

URINARY SIDEROSIS.

HEMOSIDERIN GRANULES IN THE URINE AS AN AID IN THE DIAGNOSIS OF PERNICIOUS ANEMIA, HEMOCHROMATOSIS, AND OTHER DISEASES CAUSING SIDEROSIS OF THE KIDNEY.

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PLATES 71 TO 76.

(Received for publication, June 17, 1918.)

The siderosis produced in rabbits by transfusions repeated over a long period¹ has as one of its features a pronounced pigmentation of the kidney parenchyma comparable with that encountered in the hemo-chromatosis of human beings. Great numbers of yellow-brown granules which react positively for iron are present in the cells of the convoluted tubules and the loops of Henle. They are also to be found lying free in the lumen of the tubules, and embedded in casts. This fact suggested a search for hemosiderin granules in the urine of patients with pigmentation of doubtful origin. A test case soon came to hand.

A soldier, aged 46, was admitted to the Hospital of The Rockefeller Institute November 22, 1917. He complained of weakness, loss of weight, sugar in the urine, and swelling of the legs. One brother had died of diabetes at the age of 49. The patient himself had always been strong and well, save for appendicitis relieved in 1900 by operation. A Neisser infection in 1898 was followed by a stricture which yielded to treatment. Lues was denied. The present illness may be said to have begun in 1908, when, following 3 days of hard physical exertion, with loss of sleep, there occurred a sudden edema of the legs. The patient was in bed only a week, and the trouble did not reappear.

In December, 1916, the patient's friends noted that his skin was turning gray. He consulted a physician, who found sugar in the urine. Fasting, followed by a low diet, caused the sugar to disappear; and the patient's weight and strength, which had somewhat diminished, were restored. He entered the army service in

¹Rous, P., and Oliver, J., *J. Exp. Med.*, 1918, xxviii, 629.

July, 1917, feeling well at that time, but soon began to have swelling of the feet and legs and shortness of breath. The division surgeon found sugar in the urine.

When admitted to the Hospital for treatment by Dr. Allen, the patient was not very ill. He was lean rather than emaciated. The skin of the face and of the back of the hands was somewhat freckled and looked weather-beaten, but more notable was a uniform, light, dusky gray pigmentation of these parts. The remaining body surfaces had no unusual tint, and the mucous membrane of the mouth was normal looking.

Physical examination disclosed a myocarditis, an enlarged, firm liver, ascites, and well marked edema of the feet and legs. The arteries were thickened. The liver edge was 9 cm. below the costal margin in the mm. line, very sharp and firm, and the surface of the organ was smooth, hard, and somewhat bulging. The spleen could not be felt. There was a well marked scar on the glans penis, but the Wassermann reaction was negative. The knee jerks were absent. The urine showed a large amount of sugar, but the ferric chloride test was negative. No albumin or casts were found.

The blood pressure was very low and so remained throughout the several months of hospital observation, ranging between 80 and 104 mm. systolic, and 46 to 70 mm. diastolic. There was a slight anemia: a hemoglobin averaging 85 per cent Sahli, with 4,400,000 red blood corpuscles per c.mm. Reticulated cells were rare on the one examination made, averaging 1 per thousand.

The diagnosis lay between syphilis, favored by the venereal history, genital scar, thickened vessels, absence of the knee jerks, and perhaps also by the enlarged liver, and the diabetes; Addison's disease, as indicated by the pigmentation, low blood pressure, and asthenia; and hemochromatosis, suggested by the combination of enlarged liver, pigmentation, and diabetes. Addison's disease was judged to be most likely.

Urinary Findings.

A fresh specimen of the urine was centrifugated and the slight sediment examined for hemosiderin. It consisted almost entirely of large cells containing numerous coarse, yellow-brown granules (Figs. 1 and 2). Often these granules were as big as red corpuscles, and had then the appearance of having been formed out of several smaller lumps. They were solid looking, moderately refractile, and of irregular shape, in distinction from the rounded, smooth globules of greenish yellow fat, sometimes met with them. Many of the cells were breaking down, and numerous free granules and larger lumps of the pigment were noted. All, both free and intracellular, turned a brilliant black

when submitted to ammonium sulfide, blue with potassium ferrocyanide and hydrochloric acid, and blue too in fixed specimens treated according to Nishimura's method.² There could be no doubt that they were composed of hemosiderin. The urine contained no blood, bile, urobilin, albumin, or casts.

The examination of the urine was repeated many times during the next 3 months. The output of hemosiderin granules was regularly abundant, and cells heavily pigmented with them were always obtained in large number from 20 cc. of urine. Control specimens from forty-four patients variously ill were searched for iron by the same methods. With one exception, which may be attributed to artefact, intracellular hemosiderin was found only in diseases involving, like *diabète bronzé*, a true siderosis of the kidney parenchyma. The diseases referred to are pernicious anemia and chronic hemolytic jaundice. In view of these results, the diagnosis of hemochromatosis seemed warranted in the case just described.

