

OCHRONOSIS

WITH A STUDY OF AN ADDITIONAL CASE *

B. S. OPPENHEIMER, M.D., AND B. S. KLINE, M.D.

NEW YORK CITY

Ochronosis is the name given by Virchow in 1866 to a condition characterized by the pigmentation of the cartilages, ligaments, tendons and of the intima of the large blood vessels of the body. In this first reported case the pigment deposits appeared light gray, brown and, in places, black. On thin section, however, the pigment was everywhere found to be yellow or yellow-brown and for this reason the condition was called ochronosis.

Since then, forty additional cases have been studied. From the observations made it may be stated that ochronosis is a condition dependent on a disordered metabolism of phenol or some of its derivatives; characterized by a pigmentation of the cartilages, fibrocartilages, fibrous tissues and epidermis, as well as of areas of degeneration, notably atherosclerotic plaques, albuminous masses and concretions. A further characteristic is the presence of a dark urine due to alkapton, derivatives of phenol or to melanin.

The cases of ochronosis may be divided into: (a) those due to the circulation in the blood of certain aromatic compounds with the excretion in the urine of homogentisic acid; (b) those due to the circulation in the blood of certain aromatic compounds with the excretion in the urine of melanin; (c) those due to the circulation in the blood of certain aromatic compounds following the external use of phenol.

The metabolic disorder responsible for the ochronosis in the first group is a congenital one and characterized by an alkaptonuria. More than one-half of all the ochronosis cases observed are in this group. The metabolic disorder responsible for the ochronosis in the second group results in an excretion in the urine of melanin. Only a few of the ochronosis cases are in this group. The metabolic disorder responsible for the ochronosis in the third group is an acquired one dependent on the prolonged external use of phenol. Eleven of the ochronosis cases observed are in this group.

Twenty-two of the cases in the literature are females; nineteen are males. The average age of the patients at the time of diagnosis was about 51 years. The youngest patient was 23 years of age. There

* From the Montefiore Hospital for Chronic Diseases.

* Part of the expenses of this publication were defrayed from a fund left by the late Dr. H. S. Oppenheimer.

is a tendency for this condition to occur in families where there has been inbreeding.

The diagnosis offers no difficulty. The cartilages of the ears and nose have a bluish tint. The fibrous tissue, especially about small joints, has a bluish gray appearance. There may be dark pigment deposits in the sclerae and patches of pigmentation of the skin. There is an excretion of dark urine or urine which turns dark on standing, due to the presence of alkapton body or derivatives of phenol, rarely of melanin. The pigment may be excreted to some extent by sudoriferous and ceruminous glands.

The most frequent complications in ochronosis are: (a) deforming arthritis of the spine or larger joints, and (b) cardiovascular lesions.

HISTORICAL RÉSUMÉ

1. *Clinical.*—The early cases of ochronosis were recognized clinically by the pigmentation of the external cartilages. In 1892 V. Hanseman reported a case in which dark urine was passed. Examination of this urine was negative for alkapton body and melanin. In 1902 Albrecht and Zdareck, reporting the seventh case in the literature, called attention to the association of ochronosis with alkaptonuria. In 1904, Osler likewise reported two cases of ochronosis with associated alkaptonuria. No further observations on the nature of the process were recorded until Pick reported a case of ochronosis undoubtedly due to the prolonged external use of phenol. From his chemical study in cases associated with alkaptonuria and in one following chronic phenol poisoning, Pick concluded that in the ochronosis of endogenous origin (congenital, associated with alkaptonuria) a melanin is formed by the action of an enzyme on circulating homogentisic acid and tyrosin, and that in the exogenous form (due to phenol poisoning), a melanin is formed by the action of an enzyme on circulating hydroquinone and pyrokatechin. This explanation of ochronosis, advanced by Pick in 1906, has received no appreciable modification since. In 1908 Gross and Allard reported a case of ochronosis with alkaptonuria in which there was a deforming arthritis of the larger joints. Contrary to Virchow's belief that the pigment was deposited in the inflamed cartilage of the affected joints, they maintained that these arthritic changes were specifically due to the irritation of the deposited pigment. More recently, Söderbergh¹ called attention to a deforming arthritis of the spine in four cases of ochronosis with alkaptonuria. Attention has also been called² to the frequent association of cardiovascular lesions with ochronosis and it has been suggested that these changes, like the arthritic ones, are primarily dependent on the metabolic disorder.

1. Söderbergh: Nord. med. Arch. **48**: Nos. 3 and 4, 1915.

2. Beddard: Quart. J. M. **3**:329, 1909.

The accompanying table based on Kolaczek's³ tables shows the frequency of cardiovascular and arthritic changes in the various groups.

