SIDEROSIS IN THE BANTU OF SOUTHERN AFRICA*

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Extensive deposition of hemosiderin in the viscera of the South African Bantu was first described by Strachan,[1] and later by the Gillmans and their co-workers.[2-5] Strachan considered metallic poisoning by copper, tin, or zinc the probable etiologic factor. Gillman and Gillman[3] correlated the abnormal iron deposits with pellagra and malnutrition.

The general physiology and pathology of iron storage has been reviewed recently by Finch and his associates.[6] In man, large hemosiderin deposits are found mainly in classical or idiopathic hemochromatosis,[7] in certain anemias,[6,8,9] and after multiple blood transfusions.[10-12] In undernutrition or starvation, iron pigment deposits are found also, probably due to the breakdown of blood and tissue cells.[13,14] Heavy visceral deposits of iron, associated with bone and joint deformities, have been reported also in Korean mountain dwellers.[15]

In animals, the parenteral administration of citrated blood or iron compounds leads to excessive amounts of iron in various organs; this has been observed in mice,[16] rats,[6] rabbits,[17-20] and dogs.[6,21] The addition of iron salts to certain experimental diets, especially if low in phosphorus, also has been shown to cause excessive iron deposition in various animals.[6,22-24]

The pattern of iron distribution in severe siderosis in the Bantu has been assumed to be identical to that in classical hemochromatosis;[1-5,25,26] but our findings, which are the result of anatomical, histopathologic, and chemical investigation, do not support this view and accordingly seem worthy of publication.

METHODS AND MATERIALS

Our investigation was based mainly on 44 necropsies representing siderotic cases of varying severity. The liver, spleen, heart, kidney, and pancreas were examined in each, with the exception of the kidney in one case. Blocks from the jejunum also were available in 32 of these necropsies. In selected cases, additional blocks were taken as

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desired from the gastrointestinal tract, salivary glands, endocrine glands, lymph nodes, bone marrow, breast, tongue muscle, and skin.

In 21 of these cases, the iron concentration was determined in selected organs. With two exceptions this had to be done on formalin-fixed tissues and no allowance could be made for hemoglobin iron. However, since the quantity of iron as hemosiderin was so large, the small amount of hemoglobin iron would not have been significant, as was shown by Roth, Jasiński, and Bidder.[27] The tissues were dried at 110° C. for 24 hours, ashed at 450° C., and the iron estimated by the thioglycollic acid method. In the majority of organs the iron concentration was determined in duplicate. The duplicates showed a maximum error of about 10 per cent. In addition, tissues of 4 European adult subjects were analyzed as controls. The iron concentration also was determined in the major organs of 2 cases of classical hemochromatosis in Europeans.

To establish the incidence of siderosis and its relationship to hepatic fibrosis, 252 additional necropsies were reviewed, and the livers sectioned and stained for iron. The pattern of iron distribution was confirmed in these necropsies by the study of a small number of random tissues.

Both the more detailed series of 44 necropsies and the additional 252 cases were unselected, except that children under 10 years, and patients with anemia, malaria, and hepatic necrosis were omitted.

Also examined were 110 specimens of liver obtained for biopsy from other patients, many of whom showed various stigmata of malnutrition. Additional blocks from 72 livers obtained from unselected necropsies of Bantu living in other territories in Southern Africa also were available for examination.

In general, the organs were fixed in 10 per cent formalin; but in a few cases formol-sublimate, or Carnoy's fluids, were used. All sections were stained routinely with hematoxylin and eosin. Hemosiderin was demonstrated by Perls' hot potassium ferrocyanide method, modified after Dry.[28] The sections were counterstained with basic fuchsin. Additional stains used in selected cases were Turnbull's blue, Sudan IV, Sudan black, Mallory's picric acid-stain after McFarlane, silver reticulin stain, and Schiff's periodic acid stain with or without preceding salivary digestion.

Classification of Cases

Since the liver stores a high proportion of the total body iron, the concentration of the element in this organ was used arbitrarily as a standard of severity for each case. Usually, when the iron concentra-

tion in this organ was approximately 0.1 per cent dry weight, hemosiderin could be demonstrated by histologic methods. According to the amount of iron pigment demonstrated histologically, an attempt was made to grade the liver into one of four categories (Text-figs. 1 and 2). These corresponded approximately to the following concentrations of iron: 0 = < 0.1 per cent; + = 0.1 to 0.5 per cent; ++ = 0.5 to 1.5 per cent; +++ = > 1.5 per cent. It is clear that this grading cannot

TABLE I

Cause of Death as Established at Necropsy

Primary cause of death	Male*	Female*	Total*
Cardiovascular disease	57(5)	49(6)	106(11)
Tuberculosis	22(3)	12(1)	34(4)
Neoplasia (excluding liver)	16(1)	7	23(1)
Malignant hepatic tumors	6(3)	3(2)	9(5)
Central nervous system disease	20(3)	12	32(3)
Respiratory disease	24(2)	7	31(2)
Acute bacterial infection	10(3)	8	18(3)
Genitourinary disease	8	5(1)	13(1)
Postoperative shock	1	8	9
Diabetes mellitus	0	3	3
Cirrhosis of the liver	3	1	4
Pellagra	1	0	1
Miscellaneous diseases	10(1)	3	13(1)
Total	178	118	296

* The number of cases with cirrhosis unrelated to the cause of death is shown in brackets.

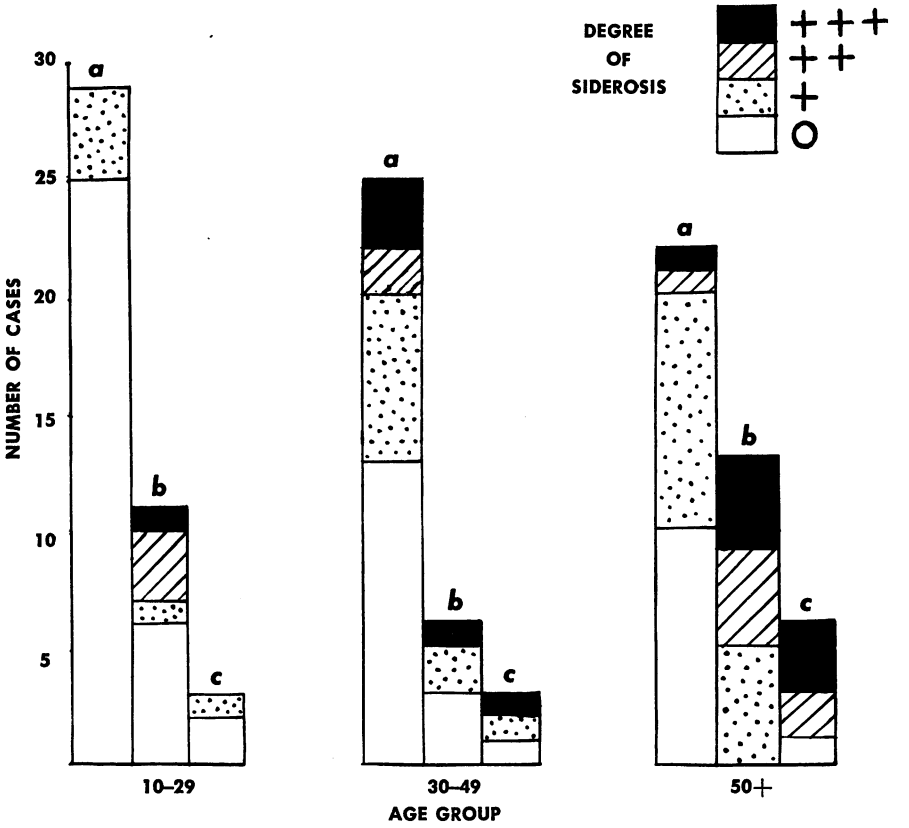
be altogether accurate as the quantitative measurements are based on only 21 cases which were studied by chemical analyses. In these, however, agreement between chemical and histologic grading was fairly satisfactory. An appropriate correlation between the chemical findings and histologic appearance was found also in other organs.

In addition the livers were classified histologically according to the degree of portal fibrosis as follows: (a) Essentially normal histology, including cases with slightly prominent portal tracts and minimal cellular infiltration. (b) Mild and moderate portal fibrosis, *i.e.*, livers with an increase in portal fibrous tissue, but without generalized confluence of the portal tracts (Fig. 2). (c) Severe portal fibrosis, *i.e.*, livers in which bands of fibrous tissue divide the organ into lobules (Fig. 3).

In this paper the term "cirrhosis" has been confined to this latter group (c).

Clinical Findings

Cause of Death. The primary diseases causing death in the complete series of 296 necropsies are shown in Table I. The degree of hemosiderin deposition was unrelated to any specific disease, and severe siderosis appeared to be an incidental post-mortem observation, not directly related to the patient's death. One patient, however, had died from the spontaneous rupture of a heavily pigmented spleen.

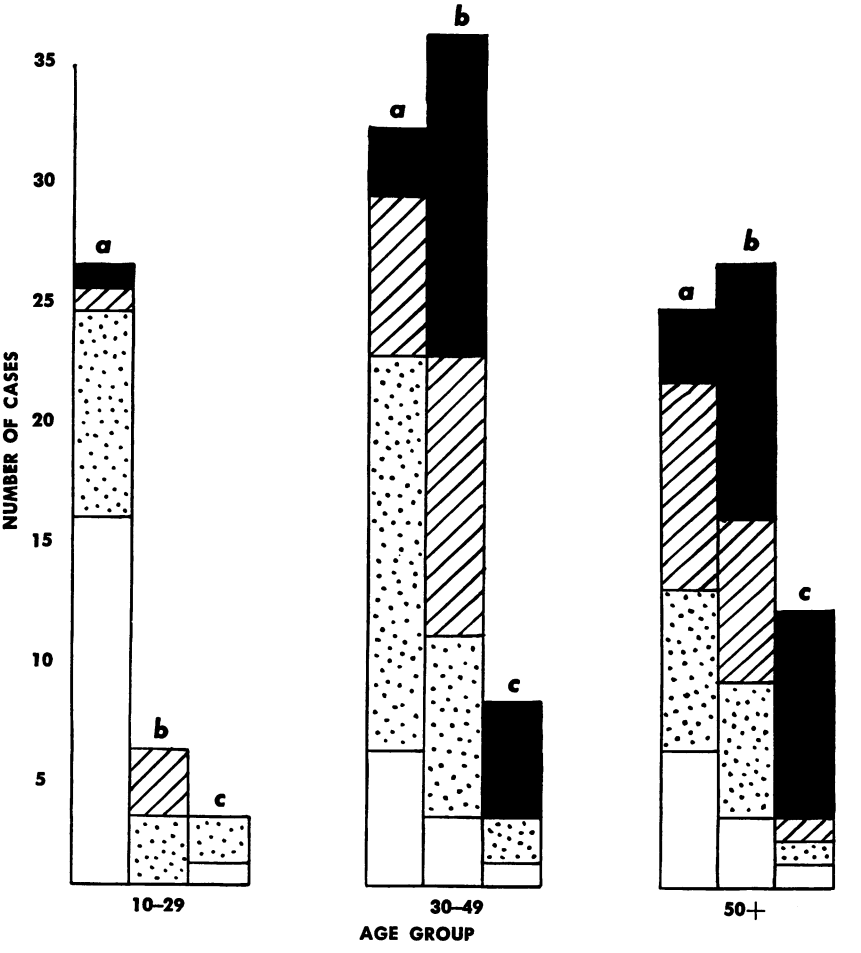


Text-fig. 1. Histogram showing the relation of hepatic fibrosis and siderosis in each age group for 118 female patients.
(a) Structurally normal livers.
(b) Livers with portal fibrosis but without confluence of the tracts.
(c) Severe fibrosis (cirrhosis).

There was no history of trauma, and except for an old focus of cerebral softening, the remaining organs and tissues were normal apart from heavy deposits of iron pigment. In 9 cases of carcinoma of the liver, a severe degree of siderosis was not found.

