled, moreover, that cirrhosis of the liver, usually of a less intense grade, has been present in the cases of simple hæmochromatosis. In all instances of hæmochromatosis, both with and without diabetes, the greatest pigment accumulation has been in the liver, and consequently a disturbed chromogenic function of that organ has suggested itself. It is conceivable that an iron-containing substance is deposited in the liver cells as the result of their inability to accomplish the normal elaboration of bile pigments from the hæmoglobin of the blood. This altered metabolism may be the concomitant of the cirrhosis of the liver, then to be regarded as the primary etiological factor. If the pigment is formed in the liver, how does it reach other portions of the body? Is there evidence that the pigment is transported by the blood stream either as emboli free in the plasma or as granules enclosed within phagocytic cells? An occasional particle of pigment has been found in blood obtained by pricking the skin, but the objection has been urged that such particles may be derived from the pigmented cutaneous glands. The demonstration in sections of an occasional pigment granule in the lumen of vessels is by no means conclusive, since an impervious material may in cutting be carried into such position by the knife. The demonstration, as in the case described by the writer, of cells containing pigment granules within the lumen of vessels is in no greater degree proof that in this way pigment is disseminated from a single depot of formation. For it is not inconceivable that from soluble substances in the plasma pigment is elaborated in those cells in which it is found. Moreover, as has been pointed out, it is probable that a certain number of pigment-containing cells are endothelial plates desquamated before death as a consequence of the pigment accumulation or after death as a result of post-mortem change.

A study of the process of pigment accumulation in widely separated organs throws more light upon the seat of its formation. The glands

I have studied most carefully are the liver, pancreas, adrenals and glands of Brunner. When the pigment is in moderate quantity, it is present as relatively fine round granules occupying that portion of the cell most distant from the capillaries, that is, in acinous glands the portion of the cell next the lumen. With greater accumulation the whole cell body contains pigment granules and finally almost the entire protoplasm is replaced by them. In cells so loaded with pigment the individual granules vary much, occurring as large round globules, often of greater size than a red-blood corpuscle. Changes may also be observed in the nucleus of the cell. It becomes smaller, its outline often becomes irregular, and it assumes a shrivelled appearance. In cells appearing to be a mere mass of granules and globules of pigment with careful focusing a very faintly staining vesicular nucleus is occasionally seen, while more frequently are found pigment masses without any trace of nucleus, but still maintaining the cell outline. Finally the cell outline is lost and a clump of pigment particles of very variable size lies free in the tissue. The same process, observed in the liver, takes place in the pancreas and adrenal gland and, indeed, in the muscle cells of the heart. It is therefore, improbable that the pigment they contain is transported as emboli or in phagocytic cells from some distant organ, as the liver. Much more probable is it that the same process is taking place simultaneously in all the organs concerned, that the pigment is elaborated by the cells in which it is found from iron-containing material dissolved in the surrounding lymph.

Although, as it appears, the liver is not the seat of formation of the pigment found in other organs, a disturbance of the chromogenic metabolism of its cells may be an important factor in causing the deposition of pigment elsewhere. It may be that iron-containing derivatives of the hæmoglobin are not eliminated in consequence of changes in the liver cells and so accumulate in the blood. The extreme pigmentation of the liver, greatly exceeding that of other organs, may hold to its chromogenic function some relation which our present knowledge of iron metabolism does not explain.

Doubtless, for the production of a condition of hæmochromatosis, some factor is necessary besides the mere disintegration of red cor-

puscles and setting free of hæmoglobin. Its absence in conditions associated with blood destruction sufficiently proves this point. Of a series of cases of cirrhosis of the liver studied by Kretz * in about one-half was found an accumulation of an iron-containing pigment resembling hæmosiderin. He comes to the conclusion that the toxic matter circulating in the blood causes a degeneration of the liver cells and at the same time acts injuriously upon the red corpuscles. It is the association of the two conditions which simultaneously produces cirrhosis and pigmentation. Possibly in hæmochromatosis the toxic material causing the blood destruction is of such a nature that it acts injuriously upon the cells of the liver and other organs so that they transform the soluble blood pigment reaching them into the insoluble hæmosiderin. Alcohol may, under certain conditions, have this action. Such speculations merely indicate the complexity of the conditions which underlie the generalized pigmentation.

Degenerate cells overloaded with pigment are in the case studied very abundant and can be readily demonstrated without prolonged search. We have thus an efficient factor for the production of a chronic interstitial inflammation. Newly formed fibrous tissue invades the lobule along the central vein and in places sends out fine radiating bands along the capillaries between the columns of liver cells. The fibrous tissue about the central vein and that between the lobules contain large quantities of pigment for the most part extracellular as a result of the degeneration of the cells in which it was formed. This pigment lies free in the tissue presumably transported along lymphatic channels. When it is massed in large quantity, there is usually evidence of active cell proliferation. In general the interlobular tissue is poor in cells, but in such areas proliferation may be indicated by the presence of small round cells. Two factors are, I believe, active in producing the scleroses: (1) pigmentary degeneration of the parenchyma cells; (2) irritation produced by the presence of the pigment in the interstitial tissue.

In the case I have described the pancreas is the organ next to the liver most conspicuously pigmented. Extreme pigmentation and con-

* Loc. cit.

sequent degeneration of the parenchyma cells can be readily seen. Fibrous septa deeply pigmented separate the lobules and in places strands of similar nature penetrate between the acini. The pancreas has been very superficially examined in many of the reported cases of bronzed diabetes, but in those in which a description of the microscopic appearance is given it is evident that chronic interstitial pancreatitis existed. The fact that the organ in the great majority of cases has not been found atrophic has probably, in certain instances, prevented the recognition at autopsy of interstitial inflammation. In but two cases apparently has it been found to be smaller than normal while it is frequently described as voluminous, enlarged or normal in size. In seven cases the weight is recorded; the mean of the figures given, varying between 95 and 195 grm., is 125.7 grm., about one-half greater than the normal weight of the organ. The average weight of the liver, recorded in thirteen cases of bronzed diabetes, is 2497 grm. and we must regard the condition present as a form of hypertrophic cirrhosis. The lesion of the pancreas differs from the more commonly observed form of chronic interstitial inflammation, accompanied by more or less atrophy of the organ and may be designated as hypertrophic pancreatitis. In my case without diabetes the pancreas weighed 170 grm., almost twice the normal weight, and was the seat of an interstitial inflammation of moderate intensity.

The etiological relationship of chronic interstitial inflammation of the pancreas to diabetes has been well established in recent years by Hansemann and others, though the exact character and degree of such inflammation necessary to the production of glycosuria has not been definitely determined. Finding, with bronzed diabetes, chronic interstitial pancreatitis constant as far as we are able to judge, it is hardly possible to doubt that the diabetic condition is pancreatic in origin and makes its appearance when the pancreatitis has reached a certain grade of intensity. In the majority of cases the symptoms of onset are those of diabetes, that is the individual is apparently in good health until the onset of glycosuria. In the three cases of hæmochromatosis without diabetes described by Hintze, diseases having no apparent relation to the hæmochromatosis caused death. In the present instance inter-

current typhoid fever caused the death of the individual before chronic interstitial pancreatitis had reached a sufficient grade of intensity to produce glycosuria and thus the hæmochromatosis was prevented from reaching its usual termination, pancreatic diabetes.

CONCLUSIONS.

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

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

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

I desire to express my obligation to Dr. Welch and Dr. Flexner for the interest they have shown in the foregoing case and for the assistance they have given me in its study.

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