Autopsy Findings.

The patient died on April 3, 1918, 3 months after hemosiderin had first been recognized in the urine. Treatment had caused the urinary sugar to disappear promptly and permanently, but hyperglycemia had persisted. There was a gradually increasing edema of the legs and scrotum, with ascites and double hydrothorax; and death ensued from cardiac insufficiency. In the last weeks of life the cutaneous pigmentation became slightly more marked.

An autopsy, 1½ hours after death, performed by the author, disclosed the characteristic lesions of hemochromatosis. The anatomical diagnosis was as follows:

Myocarditis; hemochromatosis with pronounced pigmentation of the liver, pancreas, heart, abdominal lymph nodes, spleen, kidneys, thyroid, mesentery, skin, and other organs; cirrhosis of the liver and pancreas; chronic passive congestion of the liver, spleen, and intestines; ascites; hydrothorax; anasarca; fresh infarct of the lung; old infarcts of the kidneys.

²Nishimura, J., *Centr. allg. Path. u. path. Anat.*, 1910, xxi, 10.

The condition of the kidneys has special interest. There were present a few scattered, wedge-shaped areas of local atrophy and connective tissue overgrowth, the result of old infarcts. The general siderosis, though pronounced, was limited to certain groups of cortical elements, notably the distal convoluted tubules (Fig. 3). Here the parenchymal cells were heavily laden with iron-containing pigment, and some had desquamated, while others had broken down *in situ*, liberating pigment granules into the lumen of the tubules (Fig. 4). The cells of the ascending portion of Henle's loop were also pigmented, but less so; and in many of the glomeruli were cells containing numerous fine, hemosiderin granules. The remainder of the kidney was non-pigmented, save for occasional free cells and granules in the lumen of the collecting tubules. The distribution in the organ of the hemosiderin was precisely that which Gaskell and his associates³ have described and deem characteristic of hemosiderosis.

Method of Search for Hemosiderin.

The following routine method of search for hemosiderin in the urine has proved satisfactory.

A fresh specimen of the urine, preferably warm from the body, is centrifugated at high speed and the supernatant fluid poured off as completely as possible. The sediment is suspended in the trace of fluid that remains, and slide preparations are gone over microscopically for suggestive orange or brown granules, more particularly in the cells. A mechanical stage should be used and 10 minutes at least given to the search. As a rule the sediment from a 20 cc. specimen will yield a fair number of cells from the higher portions of the urinary tract, but often that from 60 to 100 cc. must be obtained. Occasionally, in urine allowed to cool prior to centrifugation, the nubecula is copious and prevents proper concentration of the formed elements. When this is the case, a specimen should be centrifugated as soon as voided. Kept urines which have become cloudy with urates may be cleared by warming. To search a heavy crystalline sediment, or one poor in cells, or containing only leukocytes and squamous epithelium is time wasted. Catheterized specimens are necessary from female patients, since hemosiderin may come into the urine from the genital tract.

The remainder of the sediment is suspended in a fresh mixture of 5 cc. each of 2 per cent potassium ferrocyanide and 1 per cent hydrochloric acid. After 10

³Gaskell, J. F., Sladden, A. F., Wallis, R. L. M., Vaile, P. T., and Garrod, A. E., *Quart. J. Med.*, 1913-14, vii, 129.

minutes it is thrown down with the centrifuge, the fluid poured off as before, a drop of the sediment mixed on the slide with a drop of the hydrochloric acid solution, and a cover-slip put on. By this modification of Perl's reaction the cells are well preserved and are largely cleared, as are the granular casts. Often the hemosiderin will begin to turn blue as soon as the acid has been added, but, if not, the preparation should be looked at repeatedly in the course of the next half hour. Usually there is present a little foreign debris which turns blue, giving an indication of when a positive finding may be expected. As in the case of the fresh sediment at least 10 minutes of search should be given to the preparation.

The use of a more certain method to demonstrate iron, namely that of Nishimura,² is often necessary. It is well known that hemosiderin in the tissues frequently fails to yield Perl's reaction, or to turn black with ammonium sulfide. This is likewise true of urinary hemosiderin. In several pernicious anemia cases suggestive looking orange granules were seen in the fresh, urinary sediment which proved refractory to the ordinary tests but were promptly shown to be iron-containing by the Nishimura procedure. The examination of fresh sediment assumes in this relation considerable importance as indicating that the search for iron should be persevered in. On the other hand, a failure to find suggestive pigment in the fresh specimen does not rule out the presence of iron. The ferrocyanide test has several times disclosed intracellular iron granules so minute or so surrounded by fat globules as not to attract attention in the fresh specimen. By Nishimura's method such instances are found even more often.