Nutritional State. In only 2 patients was a typical pellagroid rash observed. In the remainder the nutritional state was dependent on the

primary disease and not on the degree of iron pigmentation of the viscera. It was common, however, to find hyperpigmentation and hyperkeratosis of the skin of the limbs in Bantu patients suffering from chronic disease. Severe siderosis was seen often in wasted patients, but was observed also in the apparently well nourished.



Text-fig. 2. Histogram showing the relation of hepatic fibrosis and siderosis in each age group for 178 male patients.
(a) Structurally normal livers.
(b) Livers with portal fibrosis but without confluence of the tracts.
(c) Severe fibrosis (cirrhosis).

Diabetes Mellitus. Only 3 patients had diabetes mellitus; in these, hemosiderin deposits were very scanty.

Serum Iron. In many apparently healthy Bantu a high serum iron and total iron binding capacity have been observed.[29,30] Serum iron determinations were carried out on 5 subjects from whom liver speci-

mens were available for biopsy; of 3 patients in whom some hemosiderin deposition was demonstrable, 2 had markedly increased serum iron.

Parasitic Infestation. Schistosoma haematobium infestation was observed incidentally in 7 necropsies.

Age and Sex Distribution. The histograms (Text-figs. 1 and 2) relate the degree of siderosis to age. Under 20 years of age it is seldom observed and never to a severe degree. Its incidence and severity increase with age to the fifth decade, when the number of affected persons remains relatively constant. Females are less severely affected than males, especially in the third and fourth decades. Since it is our general experience that siderosis is very rare under the age of 10 years, younger children and infants were excluded from this investigation.

Geographic Distribution. Hemosiderin deposits were observed in the livers of Bantu from other parts of the Union, and from the following territories: Rhodesias, Bechuanaland, Swaziland, Nyasaland, and Mozambique. In many of these livers, malarial or bilharzial pigment also was found. Accordingly, the condition does not appear limited to the Johannesburg area, but as yet no extensive investigation has been made in other areas.

Chemical Analysis

The concentration of iron in the major organs from 21 Bantu and 6 European subjects is shown in Tables II to V. Cases 26 and 27 present the iron concentration in the organs of the 2 European subjects who died with classical hemochromatosis. The clinical features of case 26 have been reported elsewhere.[31] The iron concentration in classical hemochromatosis is summarized in Table V after Sheldon.[7]

Gross and Microscopic Pathologic Features

Our description of the morbid anatomical distribution of hemosiderin is based chiefly on the 44 cases examined in most detail. Where desirable, use has been made of the tissues available from the additional 252 necropsies in which the liver was examined for iron. The rusty appearance of siderotic tissues was typical, and the pattern of visceral and lymph node involvement could easily be studied with the naked eye. Further, as the pattern observed in the cases examined in more detail was constant and was confirmed by microscopy, section of further tissues was considered unnecessary.

External Appearances

The hyperpigmentation of the skin in Bantu suffering from chronic

TABLE II

Cases with a "Normal" or Low Concentration of Liver Iron (Per Cent Dry Weight)

No.	Race*	Sex	Age	Cause of death	Liver	Spleen	Heart	Pancreas	Kidney	Jejunum	Other organs		
1	E	F	60	Ruptured aorta	0.07	0.09	0.01	0.01		0.01			
2	E	M	30	Stomach carcinoma	0.06	0.13	0.04	0.03		0.01			
3	E	M	74	Pyelonephritis	0.04	0.07	0.02	0.03		0.03			
4	E	M	50	Brain abscess, cirrhosis of the liver	0.11	0.16	0.04	0.03	0.06	0.02	Thyroid gland		
5	B	F	14	Typhoid	0.08	0.25	0.03	0.04			0.04		
6	B	F	14	Mitral stenosis	0.08	0.12	0.08		0.08	0.03			
7	B	F	39	Malignant hypertension	0.11	0.11	0.03	0.04	0.08				
8	B	F	26	Obstetric shock	0.05	0.12	0.04		0.04	0.05			
9	B	F	40	Cerebral hemorrhage	0.11	0.15	0.09	0.04	0.06	0.04			
10	B	F	24	Cerebral hemorrhage	0.03	0.10	0.04	0.06	0.06	0.06			
Average European according to Sheldon[7]					0.05–0.1	0.14	0.04	0.02	0.04	0.03	Thyroid gland 0.02	Stomach 0.05	Ileum 0.03

* B = Bantu, E = European.

TABLE III

Cases with a Slight Rise in the Concentration of Liver Iron (Per Cent Dry Weight)

No.	Race*	Sex	Age	Cause of death	Liver	Spleen	Heart	Pancreas	Kidney	Jejunum
11	B	M	34	Lobar pneumonia	0.24	0.31	0.05	0.06		
12	B	M	28	Ruptured aorta	0.20	0.26	0.05	0.03		
13	B	M	45	Malignant nephrosiderosis	0.14	0.52		0.04	0.07	0.16
14	B	F	48	Nutritional heart disease	0.32	0.44	0.06	0.05		0.09

* B = Bantu.

TABLE IV

Cases with Moderate Increased Concentration of Liver Iron (Per Cent Dry Weight)

No.	Race*	Sex	Age	Cause of death	Liver	Spleen	Heart	Pancreas	Kidney	Jejunum	Other organs	
15	B	M	60	Chronic nephritis	0.52	2.15	0.04	0.08		0.07		
16	B	M	30	Tuberculous meningitis	0.56	0.96	0.05	0.09	0.09	0.80		
17	B	M	63	Bronchopneumonia	0.74	2.86	0.06	0.14	0.10	0.38		
18	B	F	60	Chronic pyelonephritis	0.71	1.12				0.43	Portal lymph node	Jejunal lymph node
19	B	M	42	Nutritional heart disease	1.23	2.63	0.05	0.09	0.09	2.12	5.85	3.64
20	B	M	65	Cerebral thrombosis and tuberculosilicosis	1.19	3.73	0.09	0.07	0.05	0.33		

* B = Bantu.

TABLE V

Cases with High Concentration of Liver Iron (Per Cent Dry Weight)

No.	Race*	Sex	Age	Cause of death	Liver	Spleen	Heart	Pancreas	Kidney	Jejunum	Other organs		
											Stomach	Ileum	Thyroid gland
21	B	M	45	Tuberculous meningitis	1.55	5.16	0.07	0.08	0.18	1.43	0.07	0.06	0.05
22	B	M	42	Hypertensive congestive circulatory failure	2.34	5.75	0.05		0.17	1.08	Stomach	Duodenum	Ileum
23	B	M	50	Generalized tuberculosis	2.45	3.50	0.07	0.15	0.10	1.41	0.09	0.42	0.23
											Stomach	Ileum	Bone marrow
24	B	M	63	Pulmonary tuberculosis	3.59	6.01	0.15	0.13	0.15	1.84	0.05	0.04	1.09
25	B	F	60	Lobar pneumonia	5.52	10.5	0.07	0.49		0.31	Stomach		
26	E	F	25	Acute cardiac failure due to hemochromatosis	2.56	0.39	0.51	0.71	0.13	0.16	0.20		
											Stomach	Ileum	
27	E	M	48	Acute heart failure due to hemochromatosis	3.25	0.25	0.37	0.79	0.3	0.10	0.24	0.08	
											Stomach	Ileum	Thyroid gland
Average concentration and range in hemochromatosis according to Sheldon[7] (1935)					3.6 (1.0–7.6)	0.6 (0.2–0.8) one case, 2.6	0.5 (0.2–1.0)	2.0 (0.06–5.0)	0.2 (0.07–0.5)	0.15 (0.6–0.02)	0.2 (0.1–0.3)	0.06 (0.06–0.07)	0.5 (0.2–1.2)

* B = Bantu, E = European.

disease was due to increased melanin in the rete malpighii and was unrelated to the amount of hemosiderin in the abdominal organs. In 3 of 10 severe cases with heavy iron pigmentation of the liver, microscopic examination of the skin from the flexor surface of the arms showed a few scattered hemosiderin granules in the corium, most marked in the region of the skin appendages. No iron pigment was found in skin sections from cases with moderate hepatic involvement.

The Liver

The following description is drawn from the 292 livers examined. The gross appearance varied according to the nature of the primary disease. In livers with a moderate or severe siderosis, the organ had also a rusty brown color and gave a positive Prussian blue reaction in the cold. In 35 of these 292 livers, cirrhosis was present but in only 4 was it the direct cause of death. The weight of the organ was unrelated to the intensity of pigmentation. The mean weight for normal livers without histologic iron was 1515 gm. (range, 1120 to 2000 gm.); for those classified as severe siderosis, 1550 gm. (range, 1200 to 2350 gm.); and for those with fine multilobular cirrhosis, 1660 gm. (range, 1200 to 2450 gm.).

Microscopic Examination. Among Bantu patients it is common at necropsy to find histologic evidence of liver disease, which is apparently unrelated to the cause of death (Table I). Similar lesions are observed in liver specimens for biopsy from patients who clinically are not under suspicion of having hepatic disease. These lesions vary from prominence and slight fibrosis of the portal tracts to a fine multilobular cirrhosis (Figs. 1 and 2). There may be an associated pleomorphic portal infiltration by lymphocytes, plasma cells, and histiocytes, also polymorphonuclear cells and eosinophils. Throughout the liver, the fibrosis of the portal tracts is unequal; in some tracts there is little or no increase in fibrous tissue; elsewhere collagen fibers extend toward the neighboring tracts and between the parenchymal cells at the periphery of the lobules. The resultant cirrhosis accordingly shows both a monolobular and multilobular distribution. It seems probable that, in the late stages, such a cirrhosis may progress to a coarse cirrhosis morphologically indistinguishable from that of post-necrotic origin, but proliferation of the bile ducts is insignificant and necrosis of the liver cells is not a feature. The distribution of the livers of the various types in each group is shown in Text-figures 1 and 2.

Of the 35 cirrhotic livers, the cirrhosis in 25 was clearly a more advanced degree of the fine portal type which we have described. In

none of these was it considered the direct cause of death. There was one case of true biliary obstructive cirrhosis. The remaining 9 livers showed a coarse multilobular cirrhosis. In the latter cases the clinical history was insufficient to determine the etiology with certainty.

Distribution of Iron Pigment. In the majority of livers, hemosiderin was observed in both liver and Kupffer cells. In cases of mild siderosis the cytoplasm of the Kupffer cells usually stained a diffuse blue and sometimes contained small hemosiderin granules. In the parenchyma, on the other hand, iron pigment appeared first as fine granules at the biliary pole of the hepatic cells at the periphery of the lobules. In 8 livers, however, hemosiderin was found only in the Kupffer cells (Fig. 3), and in 8 additional livers pigment was confined almost entirely to the parenchymal cells, pigment in the reticulo-endothelial cells being insignificant.

In severe cases, the deposits of pigment in the parenchymal cells and Kupffer cells were more marked and the pigment granules of larger size. Deposits, however, were still most obvious in the liver cells at the periphery of the lobules, but the pigment was no longer confined to the biliary pole (Figs. 4 to 6). Where the Kupffer cells were heavily involved, large granules of pigment obscured nuclear detail and the cells appeared as masses of granular hemosiderin. In an occasional case, iron-laden multinucleated macrophages were present in the sinusoids. Even where deposits were marked in the liver cells, cellular degeneration was not a prominent feature. No correlation was observed between the amount of hemosiderin in the Kupffer cells and in the liver cells.

In siderotic cases of all degrees of severity, deposits of iron pigment were noted also in the portal tracts (Figs. 5 and 6). These varied from an occasional iron-laden macrophage to heavy intracellular and extracellular masses. The appearance of these latter masses suggested origin from the disruption of iron-laden macrophages. Frequently, in cases with severe pigmentation, hemosiderin was found in the epithelium of the small bile ducts, and in the endothelial cells of the portal lymphatics and venous channels. Invasion of the liver capsule by iron-laden macrophages was always present in association with heavy pigmentation of the portal tracts. The histograms (Text-figs. 1 and 2), however, show that all patterns of liver damage can be associated with any degree of hemosiderin deposition. But while there is a tendency for severe siderosis to be associated with portal fibrosis and cirrhosis, conversely, some cases with heavy iron storage show little or no fibrosis.

In siderotic livers, foci of scarring or tuberculosis were often infil-

trated by iron-laden macrophages (Fig. 7). Similar invasion of fibrous scars was found elsewhere in the body.