CLASSIFICATION OF OCHRONOSIS CASES WITH ASSOCIATED LESIONS

Group	Reported by	Age, Yrs.	Sex	Pathologic Examination	Arthritis	Cardio-vascular Lesions
a. Carbolic acid	Pick, 1906.....	47?	F	Yes	+?	+
	Pope, 1906.....	41	F	Yes	meager des.	—
	Graeffner, 1907.....	59	F	No	—	—
	Reid, 1908.....	68	F	No	—	—
	Poulsen, 1910.....	55	F	No	—	+
	Poulsen, 1910.....	44	M	No	?	—
	Poulsen, 1910.....	63	F	Yes	—	+
	Beddard, 1910.....	50	F	No	—	—
	Andrews and Branson, 1910 (Keats), 1910.....	60	M	Yes	—	+
	Beddard and Plumtree, 1911.....	73	M	Yes	+	+
	Vogelius, 1914.....	63	F	No	+	—
Total, 11	Average age.....	52.45	8 F 3 M	5	2 + 2 ?	5
b. Alcaptonuria	Osler, 1904.....	57	M	No	—	+
	Osler, 1904.....	49	M	No	—	—
	Ogden, 1895 and 1904.....	45	M	No	—	—
	Allard and Gross, 1907 u 1908, Landois, 1908.....	46	F	Yes	+	—
	van Amstel, 1910.....	42	F	No	—	?
	Poulsen, 1910.....	56	F	No	+	—
	Poulsen, 1910.....	19	F	No	+	—
	Poulsen, 1910.....	35	M	No	—	—
	Poulsen, 1910.....	68	M	No	+	—
	Poulsen, 1910.....	61	M	No	+	—
	Kolaczek, 1910.....	44	F	Yes	+	—
	Kolaczek, 1910.....	35	F	No	—	—
	Kolaczek, 1910.....	30	F	No	—	—
	Poulsen, 1912.....	23	M	No	—	—
	Jantke, 1913.....	54	F	+	+
	Umber, 1913.....	51	F	+	+
	Umber, 1913.....	59	M	+	+
	Söderbergh, 1915.....	42	M	+	—
Total, 18	Average age.....	47	9 F 9 M	2	9 +	3 + 1 ?
c. Probably alcaptonuria	Albrecht, 1902.....	47	M	Yes	—	?
	Clemens and Wagner, 1907-8..	31	M	Yes	—	+
Total, 2	Average age.....	49	0 F 2 M	2	0	1 + 1 ?
d. Melanuria and probably alcaptonuria	Poulsen, 1910.....	63	F	Yes	+	+
Total, 1						
e. Melanuria no alcaptonuria	Hecker and Wolf, 1899.....	73	M	Yes	+	+
	Oppenheimer, Janney, Kline, 1916.....	40	M	Yes	+	+
Total, 2	Average age.....	56.5	0 F 2 M	2	2	2
f. No alcaptonuria and no melanuria	Hanseman, 1892.....	41	M	Yes	—	+
Total, 1						
g. Urine not obtained or not tested	Virchow, 1866.....	67	M	Yes	+	+
	Bostroem, 1891.....	44	F	Yes	+	+
	Heile, 1900.....	36	F	Yes	—	+
	Heile, 1900.....	52	F	Yes	—	+
	Wagner, 1904.....	67	F	Yes	—	+
	Heymann, 1913.....	55	M	Yes	..	+
Total, 6	Average age.....	53.5	4 F 2 M	6	2	6
Total cases, 41	Average age.....	51	22 F 19 M	19	16 + 2 ?	19 + 2 ?

3. Kolaczek: Beitr. z. Klin. Chir. 71:254, 1910.



Moderate ochronotic pigmentation of ears, eyes and axillae; tracheal and bronchial cartilages.

In the forty-one cases of ochronosis a chronic arthritis of the larger joints or spine has been noted in sixteen. The associated arthritis has been more frequent in the ochronosis with alkaptonuria.

Cardiovascular changes have been noted in nineteen of the forty-one reported cases. These occurred in about equal frequency in cases with alkaptonuria and in cases following phenol poisoning. Not only was there extensive pigmentation of the intima and endocardium in these cases, but also not infrequently a serious chronic valvular disease.

2. *Pathologic.*—In 1866 Virchow reported on a necropsy in a male, aged 67, with an aneurysm of the ascending arch of the aorta, head

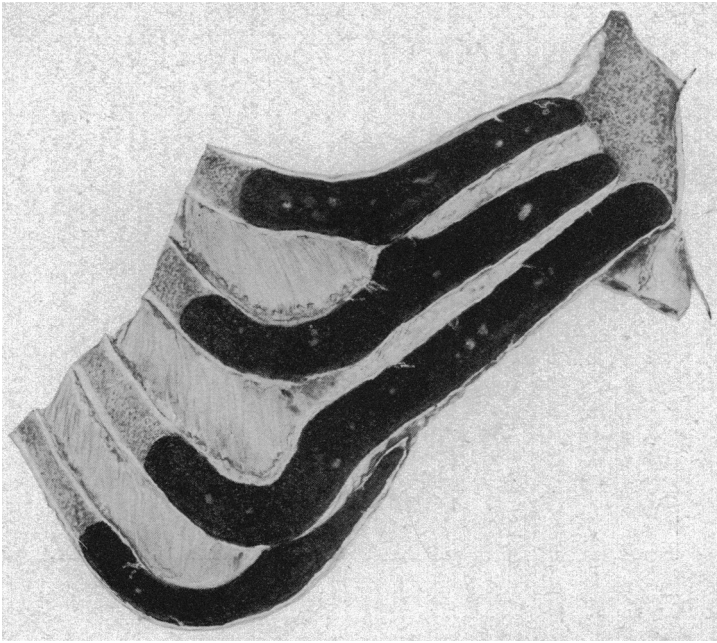


Fig. 1.—Intense ochronotic pigmentation of costal cartilages.

injury and terminal anasarca. The striking lesion, however, was the intense pigmentation of all cartilages and fibrocartilages, with pigmentation to a less extent of ligaments, tendons, perichondrium and periosteum. In this first case there was also some pigmentation of the intima of the larger vessels, especially the aorta, with intense pigmentation of the sclerotic patches in this vessel. The intensely pigmented areas were black or bluish black. The pigmentation of the tracheal cartilages was ochre colored. Histologically, the pigment everywhere was brown or ochre colored, hence the name, ochronosis. Examination of the pigment in this first case by Kühne showed an organic pigment having a definite similarity to hematin derivatives.