For the Nishimura test the fresh sediment, as free as possible from urine, is mixed with a little human serum untinted with hemoglobin and thick films are made and dried. These are fixed by heat, placed in strong ammonium sulfide for 1 hour, washed briefly with water, and subjected for 20 minutes to a fresh mixture of 2 per cent potassium ferrocyanide and 1 per cent hydrochloric acid in equal parts. After another brief rinsing with water the preparations are stained in lithium carmine for a few minutes, differentiated in acid alcohol (1 per cent hydrochloric acid), and run rapidly through 95 per cent alcohol, absolute alcohol, xylol, and mounted in balsam. The acid alcohol differentiates the red of the carmine and turns the iron granules a deep blue. Its action should be carefully followed with the microscope, since if prolonged it will dissolve the iron, or at least cause the blue tint of the latter to run and fade. Nishimura carried out two separate differentiations with acid, the first immediately after the ferrocyanide in order to bring out the blue of the iron reaction. But under these circumstances the subsequent action of the acid alcohol tends to destroy the blue color. A single differentiation is more satisfactory.

By this method permanent mounts are obtained to be looked over at leisure. The iron granules stand out in deep blue against the general carmine tint. Less satisfactory preparations may be had by submitting the films to ammonium sulfide and staining thereafter with carmine. Such hemosiderin granules as may react with the sulfide will then appear black. They lose their color rapidly in acid alcohol, so differentiation of the carmine should not be attempted with it.

Specimens left with preservatives prior to examination have proved unsatisfactory. Toluene permits autolysis of the cells, and formalin renders hemosiderin refractory to the ferrocyanide test and at length dissolves it. We have repeatedly found specimens which were negative, preserved with formalin and known to contain iron. Acid also dissolves the pigment, and it need not be looked for in very acid urines save when freshly voided. In old ammoniacal specimens it is remarkably stable and may persist undissolved for several days.

Findings in Pernicious Anemia.

The urines were examined of ten undoubted cases of pernicious anemia. In an eleventh case no proper search for iron could be made because of the heavy sediment of pus corpuscles, etc., incident to a cystitis. In two instances no hemosiderin was found. Repeated search was made of specimens from one of these having the history of a year's illness and a moderate anemia (red blood corpuscles 3,160,000; hemoglobin 69 per cent (Palmer)). In the other case the disease had lasted 3 years, during which period seventeen transfusions had been given. A single specimen only was searched for iron.

Intracellular hemosiderin was found in the urines of all the eight remaining instances, though not always easily. In two a careful search was necessary of specimens stained by the Nishimura method. The cells containing iron were very few and the pigment granules minute (Figs. 5 and 6). In a third instance Perl's reaction, applied to the fresh sediment, disclosed fairly frequent cells containing many fine, blue granules, half obscured amid fat droplets. In the five remaining instances a surprisingly large amount of hemosiderin was found (Figs. 7, 8, and 9). It attracted attention at once in the unstained sediment. Multitudes of fine, brownish, or orange-yellow, granules were seen, grouped in cells, scattered in casts, and more particularly lying free in large numbers. Save in one case, they were much smaller than in the urine of the patient with hemochromatosis already described, as would naturally follow from the relative intensity of the siderosis in the two diseases. From one to fifty or more granules were present in a single cell. They were spherical and remarkably regular in size in different specimens from the same patient, being usually somewhat smaller than eosinophil granulations. Occasionally they had cohered into lumps. The cells containing them were irregularly globular or

cylindrical, slightly larger than leukocytes, as a rule, with a vesicular nucleus of moderate size. Often they were much degenerated and contained myelin or fat. In two cases the modified ferrocyanide test caused the entire sediment to turn bright blue to the naked eye. With the microscope the color was found to be localized in innumerable, sharply defined deep blue granules. In the other instances with abundant hemosiderin the response to the test was only partial, a few of the granules turning blue or green. But with the Nishimura method all of the pigment was shown to be iron-containing.

Hemosiderin was never found in the squamous epithelium or in tailed cells from the bladder. Part, at least, of what was free in the urine obviously came from disintegrating cells. Indeed, the presence in the fresh sediment of small aggregates of orange-yellow granules held together by a remnant of cytoplasm proved significant. In the casts the granules were ordinarily few and widely separated.

A few of the urines showing iron in quantity had the deep, smoky color and the general characters usual in severe pernicious anemia. Others were pale, free from albumin, and seemed normal. No definite relationship could be worked out between the output of pigment granules and the duration and severity of the disease. The fact that pernicious anemia may long exist unsuspected has not improbably much to do with this. The findings in the individual case were remarkably constant from day to day. In one very sick patient, followed through $2\frac{1}{2}$ months, the hemosiderin output remained abundant. This was the exceptional case above mentioned, in which the granules were almost as large and abundant as in the patient with hemochromatosis.