Iron Content. On comparing the concentration of iron determined chemically and assessed histologically in 21 livers, it was clear that the fibrosed portal tracts permitted marked storage; *i.e.*, when a liver showed a high iron concentration on chemical analysis, much of the hemosiderin appeared to be situated in the portal tracts. In this series, the highest concentration of hepatic iron was 5.52 per cent dry weight (case 25). In this liver, cirrhosis was present.

Spleen

In siderotic cases the spleen showed a marked rusty color, the intensity of which was invariably greater than that in the liver. Sometimes, although the liver had a normal color, the spleen showed a distinct brownish tinge and gave a positive Prussian blue reaction. The weight and size of the organ were related to the accompanying disease process. Significant enlargement of the spleen or other evidence of portal hypertension was present in only 6 of the 25 cases with fine multilobular cirrhosis.

On microscopic examination of the 113 spleens available, a much greater concentration of iron was found than in the liver, with only 2 exceptions. This was confirmed by chemical analysis in 21 cases (Tables II to V) but the total quantity of iron, however, was less than in the liver. In those cases in which only minimal involvement of the parenchymal or Kupffer cells of the liver was present, the spleen showed significant deposits of hemosiderin in the endothelial cells and macrophages. In more severe cases, the number of iron-laden macrophages in the pulp increased to form dense masses, some of which appeared extracellular (Fig. 8), and often the entire reticulo-endothelial system was outlined by pigment. Iron-laden histiocytes were found also in the capsule and trabeculae, and the endothelium of the trabecular veins frequently contained hemosiderin granules. Occasionally, slight iron encrustation of the trabecular fibers was observed, but the elastica of the vessels was usually unaffected. The malpighian corpuscles appeared relatively free from iron pigmentation. Fibrosis was not significant unless some other factor such as portal hypertension or chronic venous congestion was present.

Pancreas

On naked-eye examination the pancreas usually appeared normal, but in 2 cases it had a distinct brown color. Of the 82 pancreases ex-

amined microscopically, 32 were from cases in which the liver was heavily pigmented. In the majority of these, slight hemosiderin deposits were noticed in scattered interstitial macrophages, but in only 7 did the acinar and islet cells contain iron-pigment granules. These were very scanty with the exception of case 25, the most severely siderotic case noted. Cases of moderate or mild hemosiderosis showed no evidence of epithelial involvement. Chemical determination confirmed the very low concentration of iron in the pancreas, in contrast to that in the liver and spleen. In a few cases there was a fine interstitial fibrosis which was unrelated to the amount of iron in the pancreas or in other viscera.

Heart

In only 4 of the 21 hearts from cases with severe hepatic siderosis were iron pigment granules observed in the perinuclear region of the myocardial fibers. In the remaining 53 hearts from cases of lesser severity, no iron could be demonstrated histologically in the myocardium. Chemical analysis confirmed the very slight increase in iron in the cardiac muscle.

Kidney

In both severe and moderate cases, scanty hemosiderin granules usually were found in the distal convoluted tubules and also in the loops of Henle. In some severe cases granules of iron pigment were found lying in the glomerular capillaries. Scattered hemosiderin-laden macrophages frequently were present in the interstitial tissues as were also slight extracellular deposits, especially in foci of fibrosis. The tubular deposits were scanty and focal in distribution. Analysis in 4 severe cases showed only a slight increase in iron concentration.

The Gastrointestinal Tract

The stomach appeared normal, even in patients with severe siderosis on gross examination. In 4 very severe cases, microscopic examination showed only traces of hemosiderin in a few acinar cells and only occasional iron-laden macrophages in the submucosa. In 6 other cases with equally heavy visceral deposits, no pigment was found in the epithelial cells.

On naked-eye examination the duodenal and jejunal mucosa from cases with slight hepatic pigmentation appeared normal. In cases with more marked visceral involvement, however, the mucosa had a rusty color and gave a positive Prussian blue reaction. This color was first noted in the doudenum (being most intense in the third and fourth parts) and upper jejunum, and then diminished and disappeared in

the lower jejunum and ileum. Microscopic examination confirmed the gross appearances in mild cases; sections of the jejunum showed only an occasional iron-laden macrophage in the substantia propia of the villi. But in severely siderotic cases all cellular detail in the villi was obscured by masses of intracellular and extracellular pigment. Similar changes were found to a lesser degree in the duodenum, but in no case examined were the glands of Brunner involved (Figs. 9 and 10). When the visceral deposits of hemosiderin were slight, the ileum showed no abnormal storage, but in severe cases a few iron-laden macrophages were found in the villi. The colon was normal, but occasionally, foci of hemosiderin-laden macrophages were found in the mucosa. In all cases post-mortem change was too advanced for examination of the epithelium.

Chemical analysis confirmed the histologic findings; the iron concentration of the stomach, ileum, and colon showed insignificant rises in comparison to the jejunum, which on one occasion contained seventy times the average normal value (case 21). Due to the presence of the muscle in these specimens, however, these values are only approximate and the actual mucosal concentration of iron would be much greater. From Tables II to V, it can be seen that a rise in the concentration of iron in the jejunum usually accompanied an increase in the liver and spleen, and this was confirmed by histologic study.

Slight deposits of hemosiderin were found in the acinar cells of only 2 of 12 *parotid glands* examined. No hemosiderin or only an occasional iron-laden interstitial macrophage was observed in 4 additional glands, although all 6 subjects showed equally heavy iron deposits in the abdominal organs.

Endocrine Glands

Sections from the thyroid gland, pituitary body, and testes showed only a few scattered hemosiderin-laden macrophages in the interstitial tissues. In only two thyroid glands from severe cases were hemosiderin granules found in the epithelial cells. Of the 19 suprarenal glands examined, in only 2 was iron pigment found in the epithelial cells. In many of the remainder, although the endothelial cells of the cortical sinuses were outlined by hemosiderin and heavy deposits were present in the medulla, no pigment was observed in the epithelial cells.

Testicular atrophy and gynecomastia were present in several cases, but no correlation with the degree of visceral siderosis or hepatic cirrhosis could be established.

Bone Marrow

On gross examination, the bone marrow, in cases with moderate and severe siderosis of the liver, was rust colored. Microscopic examination confirmed the presence of intracellular and extracellular iron pigment deposits. Numerous hemosiderin-containing macrophages have been observed also in marrow smears from Bantu patients. In one case of generalized idiopathic osteoporosis there was collapse of the vertebrae with fibrosis. The new fibrous tissue was very heavily infiltrated by iron-laden histiocytes.

Brain and Choroid Plexus

In no case was iron pigment found in the brain substance. On naked-eye examination the choroid plexus was of normal color and microscopically only minimal epithelial deposit was found in 2 of 4 very severe cases.

Voluntary Muscle

In 2 of 7 cases with severe visceral siderosis, very scanty pigment deposits were noted in the voluntary muscle of the tongue.

Lymph Nodes

According to the degree of hemosiderin deposition, the gross coloration of the nodes varied from normal to light brown or rust. On section, iron pigment first appeared in histiocytes lying in the medullary and subcapsular sinuses. In more severe cases, the deposits were both intracellular and extracellular. In some patients the nodes showed solid masses of hemosiderin granules, surrounding relatively normal lymph follicles (Fig. 11). Even in the most heavily affected nodes, fibrosis was not a feature.

The distribution of hemosiderin in the abdominal nodes followed a definite pattern. Those in the porta hepatis, pancreatico-splenic, and upper mesenteric groups contained the most iron pigment. The lymph nodes in the mesentery and those draining the doudenum and upper jejunum contained large deposits (Fig. 10), but those draining the ileum and colon, little or none; in mild cases, only the jejunal and duodenal nodes contained hemosiderin. In 3 cases examined, in which very scanty iron-laden macrophages were found in the jejunal mucosa, there were moderate pigment deposits in the corresponding jejunal lymph nodes and the nodes of the porta hepatis. In severe cases, heavy pigmentation was observed also in the glands of the lesser curvature and in the para-aortic group. In such patients, scattered

hemosiderin-laden macrophages frequently were noted also in the tracheobronchial, inguinal, axillary, and cervical nodes. The pattern of lymph node involvement was confirmed microscopically in 60 nodes, but in other necropsies the same pattern of involvement could easily be followed with the naked eye.

Lung

Hemosiderin deposits usually were scanty and limited to the interstitial tissues of the lung. In 4 cases with heavy liver pigmentation, large granules of hemosiderin were found obstructing some of the alveolar capillaries.

Other Pigments

In many livers a golden brownish pigment ("wear and tear" pigment) was found in the liver cells. This could be demonstrated by basic fuchsin. Iron was not demonstrated by the method used in this investigation. This pigment stained poorly or not at all with the periodic acid-Schiff's method, and it was sometimes sudanophilic even in paraffin sections. Although this pigment generally was more frequent with increasing age, the relationship was not absolute. Whereas hemosiderin was first found at the periphery of the lobules, this pigment was most marked at the center. In many cases the centrilobular cells contained "hemofuscin" but no hemosiderin, whereas at the periphery, iron pigment was present but no fuchsinophilic pigment. There was no correlation between the presence of this pigment and the degree of siderosis. A similar pigment which sometimes stained with the periodic acid-Schiff's technique was found in the heart muscle.

In addition, in many siderotic cases a further fuchsinophilic pigment was found. It was noted in the fibroblasts and macrophages of the portal tracts, the epithelium of the biliary ducts, the interstitial tissues of the pancreas, the capsule of the lymph glands and spleen, the myocardium, and in the smooth muscles of the blood vessels, muscularis mucosae, and myocardium (Fig. 11). It also was found occasionally in voluntary muscle, in the choroid plexus, and renal tubules. In case 25, the lymphatics of the submucosa were outlined by hemosiderin and fuchsinophilic pigment (Fig. 12). The color of this pigment varied from gray to brown in unstained paraffin sections. It differed from "wear and tear" pigment in that it was generally stained strongly by the periodic acid-Schiff's technique. Frequently it stained with Sudan black, even in paraffin section. It did not show iron. Its presence was variable and although usually most marked in severe siderosis this relationship was not absolute, in some cases little or none being found.

It must be emphasized that this pigment, although constantly fuchsinophilic, showed considerable variation in its staining reactions in organs from various parts of the body.

Although looked for in many cases, no ferrous iron was demonstrated in appropriately stained sections of the liver and spleen.

Discussion

In Table VI we have compared our observations on the major clinical and morbid anatomical features of Bantu siderosis with those in hemochromatosis and transfusional hemosiderosis as reported in the literature. For present purposes, idiopathic or classical hemochromatosis will be referred to as hemochromatosis.

Clinical Findings

According to the observations of Strachan,[1] Gillman and Gillman,[3,32] and from our present series, siderosis occurs very frequently in adult Bantu subjects examined at necropsy. It is rarely observed in the young, increases with age, and appears to affect males slightly more than females. The maximum incidence of hemochromatosis is in the fifth decade.

Diabetes mellitus was not common in our series. It is found in 78 per cent of the reported cases of classical hemochromatosis.[7] According to Brown *et al.*,[21] it has been reported in 5 of 40 cases of transfusional hemosiderosis.

Gross and Microscopic Findings

The general pattern of hemosiderin deposition in this series was similar to that reported by other local authors.[1,3,4]

On naked-eye examination, deposition of hemosiderin was most marked in the abdominal lymph nodes, spleen, liver, jejunum, and bone marrow, and was negligible or absent in the heart, pancreas, stomach, suprarenal and thyroid glands. The findings were confirmed by microscopy and chemical analyses in selected cases. The basic picture was that of storage in the liver and the reticulo-endothelial system.