Virchow suggested that in ochronosis there is an imbibition from the blood of hematin derivatives occurring in areas poor in vessels and nerves but exposed to irritation. He thought that the process was analogous to the physiologic pigmentation of the rete malpighii, the hair and the choroid and depended on a similar relationship. Furthermore, he believed that there were certain conditions of the cartilages and ligaments which might be considered lower grades of ochronosis. He had occasionally observed that the semilunar plates of the knee joints in old people had a dark yellow or brown appearance and the costal and bronchial cartilages a dark yellowish brown color. In these

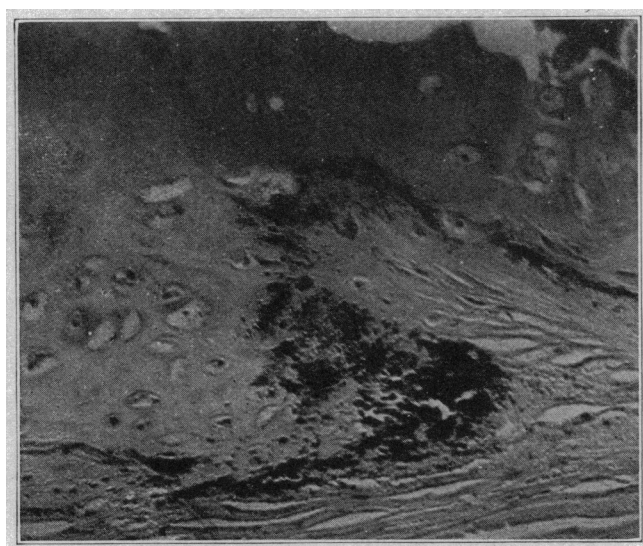


Fig. 2.—Diffuse ochronotic pigmentation of cartilaginous matrix of costal cartilage with granular ochronotic pigment in perichondrium.

instances also, the pigment was deposited in the intercellular substance and was quite homogeneous and diffuse.

Virchow, in this first case, observed changes in the larger joints, particularly the knees, similar to those in arthritis deformans. The deposition of the pigment in these irritated areas gave additional proof to him of his theory, mentioned above. In this first report, no mention of the appearance of the kidneys is made and no mention is made of granular ochronotic pigment.

In concluding his article, Virchow states: "I believe, therefore, that the case here presented, because of the intensity of the pigmentation, was only an excellent example of the more frequent ochronosis."

Hanseman⁴ observed diffuse and granular ochronotic pigment in the tissues. In regard to the pigment he states that it is produced in soluble form in the body and in this form absorbed and fixed by certain tissues having but little metabolic activity and in other places changed by cells to granular pigment.

The classical paper on ochronosis is that by Poulsen,⁵ who studied ten cases clinically and two after necropsy. He described the pathologic changes as follows:

In all cases one finds a yellowish or brown melanin-like pigment which at times is granular, at times stains the tissues diffusely. This pigment is deposited

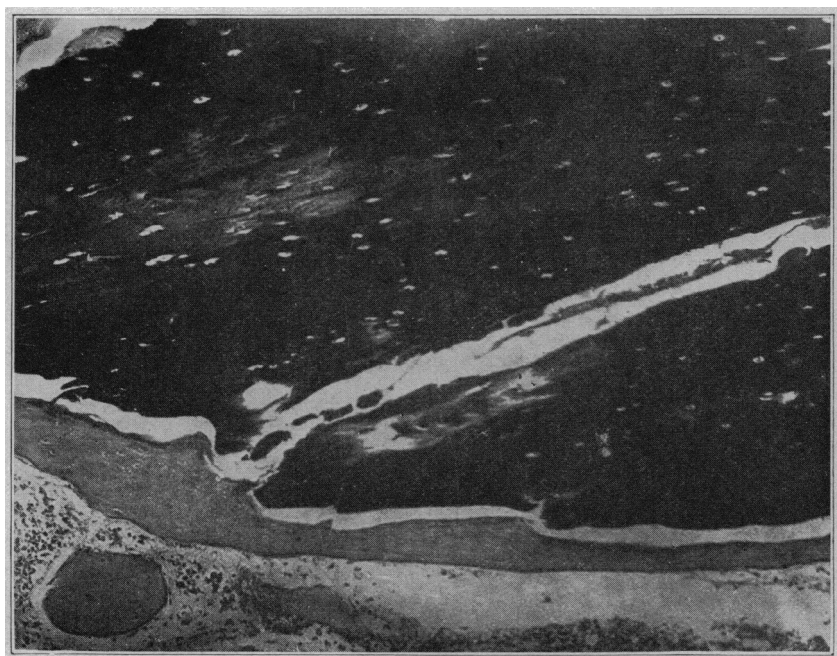


Fig. 3.—Diffuse ochronotic pigmentation of intervertebral disc.

principally in the cartilages: costal, those of the air passages and larger joints. Those of the smaller joints are usually unpigmented. The pigment is also present in all the fibrocartilages, such as the intervertebral discs and in the pelvic and intersternal cartilages. The pigment deposition is less intense in the perichondrium, periosteum, tendons, fascias and joint capsules. The bones, although usually unpigmented have shown pigment in a few cases. Outside of the skeleton, the pigment is deposited as a rule only in the endocardium, intima of the larger blood vessels and kidneys; rarely in other places, such as bits of cartilage in the tonsils, in connective tissue of the lung, and

4. Hanseman: 1892.

5. Poulsen: Ziegler's Beitr. z Path. Anat. **47**: 1910.

thyroid gland, in the fatty tissue about the perichondrium and in the dura mater. The pigment is frequently found in the sclerae, epidermis and in a few cases in the nails. Pigment masses have been observed in the prostate by a few observers, although the authors questioned their specific character. In the cartilage it is deposited in the matrix: the cartilage capsule, and the cells are faintly or not at all colored. Degenerated cells, however, are deeply pigmented. In the other tissues, this pigment is at times in the cells, at times between them. The pigment is excreted in the urine.