Findings in Hemolytic Jaundice.

Through the courtesy of Dr. George Minot of Boston it was possible to examine the urine of a carefully studied, typical case of hemolytic jaundice of the acquired type. The patient, a male, aged 28, had been more or less jaundiced since the age of 16, following what he understood was an attack of malaria with enlarged spleen. The spleen is still greatly enlarged, but the jaundice is slight, the health excellent, and the blood in good condition. At the time when the urine was searched for iron the blood showed a hemoglobin of 102 per cent Sahli,

but the red cells were rather unequal in size, with many macrocytes and about 6 per cent of reticulated corpuscles. In the urine free hemosiderin was present in quantity, and there were numerous cells stippled with it. Most of the pigment responded readily to Perl's test. The intracellular granules were small, about the size of those usual in pernicious anemia, but much of the free pigment was in coarse, brown lumps. A cast was seen so colored with these as to resemble a miniature cigar.

Findings in Control Cases.

In none of thirty-three control cases, many of them with blood derangements, were such findings as the above obtained. In the fresh urinary sediment the numerous rounded, free, orange or brown granules were lacking, save in one notable instance to be discussed further on, and clumps of them held together by disintegrating cytoplasm were never observed. Pigmented cells, on the other hand, were fairly common. Often they were tinted a diffuse yellow or contained many fine, superimposed, greenish yellow fat droplets. Large yellow or orange-brown globules were also encountered sometimes. In general they were of a fatty or lipoid nature as indicated by their high refractility, smooth outline, resistance to acid, variation in size; and as proved finally by the Scharlach R stain. But occasionally intracellular granules were seen, indistinguishable in the fresh from hemosiderin but negative to microchemical tests. According to Aschoff,⁴ an orange pigment, which fails to react for iron, is often present in the kidney cells of old people. A very fine crystalline deposit, furthermore, may simulate hemosiderin granules, free and in casts. Siderosis of the urine cannot be recognized with certainty from the fresh specimen alone. Microchemical tests must always be employed. In this connection it has been interesting to discover that Hunter⁵ in 1889 published a note on a granular pigmentation of the cells and casts in the urine of a patient with pernicious anemia. From his description there is no reason to doubt that he had to do with a true siderosis, as was his own conviction. But he made no attempt to demonstrate iron by microchemical tests or to examine the urine of controls. His observa-

⁴ Aschoff, L., *Pathologische Anatomie*, Jena, 2nd edition, 1911, ii, 431.

⁵ Hunter, W., *Practitioner*, 1889, xliii, 321.

tion has never been followed up, probably because orange and brown granules are so frequently encountered in urines taken at random.

In one control urine a single cell was found containing iron in the form of several coarse lumps which gave Perl's reaction readily. The urine was an uncatheterized specimen from a woman with a poorly compensated cardiac lesion. No free hemosiderin granules were seen, and a second specimen carefully searched was entirely negative, as was the urine of several other heart cases. In view of the character of the granules and the general circumstances of the case it seems probable that the cell came from the genital tract. The finding emphasizes the necessity for catheterized specimens from female patients.

In another control instance much free hemosiderin was present in the urinary sediment but none in the cells. The patient had a chronic nephritis in the terminal stage with extreme anemia and constant slight bleeding from the mucous surfaces. The urine, of pale straw color, gave a weakly positive guaiac reaction, and a small number of red cells were present in the sediment. This latter contained numerous aggregates of very fine, rounded, slaty brown granules, which reacted positively to the tests for iron. In a second and catheterized specimen obtained 2 days later no red cells or shadows were seen, and there was only the faintest blue coloration on test with guaiac, yet the clusters, or aggregates, of hemosiderin granules were still present. The most careful search failed to reveal any cells containing such granules.

Some of the control cases deserve special mention. Three had the diagnosis of pernicious anemia on admission to hospital treatment, at which time the urine was examined. All had an extremely severe anemia, necessitating transfusion, a high color index, and in two instances a profusion of nucleated red cells were in circulation. One of the cases, that of chronic nephritis, has just been discussed. The other two, with urines negative for both free and intracellular hemosiderin, proved on study to be instances of secondary anemia, one subsequent to a severe purpura, the other associated with chronic malnutrition. The urinary findings were negative also in a patient with chronic polycythemia, and in two instances of Hodgkin's disease with great, progressive anemia.

DISCUSSION.

The presence of hemosiderin granules in the urine seems to have been overlooked heretofore. It is advisable to make a sharp distinction between the intracellular and free pigment, since there is probably a difference in their significance. True, when the granules are found inside urinary cells, free granules are regularly present also, and usually in far greater number. But free hemosiderin has been found alone in the urine of a nephritic patient whose condition presumably did not involve siderosis of the renal cells. Furthermore, extraneous material may easily be mistaken for free hemosiderin by the inexpert. Bits of foreign detritus frequently respond to the test for iron. As a rule, they are coarse and very different in appearance from the finely granular, true pigment.