The concentration of iron in the spleen was almost invariably greater than in the liver, even in mild cases. In hemochromatosis the iron content of the spleen is usually much lower than in the liver and concentrations of the degree observed in severe Bantu siderosis have not been reported. We have been able to find descriptions of only 2 cases of hemochromatosis in which the concentrations in both organs

TABLE VI

Comparative Features of Siderosis in the Bantu, Idiopathic Hemochromatosis, and Transfusional Hemosiderosis

	Siderosis in the Bantu	Idiopathic hemochromatosis*	Transfusional hemosiderosis‡
Incidence	Very common in the Bantu	Very rare	Very rare
Age	Increases with age	Maximum incidence in middle age	No specific age
Sex	Males affected earlier and more severely than females	Males:females = 20:1	No difference between sexes
Diabetes	Very rare	78% of cases	Has been reported
Hematologic picture	Normal	Normal	Associated with blood dyscrasias
Serum iron	Frequently abnormally high	Usually increased†	Usually increased
Liver			
Cirrhosis	Present in one fourth of severe cases	Invariably present	Portal fibrosis frequently reported
Weight	Variable	Usually increased	Variable
Iron content	High in advanced stage	High in advanced stage	Depends mainly on number and volume of transfusions
Pancreas			
Fibrosis	Rare and unrelated to degree of siderosis	90% of cases	Sometimes found
Hemosiderin	Present only in severe cases	Invariably present	Deposits sometimes found
Spleen			
Weight	Within normal limits	Increased	Variable
Iron content	Very high	Increased	High
Stomach	Usually no epithelial iron present	Iron usually found in epithelial cells	Sometimes found
Intestine	Much pigment in villi of upper small bowel	Slight pigmentation of villi	Not reported (not found in one case examined by us)
Heart	Iron pigment rarely observed	Hemosiderin present in 90% of cases	Sometimes pigmented
Bone marrow	Heavily iron pigmented	Little or no iron pigment present	Iron pigment occasionally observed
Type of iron distribution	Essentially in reticulo-endothelial system	Essentially parenchymal	Both systems equally involved

* Mainly after Sheldon.[7,26]

† Rath and Finch.[49]

‡ Abstracted mainly from Schwartz and Blumenthal,[11] Wyatt *et al.*,[12] Brown *et al.*[21]

were similar, namely, the cases of Bernoulli[7a] (cited by Sheldon[7]) and Vogt.[33] Several authors have emphasized the relatively small amount of hemosiderin found in the spleen,[7,21] and our findings are in agreement (cases 26 and 27). In 2 cases of transfusional hemosiderosis which we studied, the concentration of splenic iron was approximately equal to that in the liver (2 to 3 per cent). In animals which had received iron by injection, Polson[19] found a late reduction in the concentration of splenic iron after an early rise, due to increased storage in the liver. If, however, Bantu siderosis and hemochromatosis are considered basically similar conditions, it is difficult to explain the different concentrations of iron in the spleen on this hypothesis.

A striking feature of this series was the absence of pancreatic pigmentation in the majority of cases. Even when hemosiderin deposits were marked in the liver and spleen, the pancreas showed only scattered iron-laden interstitial macrophages; in only a few very severe cases was iron pigment seen in the glandular and islet cells and then usually only in traces. This is in contrast to hemochromatosis in which heavy iron pigmentation is invariably present, the iron content averaging 100 times the normal average value.[7]

The absence of significant hemosiderin deposits in the epithelial elements of the stomach, the thyroid, salivary, and suprarenal glands, and the myocardium is also in striking contrast to hemochromatosis where these organs are almost invariably pigmented.

Although slight hemosiderin deposits occur in the intestinal villi in hemochromatosis,[7] massive pigment deposition in the jejunal and the duodenal mucosa, as found in our cases, is not a feature. Such deposits, however, are noted in the intestines of rats and guinea-pigs which have ingested large amount of iron[23,34]; and in mice[16] and dogs,[6] after the injection of saccharated iron. Cappell[16] considered these deposits to arise from the re-absorption of intestinal iron which was of either dietetic or biliary origin. Such deposits have been reported in transfusional hemosiderosis in man,[35] but in many reports on this condition, no specific mention of intestinal pigmentation has been made. In one of our 2 cases of transfusional hemosiderosis, in which the concentration of liver iron was 2.58 per cent of the dry weight, no hemosiderin was observed in the jejunal villi.

It seems reasonable, therefore, to regard the upper portion of the small intestine as an area of high iron activity, possibly related to absorption. Further, where pigment deposits were large, the endothelial cells of the submucosal lymphatics often contained iron pigment, as did the corresponding lymph nodes (Figs. 10 and 13), and

relatively little iron was observed in the ileum or colon and their lymph nodes. On anatomical grounds, this suggests that these increased hemosiderin deposits were derived from active absorption in the small intestine, rather than by retrograde spread in the mesenteric lymphatics.

The fine portal fibrosis described in the liver of Bantu patients at all ages has been confirmed. Such tracts show varying degrees of fibroblastic activity and cellular infiltration. As the proportion of patients with cirrhosis in each decade does not increase markedly, these proliferative changes in the portal tracts probably may cease to progress at any age, and cirrhosis is not an invariable result. This is also the opinion of Gillman and Gillman,[32] who considered these changes nutritional in origin. In the majority of cases, this cirrhosis is of a fine multilobular type, fibrosis apparently being the dominant feature and not necrosis. Our findings are very similar to those of Vint[36] in East Africa.

All degrees of siderosis were found accompanying these various histologic patterns. Only one fourth of the cases with severe siderosis showed cirrhosis. In 7 cases with cirrhosis, hemosiderin deposition was absent, and conversely, 11 severely siderotic livers showed no significant portal fibrosis.

Gillman and Gillman[3] classified their cases of Bantu siderosis, first, by the degree of fatty changes in the parenchymal cells, and secondly, according to the distribution of hemosiderin in the liver cells, Kupffer cells, and portal tracts. They considered these types to represent various stages in the evolution of classical hemochromatosis. It is very doubtful whether fatty change in the liver can be related to siderosis which is usually first observed in the third decade, whereas the majority of fatty livers found by these authors among the Bantu were in patients with kwashiorkor, dying during the first 2 years of life. This has been our experience also. In Uganda, kwashiorkor with fatty liver is common,[37] but siderosis in adults is not observed.[38] In our series there was no relationship between pigmentation and fatty change, the latter appearing to be dependent upon the primary disease. We also have observed no correlation between the concentration of iron in the liver and the distribution in the parenchymal cells, Kupffer cells, and portal tracts. For these reasons we consider the absolute concentration of hepatic iron a better index of the evolution of Bantu siderosis than the pattern of pigment distribution in the liver. Further, in our opinion it is inadequate to base any classification of siderosis on the pattern in the liver without considering the general distribution in the body.

It is, of course, dangerous to dogmatize on the evolution of a disease from the static picture at necropsy. However, although slight deposits of hemosiderin have been reported in chronic bacterial diseases,[39] in the majority of our cases with slight or moderate siderosis, the pigmentation could not be so ascribed. We consider it reasonable to accept these as representing an early stage in the evolution of Bantu siderosis.

Cappell[16] showed that after the injection of saccharated oxide of iron in mice, the iron first appeared in the cells of the reticulo-endothelial system, and shortly after in the epithelial cells of the liver. On this account, and arguing by analogy from Cappell's experiments, we consider cases with only reticulo-endothelial involvement to represent the earliest stage in evolution. We also believe that the development of the morbid anatomical pattern in this series is very similar to that described in mice by Cappell. It is possible that the 8 livers in which parenchymal iron alone was present correspond to those livers in mice in which new non-iron-containing Kupffer cells have replaced the older cells. In Bantu siderosis, it appears that not until the concentration of iron in the liver cells and reticulo-endothelial system is high, can hemosiderin be demonstrated histologically in the parenchymal cells of the heart, pancreas, and salivary and thyroid glands. Although chemical estimation shows some increase in the iron content of these organs, this is probably mainly due to hemosiderin-laden phagocytes and extracellular deposits in the interstitial tissues. Epithelial hemosiderin deposits can, however, usually be demonstrated in the pancreas, thyroid and suprarenal glands, and heart when the concentration of hepatic iron approaches 3 per cent dry weight and splenic iron 5 per cent dry weight, approximately. In contrast, in cases of hemochromatosis, even when the concentration of hepatic iron is as low as 1 to 2 per cent dry weight, it is usual to observe considerable pigment in the parenchymal cells of the heart, pancreas, and thyroid gland.[7] In reviewing the distribution of iron in hemochromatosis, as described by Sheldon and later authors, we agree with Brown *et al.*[21] who considered that in hemochromatosis, storage even in the early stages is essentially in the parenchymal tissues. On the other hand, it appears to us that Bantu siderosis is mainly storage of excess iron initially throughout the general reticulo-endothelial system and in the liver cells. Iron pigment was not observed in this series in the parenchyma of organs other than the liver in the absence of heavy involvement of the reticulo-endothelial system. It is not possible, however, to distinguish between Bantu siderosis, hemochromatosis, or transfusional hemosiderosis by chemical or histologic examination of the liver alone. Although epi-

thelial deposits may be considerable, as illustrated by Gillman and Gillman[5] in Figures 156 and 167, and in case 25 of our series, we consider that the distinction from hemochromatosis can usually be made by the predominantly reticulo-endothelial involvement.

In transfusional hemosiderosis, the appearance of hemosiderin in the epithelial elements occurs at an early stage. This may be partly due to rapid overload of the reticulo-endothelial system because of the short period in which the condition develops. In some cases of transfusional hemosiderosis an identical pattern to that found in hemochromatosis has been described; in others the picture resembles our cases.[35] It is, however, possible that the degree of epithelial involvement in all three conditions may depend on the length of time during which they develop.

The relationship of cirrhosis and hemosiderin deposition has received considerable attention. The presence of increased fibrous tissue in the liver and pancreas in transfusional hemosiderosis has suggested that iron-pigment can produce fibrosis.[11] This view is not held by Wyatt, Mighton, and Moragues.[12] The histograms in Text-figures 1 and 2 show that there is a high incidence of severe hemosiderosis in cirrhotic cases. But of 7 livers with cirrhosis without hemosiderosis, 5 were from patients under 35 years of age, whereas all but 2 of the severely siderotic livers with cirrhosis were in subjects over 40 years. The frequency of both siderosis and hepatic fibrosis increases with age, and the apparent relationship may, accordingly, be fortuitous. Further, it is difficult to explain the lesser degree of siderosis observed in livers from female subjects, if fibrosis and siderosis are causally related.

As iron-laden reticulo-endothelial cells tend to migrate to the hepatic lymphatics,[16] there is possibly a tendency in siderosis for iron pigment to collect in enlarged portal tracts, causing the histologic picture seen in Figures 5 and 6. This might explain the correlation between severe cases of hemosiderosis and cirrhosis. On the other hand the degree of fibrosis in individual portal tracts was unrelated to the amount of iron pigment present in them. In some tracts, only a few iron-laden macrophages were seen; in other tracts in the same section, massive deposits were observed.

It has been stated that in hemochromatosis, fibrosis of the pancreas and spleen is a function of hepatic cirrhosis, and is unrelated to iron deposition.[40] Fibrosis of the spleen, lymph nodes, and intestinal villi was not a feature of our cases and there was no correlation between the degree of siderosis and pancreatic fibrosis, when present. Deposition of hemosiderin does not produce fibrosis in animals.[16,20,21] For these

reasons we agree with Gillman and Gillman[32] that fibrosis cannot be regarded as dependent upon hemosiderin deposition. Further, fibrosis and cirrhosis of the liver are commonly observed in other parts of Africa, where siderosis has not been reported.[36,38,41]

The classification of the non-iron-containing fuchsinophilic pigments in the body is difficult as they show a variety of staining reactions. In Bantu siderosis there is, however, a general increase in fuchsinophilic pigment. We agree, however, with Cappell[42] that the term "haemofuscin" is poorly defined and suggest that until these various pigments have been adequately classified they should be described according to their staining reactions.

ETIOLOGY

The hypothesis that siderosis in the Bantu is due to metallic poisoning[1] has received no confirmation. Sheldon[7] suggested that parasitic infestation may be responsible; but we regard this as unlikely, as has been shown by Gillman and Gillman.[3]

Gillman and associate workers[2-4,32] maintained that malnutrition and pellagra cause hepatic damage, with deposition of hemosiderin in the liver cells (cytosiderosis); later, this is followed by excretion of iron in the bile, with consequent reabsorption and widespread iron deposition (siderosis). Our post-mortem findings, however, indicate that iron deposition is widespread in the reticulo-endothelial system from the beginning, and division into two stages is not possible. Moreover, we wish to reiterate that it is unwise to isolate changes in the liver from those in the rest of the body.