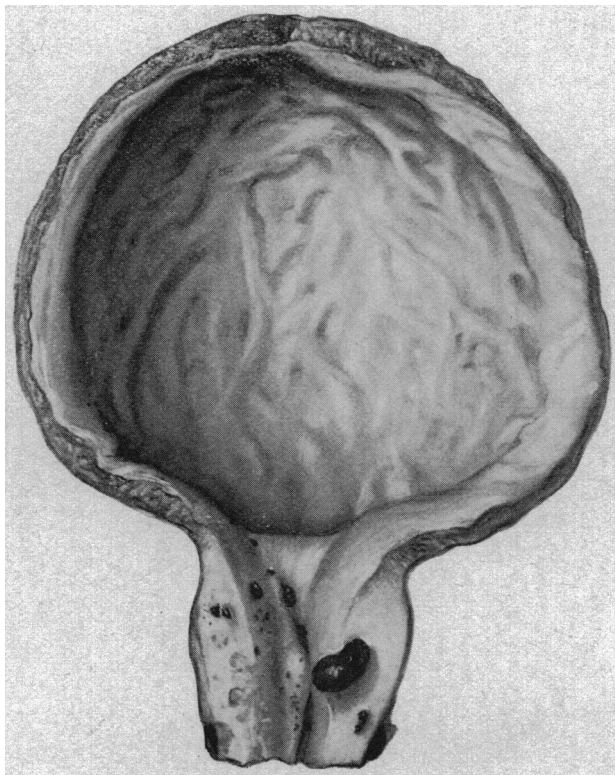


Fig. 4.—Ochronotic concretions in prostate.

REPORT OF CASE

History.—Male, aged 40, presser, admitted to Montefiore Hospital, Nov. 18, 1915.

Chief Complaints.—Lancinating pains along spinal column radiating along the lower intercostal spaces to both sides of the abdomen; slight productive cough; occasional hemoptysis; chronic constipation; general weakness; occasional spells of vomiting.

Family History.—Negative for consanguineous marriage.

Past History.—Occasional attacks of influenza. Frost bite of ears three years ago. Habits: Ten cigarets daily. Eight years before patient's admission to the hospital he was supposed to have had sugar in his urine. Seven years before admission he first noticed peculiar bluish discoloration of the cartilage of each ear.

Present Illness.—Eighteen months before admission, while bathing, he experienced sharp stabbing pains along the spinal column, extending forward along the costal spaces to both hypochondriac regions. He left the water at once and went home. The pains, however, continued to grow more and more severe until the following morning when he was unable to resume his occupation. In addition to this sharp pain he noticed stiffness of all the back muscles. He remained at home for the next six months where he was treated with no apparent relief. He then visited Mt. Clemens, Mich. On his return from Mt. Clemens he began to complain of a persistent cough accompanied by profuse greenish-yellow expectoration, blood tinged only for a period of two days,

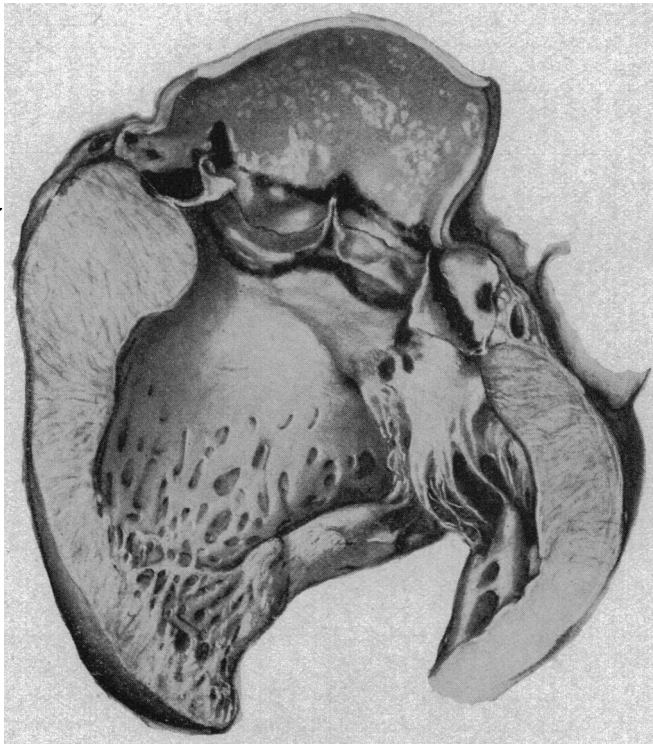


Fig. 5.—Ochrotonic pigmentation of atherosclerotic plaques of aortic and mitral valves and in neighborhood of attachment of aortic cusps.

three weeks before admission. In addition he suffered with night sweats and general weakness. He lost twenty-five pounds in weight during the first year of his illness. At the time of admission, cough and loss of weight were almost negligible symptoms.

During the first twelve months of the present illness the patient was treated at various clinics. For the past three months the urine has been reddish-black; the underclothes were often stained black. Associated with this there has been marked polyuria and dysuria. The patient became frightened because of this condition and discontinued taking some white medicine which he was then receiving at the St. Paul's Tuberculosis Clinic and which he felt caused the disorder. He claims that the urinary symptoms mentioned subsided when the drug was discontinued and recurred when the drug was again taken. On being

given various drugs to smell he stated that he was positive the drug he took had the same odor as creosote.