The free hemosiderin granules occurring in the urine of patients with a true siderosis of the kidney are obviously of intracellular derivation as a rule. The granules have the size and appearance of those in the accompanying cells, and often a remnant of cytoplasm is attached to them or holds together a number of them in its matrix. The rest lie scattered broadcast in the sediment. In one instance, though, the free hemosiderin was of very different character, resembling that in the urine of the nephritic above mentioned. The granules, which were extremely minute, formed aggregates or clusters, sometimes of many hundreds, lying here and there in the urinary sediment (Fig. 10). Intracellular granules were rare. The findings varied little from day to day. The patient, a woman with severe pernicious anemia, had not been transfused, and there was no blood in the urine (guaiac reaction). A possible origin of the pigment from the genital tract was ruled out by catheterization. The inference would seem to be that in this case, as also in the nephritic, hemosiderin was circulating in solution within the body and was directly excreted by the kidney. This assumption is contrary to the general view, according to which during life hemosiderin arises only in cells, and as a granular solid limited to them or their neighborhood.⁶ The problem presented is now under investigation in animals.

⁶ Brown, W. H., (*J. Exp. Med.*, 1910, xii, 623) has demonstrated that free hemosiderin may be formed in the blood vessels of the autolyzing liver.

The evidence seems convincing that the presence of cells containing hemosiderin in urine obtained under proper precautions is the expression of an actual siderosis of the kidney parenchyma. These cells may be found in most instances, if not all, of diseases that involve such a condition. Fortunately the diseases are few and are readily distinguished from one another, whereas those with which they are oftenest confused produce no renal siderosis. The presence of intracellular hemosiderin in the urine assumes in this light importance for diagnosis.

On *a priori* grounds one may predict with some confidence that the examination of urinary cells for iron pigment will prove to be a decisive method of determining the presence of hemochromatosis in doubtful clinical instances of cutaneous pigmentation. For in hemochromatosis the siderosis of the skin is far surpassed by that of the internal organs. In hemolytic jaundice, congenital or acquired, the history, clinical features, and condition of the blood amply suffice for diagnosis; and the presence or absence of hemosiderin in the urine has interest merely as indicating the condition of the internal organs. In some of these jaundice cases no siderosis of the kidney is found at autopsy.⁷ The exact bearing of the urinary findings on the diagnosis of pernicious anemia will require many observations. Positive findings cannot be expected in early stages of the disease before siderosis is established. But do cases come into the physician's hands then? Observations on the urine will throw light upon the point. This much, at least, is already certain, that a positive finding in the urine has significance for the diagnosis of pernicious anemia, whereas a negative one may have none. Even in advanced cases of the disease, as the present work has shown, cells containing hemosiderin may be so rare as to require, by the rather crude methods described, a persevering search for their discovery. Iron pigment is known to be relatively stable, once it has been deposited in the tissues. But whether it will persist sufficiently in the kidney—and the urine—to be useful in diagnosis during the remissions of pernicious anemia remains to be seen.

Besides the diseases mentioned, certain local or general conditions, fortunately rare, may conceivably lead to a urinary siderosis. Severe, long continued hemolysis of any kind, as for example that from malaria,

⁷ Guizzetti, P., *Beitr. path. Anat. u. allg. Path.*, 1912, lii, 15.

may be expected to do so. According to Aschoff⁴ a patchy siderosis of the renal parenchyma sometimes results from local hemorrhages. Furthermore, according to the same authority, hemoglobin excreted into the tubules may be taken up again by the living cells and converted into hemosiderin. Urinary siderosis becomes a possibility, therefore, in paroxysmal hemoglobinuria, or after the transfusion of incompatible blood. Finally, hemorrhages into the mucosa of the urinary passages may perhaps lead to a desquamation of iron-containing cells.

All but two of the pernicious anemia cases examined in the course of the present work had been transfused, some of them many times. One of the two untransfused patients had much hemosiderin in the urine, and the other none. The influence of successful transfusion to induce of itself a renal siderosis must be considered, since in normal animals transfusions frequently repeated over a long period undoubtedly have this result.¹ But the findings in transfused human beings who were among the controls in the present work are in agreement with the results in animals in showing that much alien blood may be introduced into the body before any renal siderosis develops. The urines of these clinical controls, some of whom had been many times transfused, were uniformly negative for iron-containing pigment granules. In one case, that of a girl of 14 with purpura, nine transfusions, totalling 6,000 cc. of blood, had been given in the month prior to the urinary examinations. Yet the urine, searched on several occasions, proved completely free from hemosiderin. The physiological conditions are different in pernicious anemia. Here transfused blood is in the end just so much more material to be destroyed in the course of the disease, with a resulting increased retention of blood derivatives. That siderosis may be enhanced thereby can scarcely be doubted.