If iron deposition was a feature of pellagra in South Africa, one would expect an approximately similar histologic picture in all cases of acute pellagra on admission to hospital, if the metabolic processes involved were similar in each. This was not reported by these authors, nor has it been our experience. Further, our liver biopsies from patients suffering from many different diseases have shown the same range of histologic pattern.

In undernutrition and starvation, hemosiderin deposits occur in both liver and spleen.[14] This is associated with general atrophy of the organs, and has been ascribed to breakdown of tissue. In our series, many patients were clearly not optimally nourished, but significant visceral atrophy was not observed, even on microscopic examination. In the Japanese series[14] the average weight of the liver was 900 gm., as against 1550 gm. in severe siderosis in this series. Further, one fifth of our patients with marked siderosis were apparently well nour-

ished. While undernutrition and infection may accentuate pre-existing siderosis in the Bantu, we do not consider these factors of major importance in the etiology of the condition.

It has been found that when mice, rats, and dogs are fed a corn grit diet, abnormal deposition of iron occurs, such deposition being aggravated by a high iron intake.[6,23,24] This phenomenon was found to be due almost wholly to a deficiency of phosphorus. We have been able to find no reports of such studies in man. In one case of hemochromatosis examined by Bothwell[43] no effect was noted on iron absorption by the addition of phosphates to the diet. It is doubtful, moreover, whether deficiency of this element could be involved in Bantu siderosis, since the high cereal diet of these people is rich in phosphorus.

Allusion has been made also to the observation that when rats, rabbits, and dogs ingest an abnormally large amount of iron, excessive absorption, retention, and deposition occur, even when the diet consumed is adequate. Walker and Arvidsson[44] reported that large amounts of adventitious iron are frequently present in the diet of the Bantu, as much as 200 mg. per day being ingested. Walker[45] considered that there is enough published experimental evidence in man to show that this intake is sufficiently high to permit unrequired iron to be absorbed, retained, and deposited in the body; and that this may perhaps account for the condition under consideration. Further information is needed, of course, on the effects of malnutrition plus high iron intake on iron absorption in man before this view can be accepted or rejected.

The etiologic fault in hemochromatosis is unknown. Sheldon[7,26] suggested that there is an inborn error of metabolism. Granick[46] put forward the hypothesis of increased iron absorption due to a greater reducing tendency of cells for iron. That such a high absorption does exist in some acute cases has been shown,[47] although this phenomenon may be secondary. Althausen *et al.*[48] did not consider malnutrition to be an etiologic factor. Despite these uncertainties, it will be apparent from evidence presented in this paper that the morbid anatomical pattern of hemosiderosis in idiopathic hemochromatosis is different from that observed in Bantu siderosis. This fact, together with the other points discussed, suggests that it is improbable that the two conditions are due to the same abnormality.

Summary

In the South African Bantu, siderosis is a common phenomenon.

Its morbid anatomical features and the pattern of iron distribution (histologic and chemical) have been described.

It has been suggested that iron storage occurs principally in the reticulo-endothelial system and liver and not until heavy deposits are present in this system does the element appear in the epithelial tissues. This basic pattern of storage in the liver and reticulo-endothelial system continues to be observed, even in severe cases. By contrast, in classical hemochromatosis, iron storage is believed to be mainly parenchymal.

The relationship of hepatic fibrosis to siderosis has been examined. It has been confirmed that varying degrees of portal tract fibrosis in the liver are a frequent incidental observation among Bantu patients. No constant correlation was found between the degree of fibrosis and the amount of iron pigment in the liver. Further, cases of severe siderosis were seen without cirrhosis, and conversely, cases of cirrhosis without siderosis. Fibrosis was not observed in other markedly hemosiderotic organs.

The possible etiology of the condition has been discussed. It is unlikely to be due to metallic poisoning or parasites; it is doubtful whether undernutrition, malnutrition, or pellagra can be regarded as major etiologic factors. The possibility of oral iron overload occurring among these people would seem to merit further investigation. Finally, the different pattern of iron deposition in idiopathic hemochromatosis and Bantu siderosis argues against these conditions having a common etiology.

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REFERENCES

1. Strachan, A. S. Haemosiderosis and Haemochromatosis in South African Natives, with a Comment on the Aetiology of Haemochromatosis. M. D. Thesis, Glasgow, 1929.
2. Gillman, J., Mandelstam, J., and Gillman, T. A comparison of chemical and histological estimations of the iron and copper content of the livers of Africans in relation to the pathogenesis of cytosiderosis and cirrhosis (haemochromatosis). *South African J. M. Sc.*, 1945, 10, 109–136.
3. Gillman, J., and Gillman, T. Structure of the liver in pellagra. *Arch. Path.*, 1945, 40, 239–263.

4. Gillman, J., and Gillman, T. The pathogenesis of cytosiderosis (hemochromatosis) as evidenced in malnourished Africans. *Gastroenterology,* 1947, **8,** 19–23.

5. Gillman, J., and Gillman, T. Perspectives in Human Malnutrition. Grune & Stratton, New York, 1951, pp. 266–273.

6. Finch, C. A., Hegsted, M., Kinney, T. D., Thomas, E. D., Rath, C. E., Haskins, D., Finch, S., and Fluharty, R. G. Iron metabolism. The pathophysiology of iron storage. *Blood,* 1950, **5,** 983–1008.

7. Sheldon, J. H. Haemochromatosis. Oxford University Press, London, 1935, 382 pp.

7a. Bernoulli, E. Ueber Bronzediabetes. *Cor.-Bl. f. schweiz. Aerzte,* 1910, **40,** 610–615.

8. Ryffel, J. H. The amount of iron in the organs in cases of pernicious anaemia. *J. Path. & Bact.,* 1909–10, **14,** 411–413.

9. Stasney, J. Erythrophagocytosis and hemosiderosis in the liver and spleen in sickle cell disease. *Am. J. Path.,* 1943, **19,** 225–237.

10. Kark, R. M. Two cases of aplastic anaemia, one with secondary haemochromatosis following 290 transfusions in nine years, the other with secondary carcinoma of stomach. *Guy's Hosp. Rep.,* 1937, **87,** 343–353.

11. Schwartz, S. O., and Blumenthal, S. A. Exogenous hemochromatosis resulting from blood transfusions. *Blood,* 1948, **3,** 617–640.

12. Wyatt, J. P., Mighton, H. K., and Moragues, V. Transfusional siderosis. *Am. J. Path.,* 1950, **26,** 883–897.

13. Sherlock, S., and Walshe, V. M. Hepatic structure and function. *Medical Research Council, Special Report Series,* No. 275, His Majesty's Stationery Office, London, 1951, pp. 111–134.

14. Aoki, T., and Nakamura, I. Pathological studies on malnutrition, particularly the pathology of the liver and kidney. *Keijo J. Med.,* 1952, **1,** 1–19.

15. Hiyeda, K. The cause of Kaschin-Beck's disease. *Jap. J. M. Sc.,* 1939, **4,** Pt. 5, 91–106.

16. Cappell, D. F. The late results of intravenous injection of colloidal iron. *J. Path. & Bact.,* 1930, **33,** 175–196.

17. Rous, P., and Oliver, J. Experimental hemochromatosis. *J. Exper. Med.,* 1918, **28,** 629–644.

18. Polson, C. J. The fate of colloidal iron administered intravenously. *J. Path. & Bact.,* 1928, **31,** 445–460.

19. Polson, C. J. The fate of colloidal iron administered intravenously. *J. Path. & Bact.,* 1929, **32,** 247–260.

20. Polson, C. J. Failure of prolonged administration of iron to cause haemochromatosis. *Brit. J. Exper. Path.,* 1933, **14,** 73–76.

21. Brown, E. B., Moore, C. V., Reynafarje, C., and Smith, D. E. Intravenously administered saccharated iron oxide in the treatment of hypochromic anaemia; therapeutic results, potential dangers and indications. *J. A. M. A.,* 1950, **144,** 1084–1089.

22. Polson, C. J. The storage of iron following its oral and subcutaneous administration. *Quart. J. Med.,* 1929–30, **23,** 77–84.

23. Kinney, T. D., Hegsted, D. M., and Finch, C. A. The influence of diet on iron absorption. I. The pathology of iron excess. *J. Exper. Med.,* 1949, **90,** 137–146.

24. Hegsted, D. M., Finch, C. A., and Kinney, T. D. The influence of diet on iron absorption. II. The interrelation of iron and phosphorus. *J. Exper. Med.*, 1949, **90**, 147–156.

25. Feder, I. A., Gitman, L., and Hoffman, J. B. Hemochromatosis. *Rev. Gastroenterol.*, 1950, **17**, 1048–1057.

26. Sheldon, J. H. Haemochromatosis. In: British Encyclopaedia of Medical Practice. Butterworth, London, 1951, ed. 2, **6**, 130.

27. Roth, O., Jasiński, B., and Bidder, H. v. Das Gewebeeisen beim Menschen bei normalen und pathologischen Zuständen. *Helvet. med. acta*, 1951, **18**, 159–174.

28. Dry, D. S. Improved methods for the demonstration of mitochondria, glycogen, fat and iron in animal cells. *South African J. Sc.*, 1945, **41**, 298–301.

29. Squires, B. T. Serum iron in the Tswana (Bechuanaland). *South African J. M. Sc.*, 1952, **17**, 1–2.

30. Gerritsen, T., and Walker, A. R. P. Serum iron and iron-binding capacity in the South African Bantu. *Nature, London*, 1953, **171**, 699.

31. Bothwell, T. H., van Lingen, B., Alper, T., and du Preez, M. L. The cardiac complications of hemochromatosis. *Am. Heart J.*, 1952, **43**, 333–340.

32. Gillman, J., and Gillman, T. Liver disease in Johannesburg; relation to pellagra. *Lancet*, 1948, **1**, 169–173.

33. Vogt, J. H. Hemochromatosis. *Acta path. et microbiol. Scandinav.*, 1944, **21**, 461–471.

34. Gillman, T., and Ivy, A.C. Histological study of participation of intestinal epithelium, reticulo-endothelial system and lymphatics in iron absorption and transport; preliminary report. *Gastroenterology*, 1947, **9**, 162–169.

35. Graef, I., Gordon, B. S., Newman, W., Olivetti, R. G., and Klein, B. Observations in exogenous hemochromatosis apparently due to multiple transfusions. (Abstract.) *Am. J. Path.*, 1952, **28**, 538–539.

36. Vint, F. W. Cirrhosis of the liver in the East African native. *Kenya & East African M. J.*, 1931, **7**, 349–374.

37. Davies, J. N. P. The essential pathology of kwashiorkor. *Lancet*, 1948, **1**, 317–320.

38. Davies, J. N. P., and Trowell, H. C. Haemosiderosis in the African. *Brit. M. J.*, 1951, **1**, 1514.

39. Rechenberger, J., and Schairer, E. Leber- und Milzeisen bei verschiedenen Infektionskrankheiten. *Virchows Arch. f. path. Anat.*, 1948, **315**, 326–340.

40. Herbut, P. A., and Tamaki, H. T. Cirrhosis of the liver and diabetes as related to hemochromatosis. *Am. J. Clin. Path.*, 1946, **16**, 640–650.

41. Davies, J. N. P. Primary carcinoma of the liver in Uganda Africans. *East African M. J.*, 1952, **29**, 413–414.

42. Cappell, D. F. (ed.) Muir's Textbook of Pathology. Arnold, London, 1951, ed. 6, p. 162.

43. Bothwell, T. H. Personal communication.

44. Walker, A. R. P., and Arvidsson, U. B. Iron intake and haemochromatosis in the Bantu. *Nature, London*, 1950, **166**, 438–439.

45. Walker, A. R. P. Absorption of iron. *Brit. M. J.*, 1951, **1**, 819–820.

46. Granick, S. Iron metabolism and hemochromatosis. *Bull. New York Acad. Med.*, 1949, **25**, 403–428.

47. Alper, T., Savage, D. V., and Bothwell, T. H. Radioiron studies in a case of hemochromatosis. *J. Lab. & Clin. Med.*, 1951, **37**, 665–675.