Physical Examination.—The patient, an adult male, poorly nourished, appears to be suffering from some chronic illness. Weight, 104 pounds. Gait is very slow and careful. The sclerae of both eyes present a faint bluish tint. In addition there is a wedge shaped bluish-black area of pigmentation of the sclerae to the right of each cornea. Both ears show a peculiar leaden blue discoloration of the cartilage. The same discoloration appears to be present in the nasal cartilage on the right side. Both axillae are diffusely bluish green in color. Some of this discoloration is removable by soap and water and is apparently due to pigment from the sweat and sebaceous glands. There is a pale, brownish diffuse pigmentation of the skin of the neck and temporal regions. The fingers and toes are clubbed; nails pale, not pigmented. Chest: Supraclavicular fossae deep; clavicles exceptionally prominent. Examination of lungs shows few signs at right apex posteriorly suggestive of pulmonary

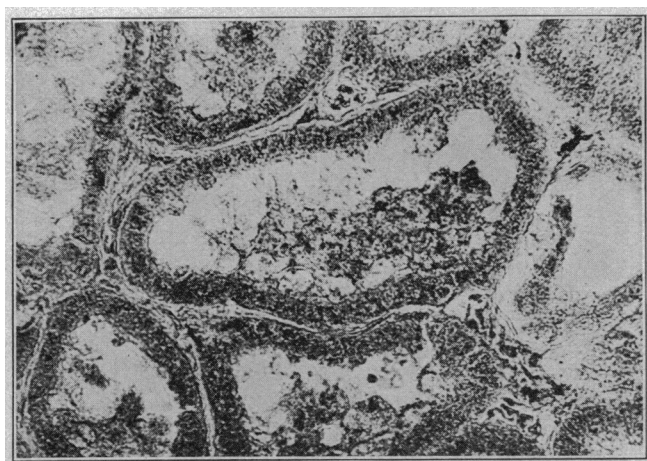


Fig. 6.—Fine ochronotic pigment granules in cells of proximal convoluted tubules of kidney.

tuberculosis. Heart: Not appreciably enlarged. The first and greater part of the second sound at the apex is replaced by a loud harsh murmur transmitted to the axilla. There is some thickening of radial arterial walls; pulse regular; good tension. Liver: Palpable 4 cm. below costal margin in right mammillary line; tender. Extremities: Reflexes increased. Vertebral column: Absolutely rigid, presenting a general bow deformity. Lumbar curve obliterated. There is a great deal of tenderness on any manipulation of either thoracic or lumbar regions of spine.

Laboratory Findings.—Sputum: negative on first five examinations. On sixth examination a few tubercle bacilli were found. Blood: hemoglobin, 80 per cent.; leukocytes, 15,000; 85 per cent. neutrophils. Wassermann reaction of blood, negative. Urine: First specimen reddish black when voided; second specimen, when voided, light amber color, turning to yellowish black. Next two specimens were voided black. The following three specimens were smoky but on standing became black. The quantity excreted in twenty-four hours was usually 500 c.c.; specific gravity, 1.010. Albumin, marked trace. Sugar, slight reduction with Fehling's. Examination for bile and blood negative. Occasional

hyalin casts. Chemical analysis of the urine by Dr. Janney showed no homogentisic acid. On the other hand, a pigment was isolated exhibiting characteristics similar to the melanins previously obtained from the urine and tumors in cases of melanosis.

*Roentgen-Ray Examination of the Bones.*⁶—Spine: Almost complete calcification of the intervertebral discs from the first dorsal down. The cervical spine appears practically normal. The lumbar spine shows marked lipping of the lower and upper borders of the bodies of the vertebrae (Spondylitis deformans).

Pelvic Bones: Complete calcification of the interpubic disc. Moderate amount of irregular outgrowth along the outer portions of the crests and the ossa ischia.

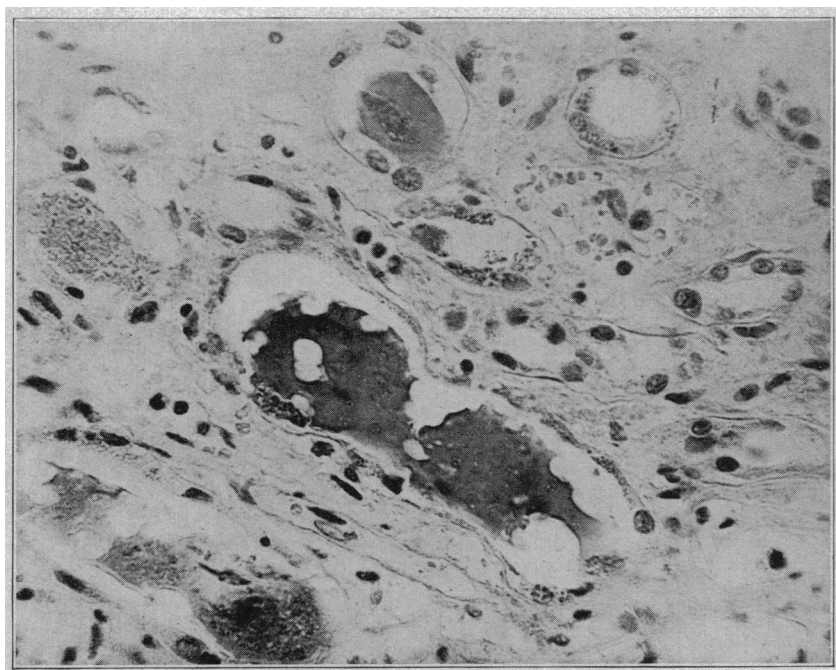


Fig. 7.—Diffuse ochronotic pigmentation of renal casts; granular ochronotic pigment granules in cells of ascending loops of Henle and collecting tubules.

Hips: Marked lipping of the upper portion of the acetabulum. Great amount of calcification around the trochanter major, with some bony excrescences at its base.

Legs: Some calcification along the insertion of the upper portion of the membrana interossea.

Skull: Marked thinning out of both clinoid processes. Complete obliteration of the frontal sinuses.

Shoulders: The joints are free. The upper portions of the humeri show a condition such as we usually see in osteitis fibrosa; rarefaction, lack of clear demarcation between compacta and spongiosa and beginning cystic degeneration.

Clinical Course.—The patient vomited persistently, ran an irregular subfebrile temperature until the day of death when temperature rose to 103 F. A half hour after death it was noticed that the entire eyeball, exclusive of the

6. We are indebted to Dr. Th. Scholz for the roentgen-ray report in this case.

cornea, had become brownish black in color and the following day at the necropsy it was noticed that the pigment in the axillae had become much darker than during life.