The circulating leukocytes in the case of hemochromatosis were, in general, free from hemosiderin. Several examinations were made, using thick films of washed leukocytes stained for iron by Nishimura's method. After long search one cell was found containing a few small, blue granules.

SUMMARY.

In diseases which bring about a siderosis of the kidney there are ordinarily present in the urinary sediment cells containing granules of hemosiderin, and often many free granules as well. The finding has proved useful in the diagnosis of hemochromatosis and will probably be of service in the recognition of pernicious anemia, and possibly some other diseases. But in this relation the fact should be emphasized that urinary siderosis, as one may term it, is the indication of a renal condition, not of a disease.

My special thanks are due to Dr. Walter W. Palmer, to Dr. George Minot of Boston, and to Dr. Edward Lindeman, for their kindness in providing the clinical material essential to the work.

EXPLANATION OF PLATES.

PLATE 71.

FIG. 1. Free and intracellular hemosiderin in the urinary sediment of a patient with hemochromatosis. Nishimura stain.

PLATE 72.

FIG. 2. Drawing of an actual field in a fresh preparation of the same sediment as in Fig. 1. The large size and irregular shape of the pigment granules should be noted.

PLATE 73.

FIGS. 3 and 4. Kidney of the patient with hemochromatosis. Nishimura stain. In Fig. 4 pigmented cells and free granules can be seen lying free in the lumen of a tubule.

PLATE 74.

FIGS. 5 and 6. Minute hemosiderin granules in the urinary cells of a case of pernicious anemia. Nishimura stain. $\times 1,060$.

FIG. 10. Masses of free granular hemosiderin in a urine with scarcely any of the intracellular pigment. The specimen is from a case of pernicious anemia. Nishimura stain. $\times 1,000$.

PLATE 75.

FIGS. 7 and 8. Hemosiderin, free and intracellular, in the sediment from a patient with pernicious anemia. The abundant pigment has the form of rounded granules. One of the cells of Fig. 7 is so crowded with it as to appear almost black. The amount of free pigment is noteworthy.

PLATE 76.

FIG. 9. Drawing to show the appearance of the hemosiderin in fresh preparations from a pernicious anemia case. The cells are taken from several fields.

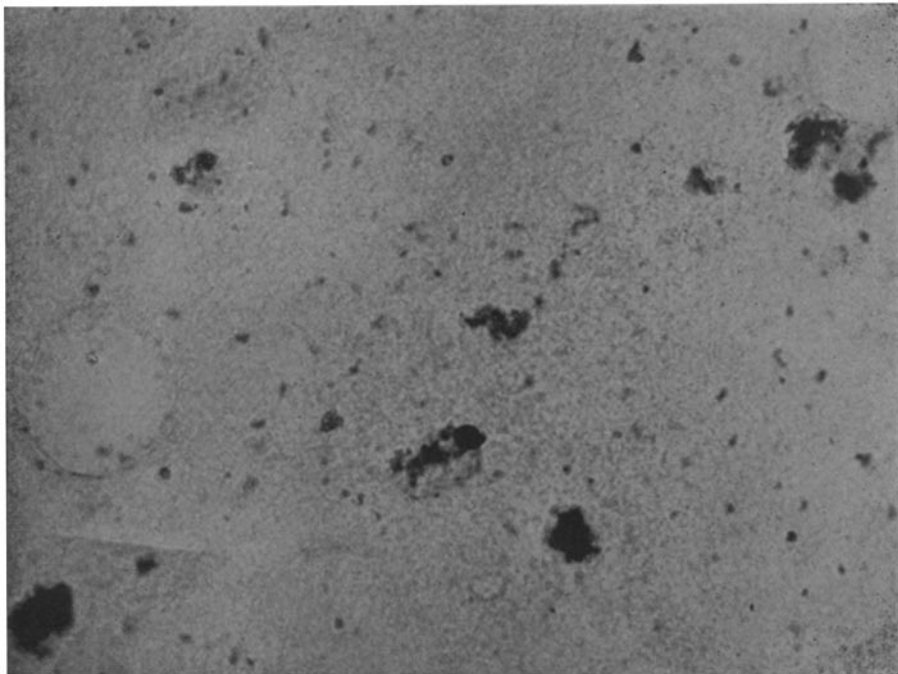


FIG. 1.

(Rous: Urinary siderosis.)



FIG. 2.

(Rous: Urinary siderosis.)