48. Althausen, T. L., Doig, R. K., Weiden, S., Motteram, R., Turner, C. N., and Moore, A. Hemochromatosis; investigation of twenty-three cases, with special reference to etiology, nutrition, iron metabolism, and studies of hepatic and pancreatic function. *A. M. A. Arch. Int. Med.*, 1951, **88**, 553–570.

49. Rath, C. E., and Finch, C. A. Chemical, clinical, and immunological studies on the products of human plasma fractionation. XXXVIII. Serum iron transport. Measurement of iron-binding capacity of serum in man. *J. Clin. Investigation*, 1949, **28**, 79–85.

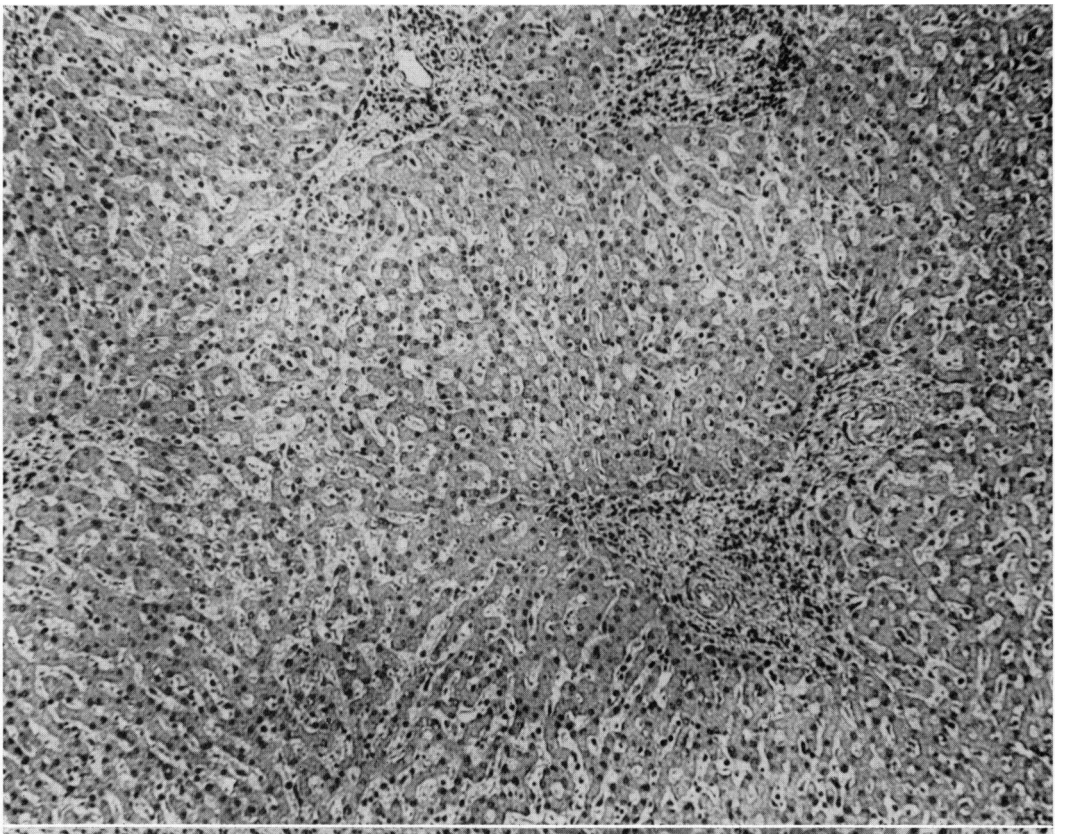
LEGENDS FOR FIGURES

Unless otherwise stated, all sections are stained for iron-containing pigment by hot potassium ferrocyanide and hydrochloric acid, and counterstained with basic fuchsin.

FIG. 1. Section of liver showing the slight portal fibrosis which is common among Bantu patients. Hematoxylin and eosin stain. × 105.

FIG. 2. Fine multilobular cirrhosis in non-pigmented liver. Hematoxylin and eosin stain. × 105.

1



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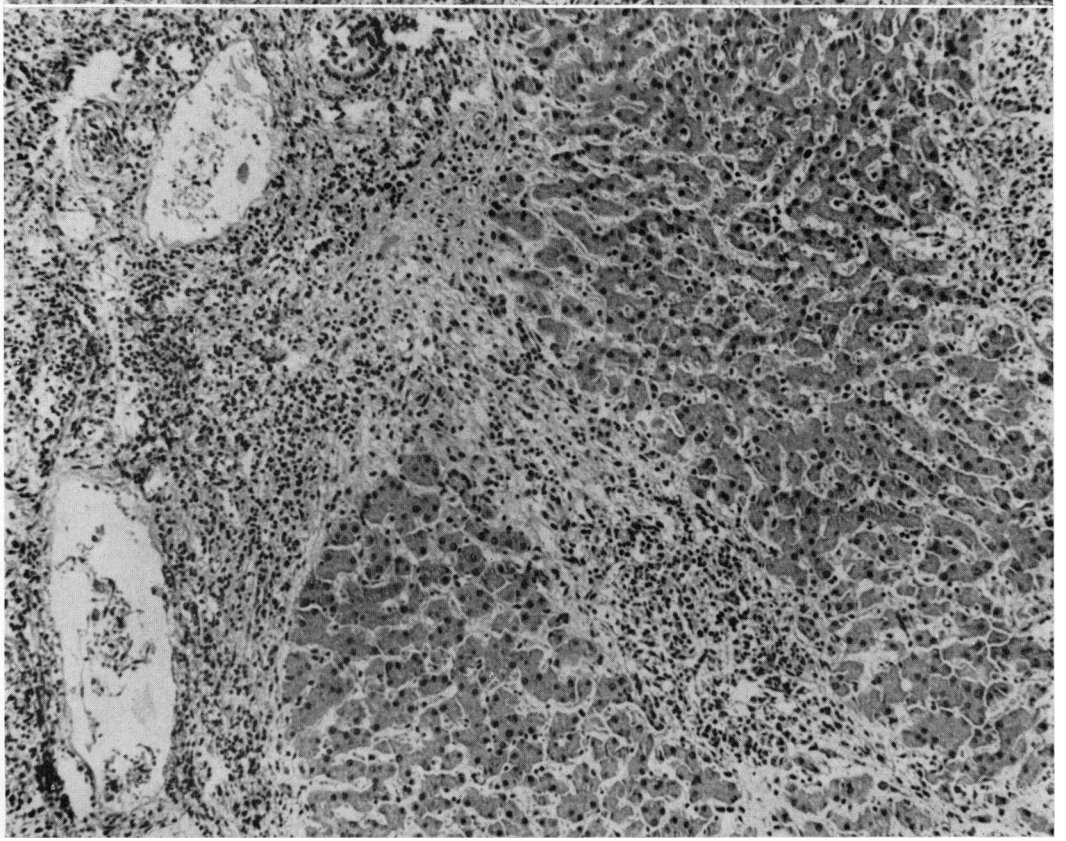
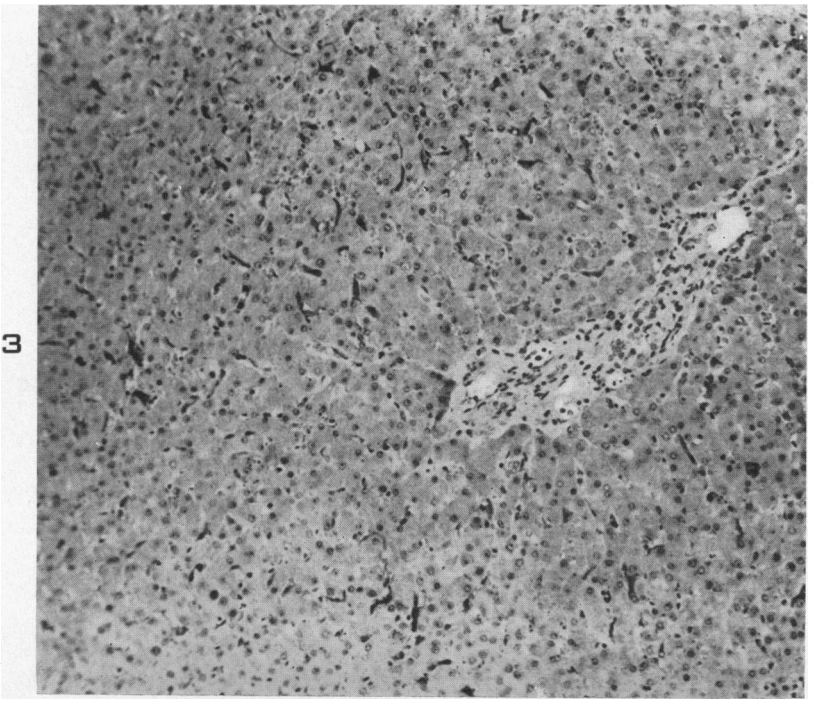
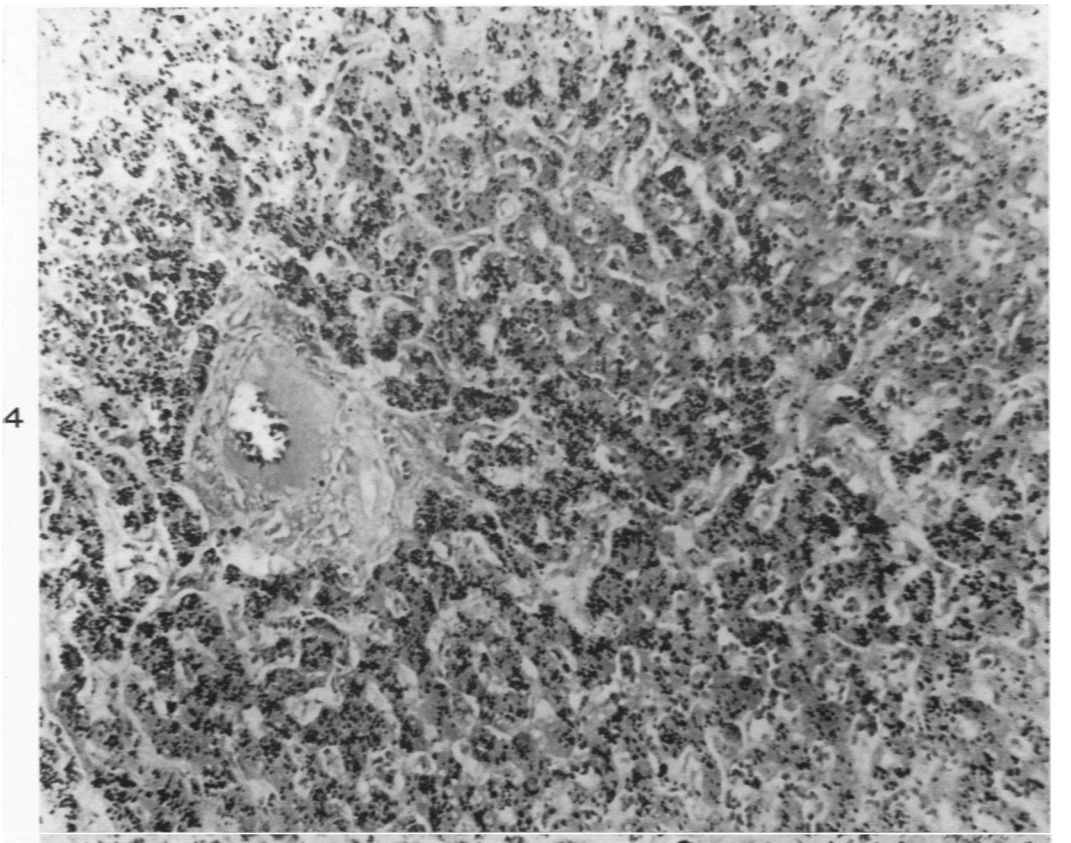


FIG. 3. Section of liver from case 14. Hemosiderin is almost entirely confined to the Kupffer cells. The spleen in this patient showed moderate iron pigmentation. × 140.