Diagnosis.—The diagnosis of ochronosis in the case was readily made because of the bluish discoloration of the cartilages of the ears and the skin of the axillae; the pigmentation of the sclerae and the excretion of a dark urine becoming black on standing.

*Chemical Report.*⁷—Examination of the urine in this case was repeatedly negative for homogentisic acid (alkapton body). On the other hand, the pigment obtained from the urine, from a costal cartilage and from the prostate gave reactions for melanin. The pigment from these sources had similar characteristics.

Pathologic Report.—Anatomic diagnosis: ochronosis. Pigmentation of costal, tracheal, bronchial, auricular and xiphoid cartilages, intervertebral discs, aorta, endocardium, prostate, skin, sclerae, kidneys; deforming arthritis of larger joints and spine; subacute bacterial endocarditis, mitral valve; subacute glomerulitis; infarct, spleen; healed pulmonary tuberculosis; arteriosclerosis of aorta, pulmonary arteries, mitral valve; pulmonary edema.

Necropsy Record (abridged).—Necropsy performed 33½ hours after death. The body is that of a considerably emaciated adult, 153 cm. in length. The skin in general is thin, sallow in appearance. There are tattoo marks on the left forearm. The nails show moderate double curvature. The skin of both axillae, under the arms, has a purplish color. The cartilages of the ear are deep blue in the inner portion, less intensely colored peripherally. The sclerae have a faint blue tinge, except just below the cornea of each side where there is a much greater deposition of the pigment and, in addition, a wedge shaped, brownish, green-blue area about 2 x 1 cm. (These masses were not present during life, but noticed a few minutes after death.) Eyes: The right pupil is slightly larger than the left which is of about average size; both eyeballs sunken. The ears are small. The auricular cartilages through the skin appear leaden gray. There is a small nodule on the upper margin of the left ear, grape seed in size, shows grayish-pink pigmentation in the deeper portion. The external genitalia show no abnormalities, except a faint bluish discoloration on the upper surface of the glans.

(The organs removed through abdominal incision).

HEART: Somewhat enlarged, weighs 360 gm. There is considerable diminution of fat below the epicardium. The right side of the heart shows no abnormalities, except at the base of one pulmonary valve cusp and at its attachment to the artery in two places there is bluish discoloration of the intima. The left auricle is moderately dilated, the walls not thickened; the endocardium has the usual appearance except at one place above the auriculoventricular ring where there are numerous, small friable vegetations. Mitral valve—the aortic leaflet shows on its upper surface, near the auriculoventricular ring, a number of small friable, grayish vegetations. The other cusp is strikingly altered. There is a large irregular, friable mass along the line of closure and free edge, yellow in color, in part calcified; the vegetation continues down the associated chordae. The left ventricle is moderately dilated, not appreciably thickened. The papillary muscles are stretched, somewhat flattened; the endocardium thin and glistening. Aortic valve: cusps thin and delicate. At the attachment of the cusps to the ventricle and aorta there is extensive bluish black pigmentation of the endothelium over a considerable area. This pigmentation is visible also on the posterior aspect of the aortic leaflet of the mitral valve. The base of the aorta shows numerous slight elevations, due to small,

7. Dr. N. W. Janney has already published a report of the chemistry of this case. *Am. J. M. Sc.* **156**:59, 1918.

soft, yellow, opaque patches in the intima. The coronary vessels are not tortuous. The walls are somewhat thickened and show scattered soft yellow opaque patches in the intima; just beyond the left coronary orifice there are a few patches of bluish pigmentation of the intima. Left myocardium on section pale and flabby. Here and there are gray flecks replacing muscle. There are also gray streaks associated with the vessels. No abnormal pigmentation of myocardium.

LUNGS: The right lung weighs 690 gm. It is voluminous. The upper lobe is strikingly cushiony, especially anteriorly. The lobe also feels soggy. The pleura in general is thin and glistening, except at the apex where there are numerous puckered scars to which are attached dense fibrous tags. Below these pleural scars there is an irregular, indurated pigmented mass about the size of a robin's egg. In portions of this scarred area there are small, dry, cheesy and calcified masses. The remainder of the lobe has a watery, dull, pinkish red color, mottled with black; although crepitation is made out the air spaces contain a considerable quantity of thin fluid. Dissection of the branches of the pulmonary artery show a number of soft yellow patches in the intima. The bronchi show nothing abnormal. The hilic lymph glands not appreciably enlarged, show intense black pigmentation.

The left lung weighs 650 gm. It is voluminous. The upper lobe is inelastic, cushiony. The lower lobe feels soggy. Dissection of the vessels shows atheromatous patches in the arteries, similar to those on opposite side. The cartilaginous rings of the larger bronchi appear bluish through the mucosa. On cross section, however, they appear ochre colored. The pleura is thin and glistening everywhere. On section the upper lobe crackles. A mottled pink and black surface presents. The air spaces contain a small amount of thin fluid, especially in the lower portion of the lobe. The lower lobe on section shows a pinkish-red moist surface. Thin fluid exudes in considerable quantity from the air spaces.

LIVER: Weighs 1,750 gm.; shows no macroscopic abnormalities.

SPLEEN: Weighs 350 gm.; measures 16 x 9 x 4 cm. About twice average size. It has the average consistency. The capsule is thin. Toward the upper pole there is a triangular area with sides 2½ cm. and base 1¼ cm., yellow in color, opaque, depressed a few millimeters below the general level. On section of the spleen a striking picture presents. The surface is soft and pasty, red in color. Scattered throughout the pulp are numerous small gray areas about pinhead in size. The pulp scrapes off readily on the knife. The trabeculae are increased in number, but not in size. The depressed area noted on the surface is found to be a part of a typical wedge shaped infarct, homogeneous throughout, dry, yellow and opaque, except at the apex where for a considerable distance the tissue has a decidedly bluish color.