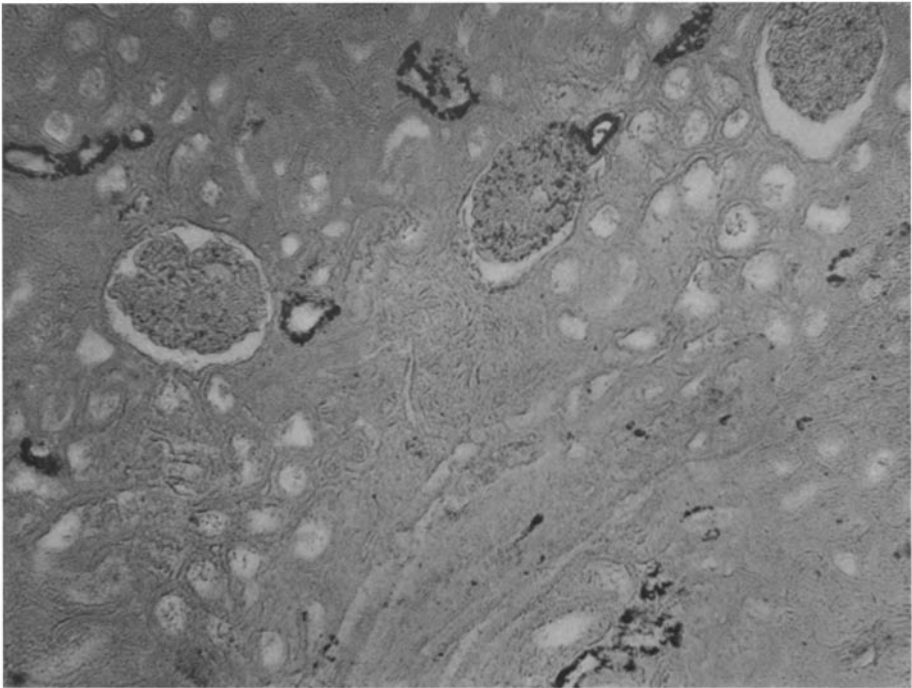


FIG. 3.

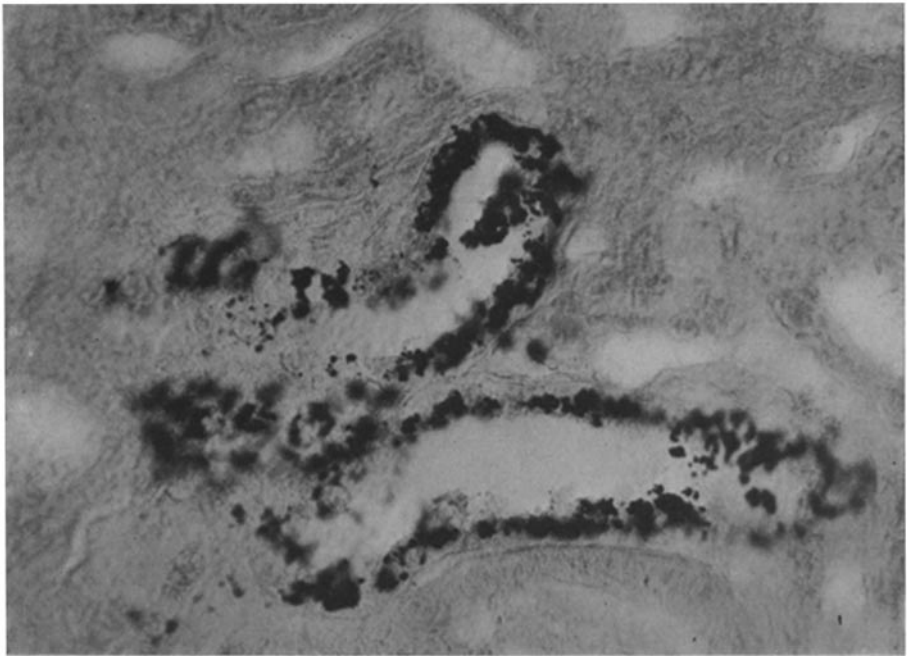


FIG. 4.

(Rous: Urinary siderosis.)

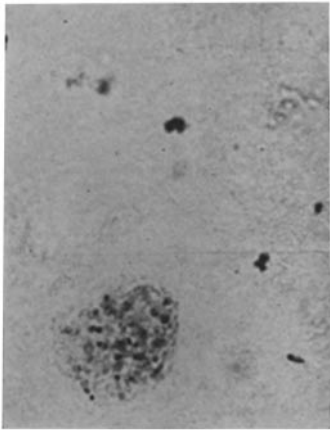


FIG. 5.

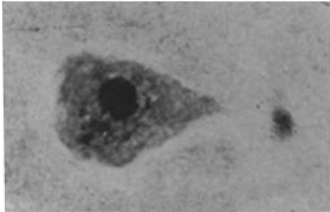


FIG. 6.



FIG. 10.

(Rous: Urinary siderosis.)