FIG. 4. Large hemosiderin granules filling the parenchymal cells of the liver. This liver was classified as structurally normal. × 180.

FIG. 5. This section shows Kupffer cells containing dense masses of hemosiderin lying in the sinusoids of the liver. In addition, heavy deposits of intracellular and extracellular pigment are present in the portal tracts. × 180.





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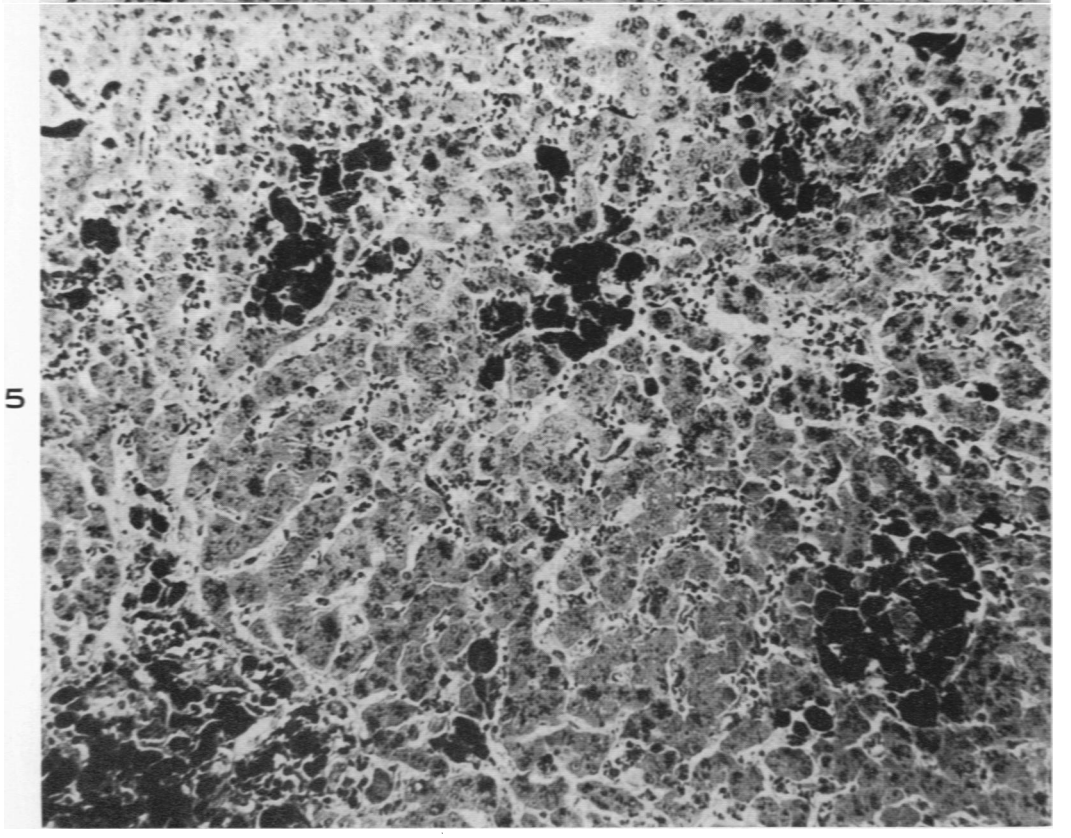

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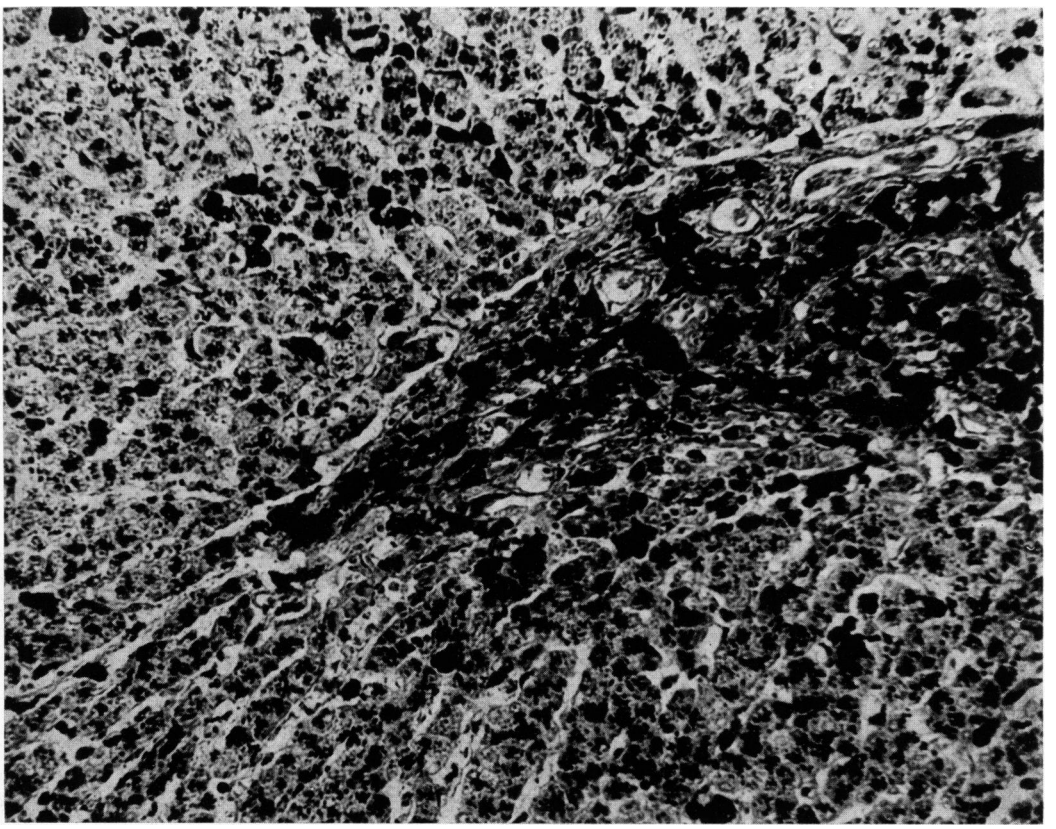
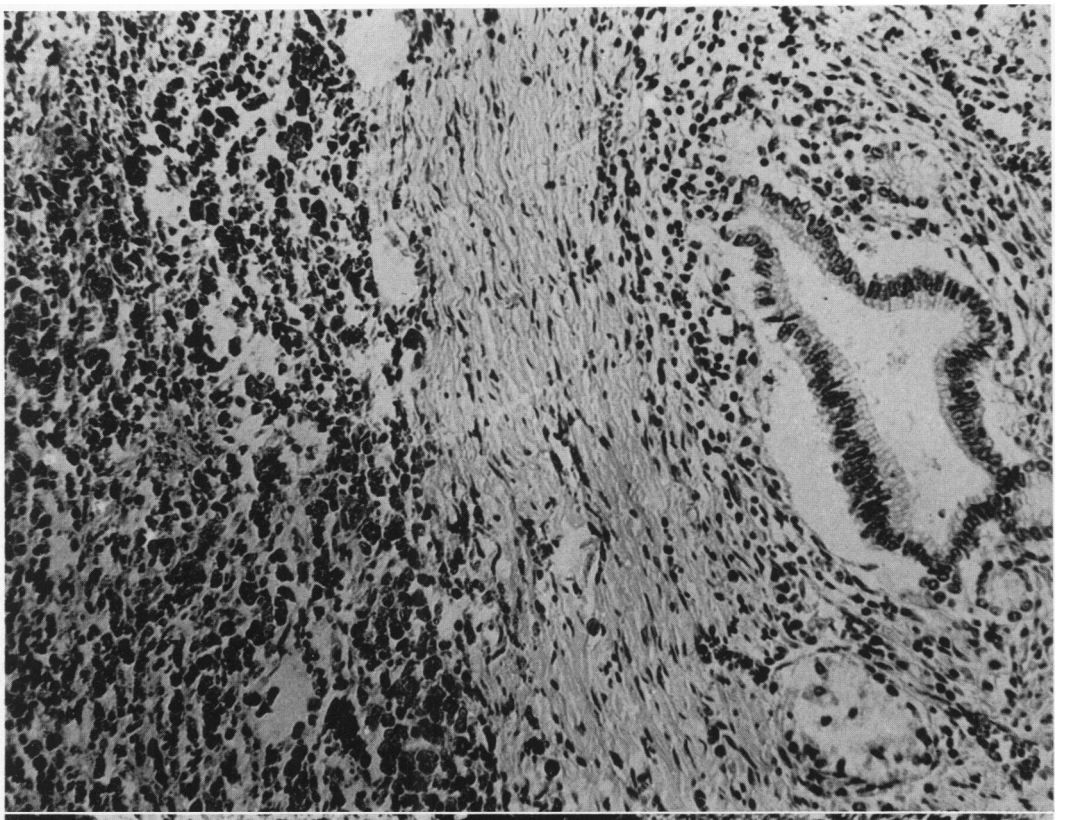
FIG. 6. Severe siderosis of cirrhotic liver (case 25). × 210.

FIG. 7. Infiltration of hemosiderin-laden macrophages into an area of fibrous scarring in the liver. Hematoxylin and eosin stain. × 210.

FIG. 8. Dense masses of hemosiderin in splenic pulp. × 210.





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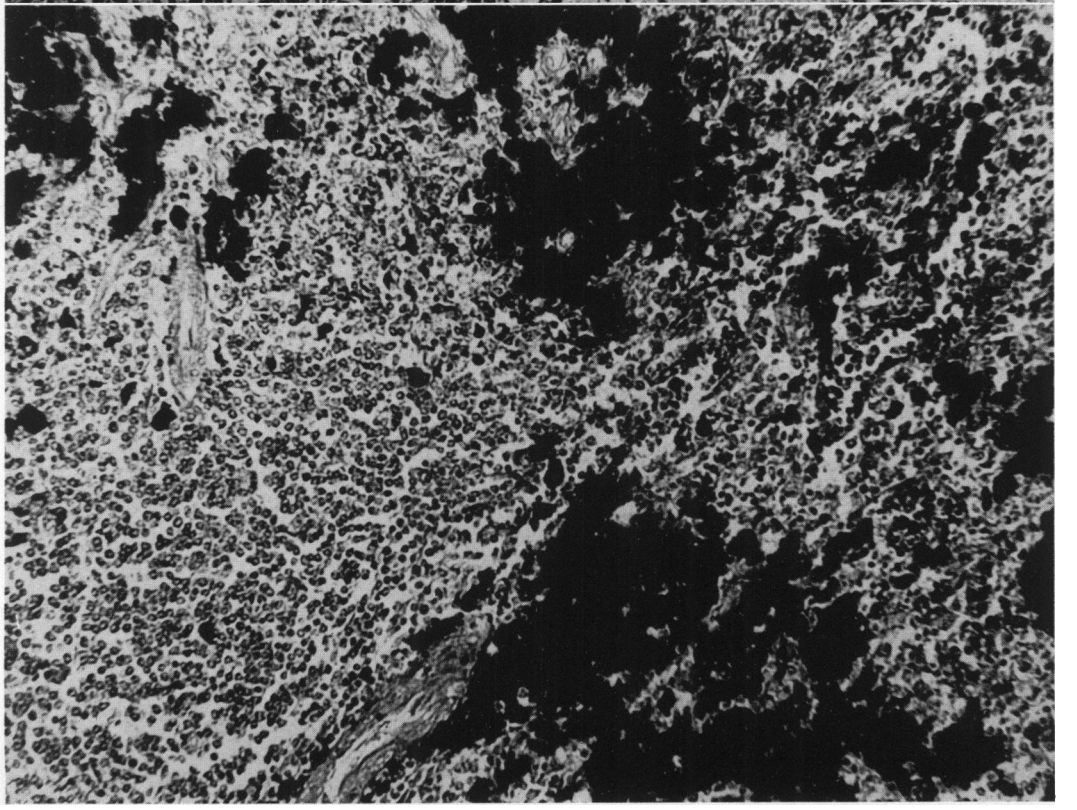