PANCREAS AND SUPRARENALS: No appreciable abnormalities.

KIDNEYS: The kidneys together weigh 500 gm. Both are apparently alike. Each measures 12½ x 8 x 6 cm. Each moderately enlarged. The capsule strips readily, showing a smooth surface in which the veins are prominent. In addition, innumerable pinpoint and larger bluish black spots are seen. On section, a striking picture presents. The cortex is quite uniform in width, averages from 8 to 9 mm., has a watery gray-reddish appearance, streaked and dotted with brownish and bluish pigmentation. The striations are not very distinct but are fairly regular. The glomeruli are inconspicuous. Brownish and bluish pigment streaks and dots are quite extensive in the medulla and most striking in the papillae.

BLADDER: The bladder of average size, the walls of average thickness, contains turbid urine. The mucosa is pale except for a few scattered areas of injection, especially marked in the trigone. The prostatic urethra presents a striking picture; there are stony, bluish pigment masses varying in size from

pinpoint to grape seed; in some places entirely covered by mucosa, elsewhere only partially covered. There is no injection about these masses.

PROSTATE: The prostate is of average size and consistency. On section it contains a number of bluish black pigment masses varying in size from pinpoint granules, to several as large as peas. The nodules are stony in consistency.

SEMINAL VESICLES: The seminal vesicles are thin walled, not pigmented.

VESSELS: The aorta is elastic, the walls of average thickness, the circumference in upper thoracic portion 5 cm. There are numerous rather broad longitudinal yellow opaque masses in the intima throughout the length of the aorta. Just at the commencement of the thoracic portion there is an atherosclerotic plaque which shows considerable bluish black pigmentation over a surface of about a square centimeter. In addition there is a slight diffuse bluish pigmentation of the intima for a distance of 4 cm. in the neighborhood of the intercostal vessels.

NECK ORGANS: Only the lower part of the trachea was removed. This shows a pale, thin mucosa through which the cartilaginous rings have a decidedly bluish color. This is true also of the bronchi. On cross section, the pigmentation of the cartilaginous rings is found to be central; in some, it is most marked on the convex portion. The outer rim of pigmentation has a bluish cast; the deeper portions are brown.

INTESTINES: There is some apparent hyperplasia of the lymphoid tissue of the small and large intestines. In the colon there are also a number of irregular areas from 1 to 2 cm. square, having a smooth, pearly scarred appearance with thin brown pigmented periphery, suggesting healed ulcers.

SPINE: The bodies of the lumbar vertebrae are considerably flattened, the intervertebral discs are narrower than normal and almost bony in consistency; the striking change of the discs is the diffuse, intense bluish black pigmentation. The anterior ligament of the spine macroscopically shows no pigmentation.

THORAX: The lower portion of the sternum and adjoining costal cartilages and ribs were removed through the abdominal incision. The costal cartilages present a striking picture; they are hard and everywhere show an intense bluish black pigmentation. The removed ribs and portions of sternum, however, show no apparent pigmentation.

Owing to the fact that permission was granted for a partial necropsy only, the larger joints of the body could not be investigated.

Roentgenograms of all the joints were made, however, and showed changes characteristic of arthritis deformans of the spine with well marked changes of the larger joint (hip and knee) especially about the attachments of the capsules. The smaller joints showed very little change. (Dr. Th. Scholz).

Histologic Report.—**TRACHEAL CARTILAGES:** Sections show diffuse pigmentation of the matrix about the cartilage cells and clumps of fine brown granules in the perichondrium. Most of the pigment is deposited in the matrix and immediately surrounding the cartilage cells.

COSTAL CARTILAGE: Section shows diffuse brown pigmentation of the matrix. In addition, a number of degenerated cartilage cells contain diffuse and granular brown pigment. The perichondrium is pigmented in places; the pigment present in the form of small brown granules.

INTERVERTEBRAL DISC: Intervertebral disc considerably narrower than average, in part composed of fibro-cartilage, in part there are large cartilaginous like plaques. In the matrix of these latter there is diffuse brown pigmentation. In the fibrous portion near the anterior ligament there is considerable granular brown pigmentation.

AORTA: Section shows a few atherosclerotic patches in the intima, associated with which there is a considerable amount of extracellular brown pigment in diffuse and small granular form.

PROSTATE: The architecture in general is normal. There are rather numerous corpora amylacea in the glands. These vary in appearance. A few show a large amount of diffuse brown pigment in the central portions, the peripheral portions unpigmented, stained pink (eosin). Various stages of pigmentation are seen, including large and small corpora amylacea, diffusely and homogeneously brown stained. About a few of the glands containing the pigmented corpora, there are accumulations of round cells, principally mononuclears. A number of the glands containing these masses show partial or complete absence of the epithelium.

ENDOCARDIUM: This is considerably thickened. To it is attached a large thrombus mass, composed of strands of fibrin, red cells and fragmented leukocytes. Another section shows an area of the thrombus in which there is beginning calcification. In the deeper layers of the endocardium there are small masses of extracellular brown pigment in the form of fine granules. Section stained by Gram-Weigert stain shows in the outer portions of the thrombus numerous small round diplococci, many in small chains.