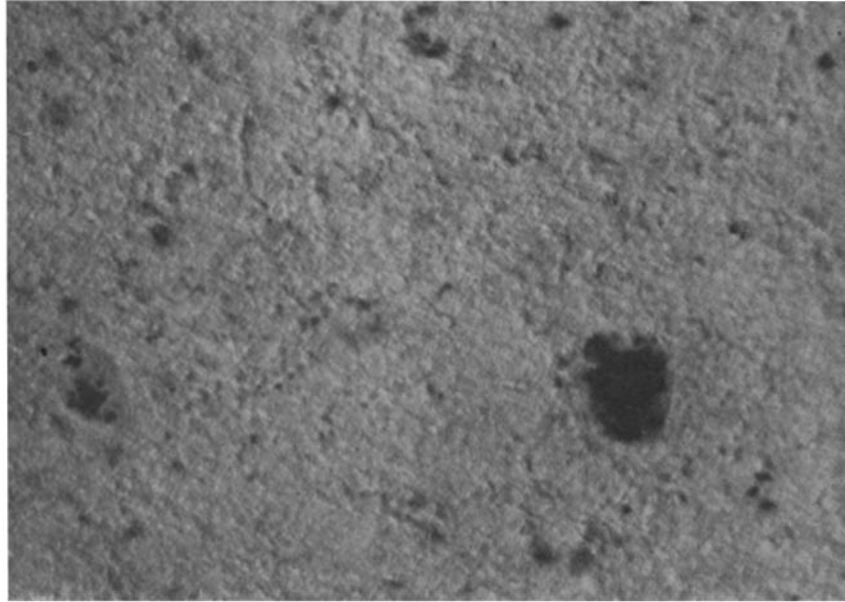


FIG. 7.

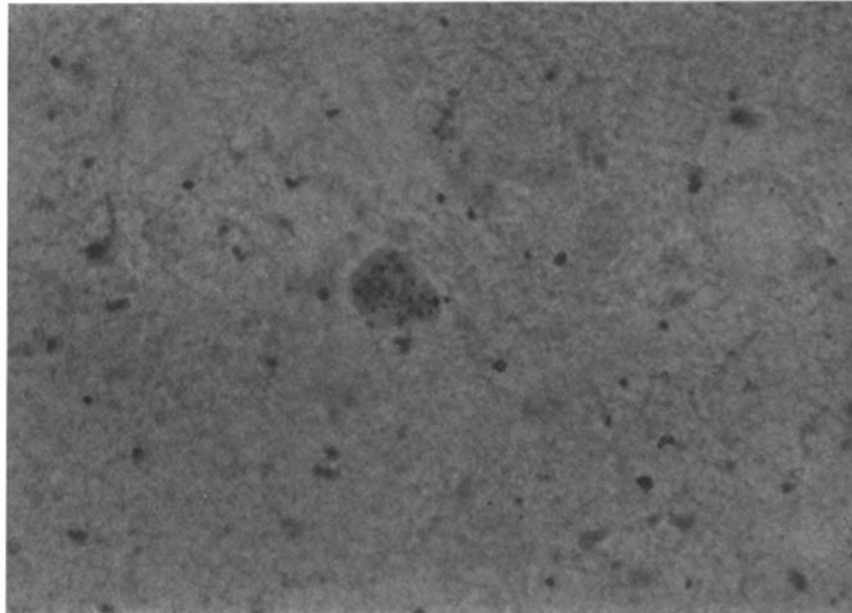


FIG. 8.

(Rous: Urinary siderosis.)

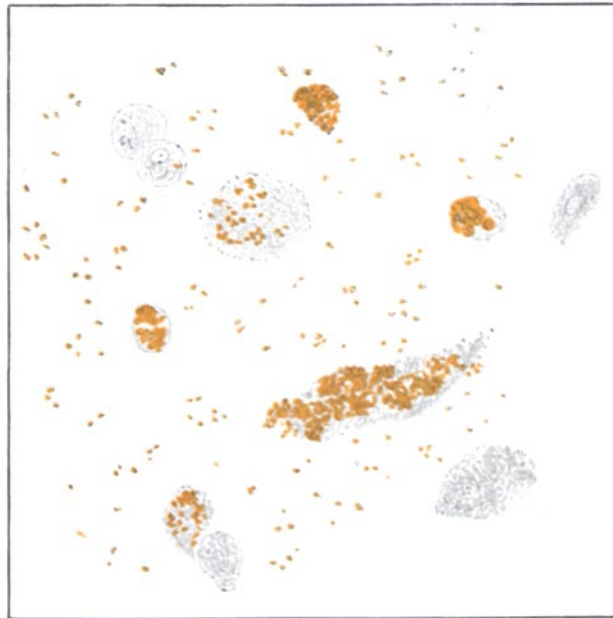


FIG. 9.

(Rous: Urinary siderosis.)