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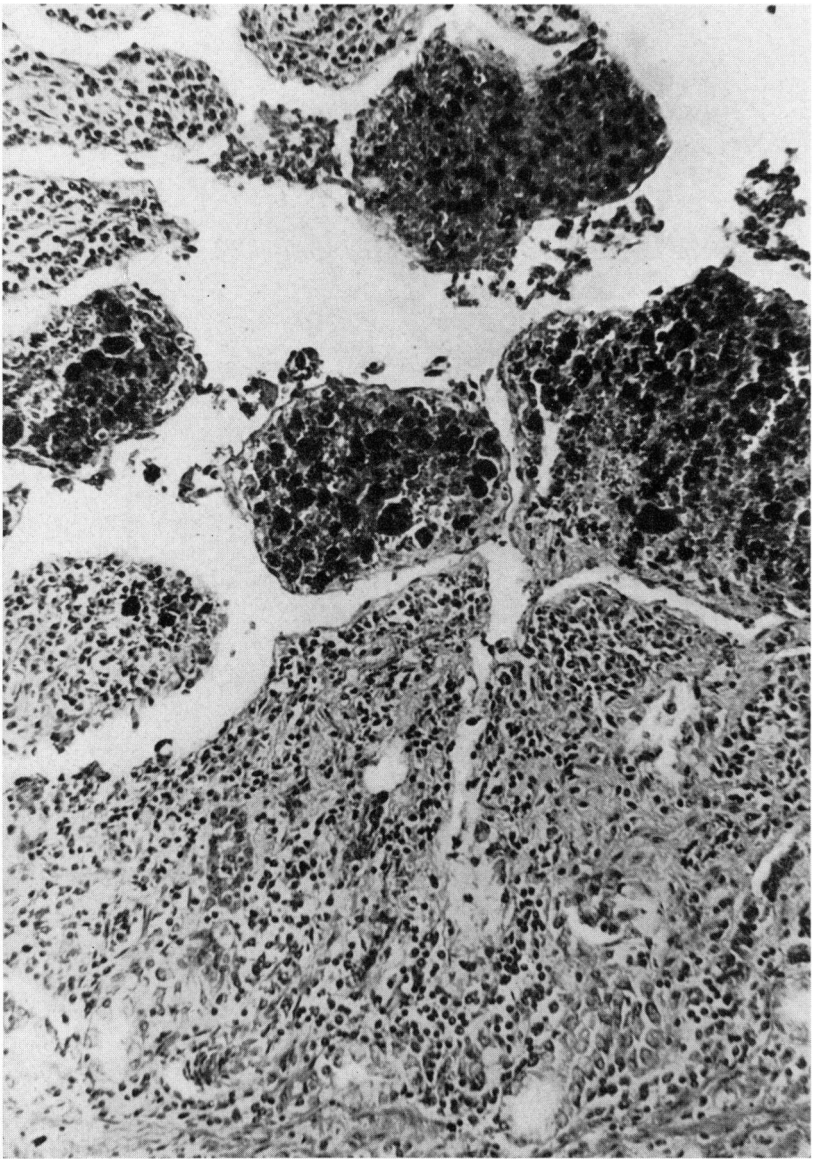
FIG. 9. Heavy hemosiderin deposits in substantia propria of duodenal villi. No pigment was found in Brunner's glands. × 180.

FIG. 10. Low-power view of duodenum and draining lymph glands. There are heavy deposits of hemosiderin in mucosa and glands. Same case as that from which Figure 9 was derived. × 20.

FIG. 11. Dense masses of hemosiderin in portal lymph gland. The lymph follicle is relatively unaffected. × 180.



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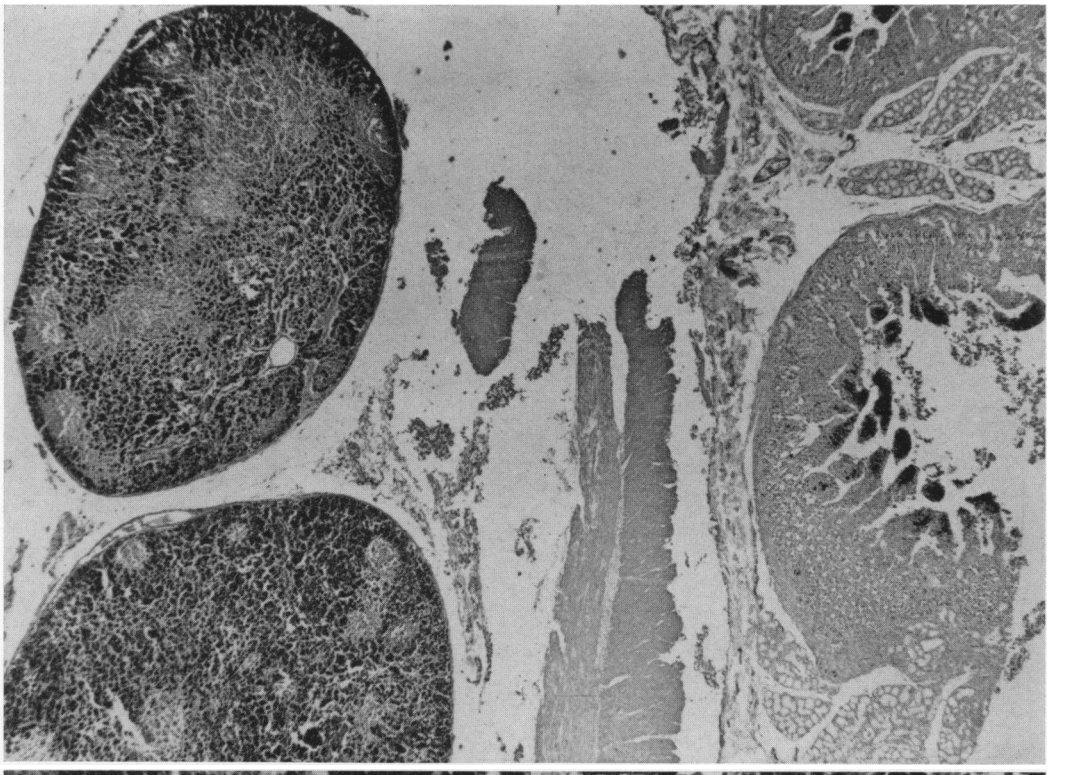

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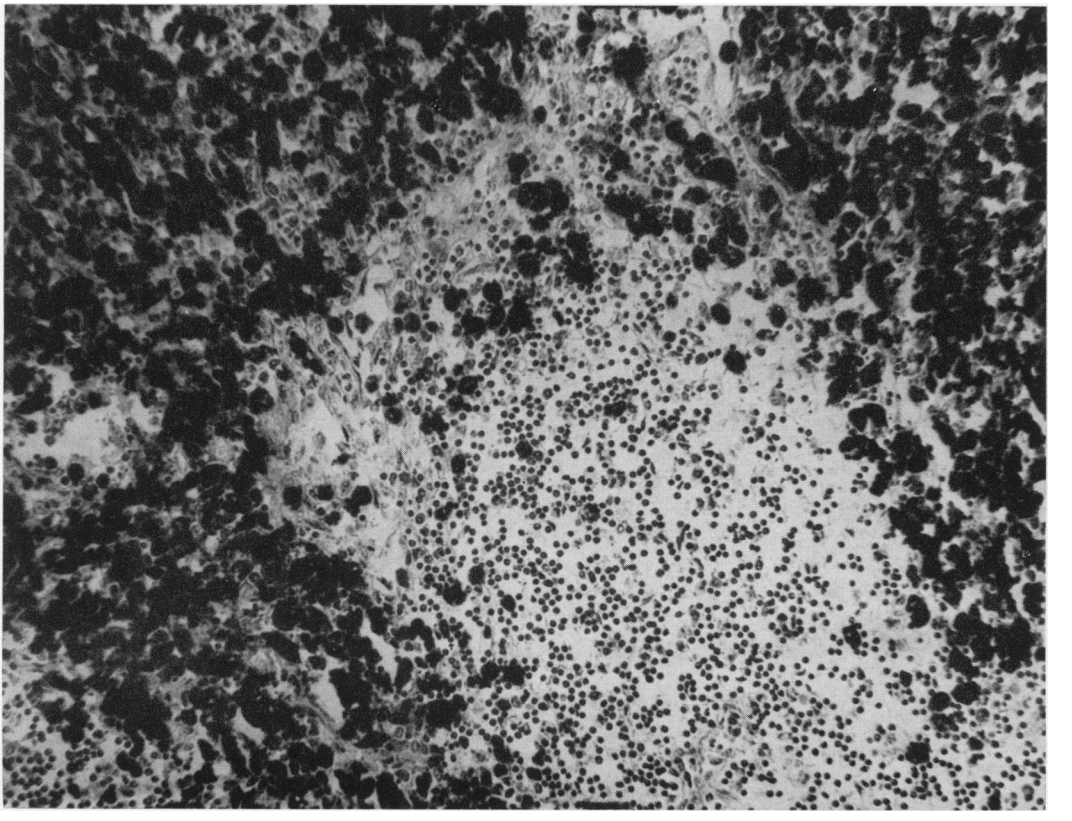

FIG. 12. Hemofuscin pigment in cells of muscularis mucosae of the stomach. Periodic acid Schiff's stain. × 1200.

FIG. 13. Submucosal lymphatic in jejunum. The pigment (A) is hemosiderin; the finer granules (B) are fuchsinophilic pigment. × 525.

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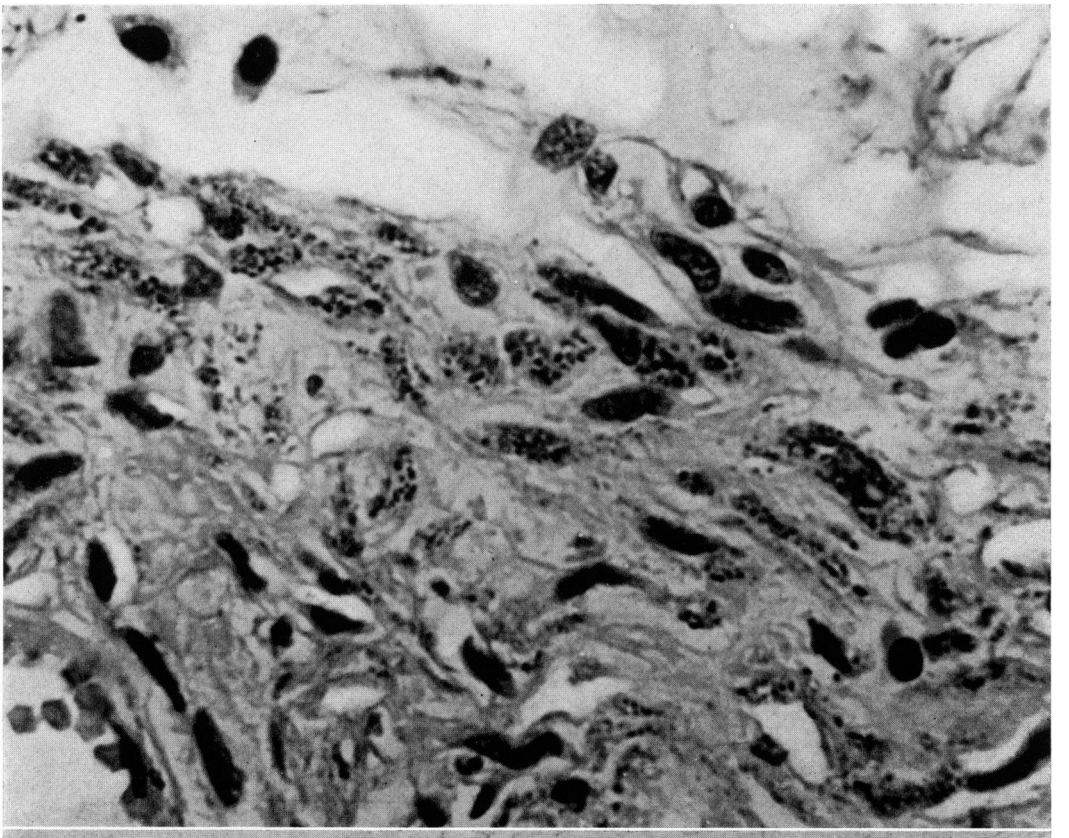

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