KIDNEY: There is some distortion of the striations. In areas there is an increase in the interstitial connective tissue; in some of these areas there is an accumulation of round cells in considerable number. In a number of these areas and also elsewhere the glomeruli have an altered appearance. The glomerular tuft is adherent to the capsule in one or more places. In places the glomerular sac contains amorphous, pink stained material and a few large mononuclear cells. In a very few glomeruli there are a large number of mononuclear cells within the sac, all filled with fine, brown pigment granules. The neighboring convoluted tubules also show a deposition of a large amount of granular brown pigment in the epithelium. In sections stained with silver nitrate, the ochronotic pigment is found in the form of very fine granules in cells of the proximal convoluted tubules and in the form of larger granules in the intact and desquamated cells of many of the ascending limbs of the loops of Henle and the various collecting tubules. The cells of the distal convoluted tubules contain the granular pigment in moderate amount. In general the pigment in the lumina of the tubules is diffuse. In places, however, desquamated cells containing granular pigment are present. In addition to these changes, a number of the tubules contain nucleated cells mostly polymorphonuclear leukocytes and in places the interstitial tissue shows accumulations of similar cells. In addition, in the interstitial tissue of cortex and medulla there are scattered large mononuclear cells containing brown pigment.

SPLEEN: Section shows a very large, triangular area of homogeneously pink stained amorphous material in which phantoms of former splenic structures are seen. In addition to the pink stained material there is, in places, some nuclear dust and more strikingly there are clumps of intra and extra cellular brown pigment. The greatest deposits of the pigment are found immediately surrounding this infarct, in the new formed connective tissue, which is present as a fairly wide band; the remainder of the section shows normal looking trabeculae and vessels. The malpighian bodies are very small, and lessened in number. There is, however, an increase in the nucleated cells of the pulp. There are numerous plugs of cocci in the splenic capillaries. Another section of the spleen shows the presence of a number of clumps of yellowish brown pigment scattered throughout the infarct. In the center of this infarct there is the remains of a large blood vessel plugged with homogeneous, pink stained material.

LIVER: This shows considerable engorgement of the blood vessels in the central portions of the lobules. There is a striking increase in the number of nucleated cells in the capillaries. In one capillary a very large clump of cocci is seen.

Microchemical Report.—In sections stained by Nishimura's method, the ochronotic pigment, diffuse and granular, does not show the reaction for iron.

In formalin-fixed material, the diffuse ochronotic pigment is stained orange red by neutral red (1 per cent. aqueous solution, three hours at 56 C.); the granular ochronotic pigment, however, is not stained by this method.

The granular ochronotic pigment behaves microchemically very much like the pigment of brown atrophy. Both are decolorized by (1) potassium permanganate, sodium sulphite, oxalic acid. (Potassium permanganate, 1/4 per cent. solution, one half hour; equal parts of oxalic acid and sodium sulphite, 1 per cent. solution, 10 minutes.); (2) surgical solution of chlorinated soda (from 15 to 30 minutes), and (3) bichromate sulphuric acid solution (potassium bichromate, 10 gm.; sulphuric acid concentrated, 12 c.c.; water, 100 c.c.) one half hour. Both the diffuse and the granular ochronotic pigment are stained brownish black by silver nitrate (fresh 2 per cent. solution silver nitrate, twenty-four hours at 56 C.). The form and distribution of the pigment are best demonstrated by this method.

SUMMARY OF FORTY-FIRST CASE

Clinical.—The diagnosis of ochronosis was made in this case because of the bluish discoloration of the cartilages of the ears and skin of the axillae; the pigmentation of the sclerae and the excretion of a dark urine becoming black on standing. In addition the patient had a deforming arthritis of the spine and larger joints and a mitral endocarditis: complications frequently present in ochronosis.

Chemical.—Examination of the urine was repeatedly negative for alkapton body. The pigment obtained from the urine, from a costal cartilage and that from the prostate of the case gave the reactions for melanin. The pigment from these three sources had similar characteristics. The chemical findings are in accord with the belief that ochronosis is dependent on a disordered metabolism of phenol derivatives.

Pathologic.—As in the cases previously reported, the cartilages (costal, tracheal, bronchial, auricular and xyphoid), and fibrocartilages (intervertebral discs) are deeply pigmented (bluish black). Large stony masses of bluish pigmentation are found in the prostate and prostatic urethra. The kidneys likewise show extensive pigmentation. The endocardium, intima of the aorta and coronary arteries, skin and sclerae are less intensely pigmented. The pigment is not deposited in any quantity in intact intima and endocardium but in areas of degeneration in these structures, however, macroscopic deposits occur. Diffuse ochronotic pigment is present in albuminous masses (renal casts) and concretions (corpora amylacea of prostate). Fine pigment granules are present in the epithelium of proximal convoluted tubules, and coarser granules are present in the cells of the ascending loops of Henle, distal convoluted tubules and the collecting tubules.

The pigment is predominatingly diffuse in the matrix of the cartilage and fibrocartilage and when associated with albuminous masses and concretions. It is predominatingly granular in perichondrium, periosteum, tendons, fascias, connective tissue and in certain

renal cells. It is present in diffuse and granular forms in injured and degenerated areas.

The histologic picture in the kidney sections suggests excretion of the pigment by the cells of the proximal convoluted tubules. The picture likewise suggests a partial reabsorption of the fine pigment by the cells of the loops of Henle, distal convoluted tubules and collecting tubules, and a transformation of the pigment into a more granular form. The form and distribution of the pigment is demonstrated best in histologic sections stained with silver nitrate.⁸

We are indebted to Mrs. H. G. Friedman for her kind assistance in preparing this paper.

8. Other references bearing on this subject are: Poulsen: Literature to 1910, *Beitr. z. path. Anat. u. z. allg. Path.* **48**:346, 1910; Literature to 1912, *Münch. med. Wchnschr.* **59**:364, 1912; Beddard and Plumtree: *Quart. J. M.* **12**:505, 1911; Umber and Bürger: *Deutsche. med. Wchnschr.* **48**:2337, 1913; Jantke: *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **26**:617, 1913; Heymann-Giessen: 1913; Vogelius: *Hospital tidende.* 1164, 1914; Sprunt: Ochronosis, *Nelson's Living Medicine* **3**:211, 1920; Howard: Ochronosis, *Oxford Medicine* **4**:223, 1921.