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Alcaptonuria and Ochronosis with Diabetes Mellitus and Mycosis Fungoides

A Case Report

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A Negro woman with alcaptonuria, ochronosis, ochronotic arthropathy, diabetes mellitus and mycosis fungoides died of acute renal failure due to diabetic glomerulonephropathy and ochronotic nephrosis. The role of the renal lesions of ochronosis is presented in potentiating the effect of an underlying renal disease producing rapidly progressive kidney failure. The occurrence of ochronosis, diabetes mellitus and mycosis fungoides is apparently coincidental only. Special stains of tissue sections confirm the similarity of melanin and ochronotic pigment.

Congenital absence of the enzyme homogentisic acid oxidase results in alcaptonuria and ultimately ochronosis. Homogentisic acid, a product of the metabolism of tyrosine, accumulates in the tissues in the absence of homogentisic acid oxidase and is excreted in the urine. When alkaline this urine gradually blackens as it is exposed to air, due to the polymerization of oxidation products of homogentisic acid resulting in alcaptonuria. In tissues, homogentisic acid is gradually converted to a similar black pigment which is deposited in large amounts in cartilage and connective tissue, and as casts in kidney tubules. Ochronosis is the result of the deposition of this pigment in tissues. Blackened by pigment, intervertebral discs become brittle, calcify and ossify. Characteristically the back, knees, and shoulders and other joints are symptomatically affected in ochronotic arthropathy. Herniation of friable intervertebral discs occurs frequently. Pigment is deposited in the dermis and in secretory cells as well as basement membranes of sweat glands. A brownish or bluish discoloration of the skin may be seen in the axillae and genital regions due to pigment in the large number of sweat glands in these areas. In regions where tendons or cartilage lie close under the skin, pigment in these tissues shows through as a bluish gray hue. O'Brien, LaDu and Bunim[1] published a comprehensive review of the world literature on alcaptonuria, ochronosis and ochronotic arthropathy. These authors found reports describing 604 patients with these conditions in the literature from 1584 to 1962. The disease is hereditary and is transmitted as an autosomal recessive trait.

Recently a patient with alcaptonuria, ochronosis and ochronotic arthropathy was examined and treated at Henry Ford Hospital. This patient also had mycoses fungoides and diabetes mellitus. Renal failure due to diabetic glomerulosclerosis and ochronotic nephrosis caused her death. The rarity of ochronosis and its occurrence with

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mycoses fungoides and diabetes mellitus prompt this report.

Case Report

E.T., a 45-year-old Negro woman, was referred to Henry Ford Hospital in July 1968 because of a skin rash which had been present for three years and which first involved the forehead and later the groins and the dorsum of the left hand. The condition began as a pruritic nodule which enlarged to form a plaque with an erythematous base and a central oozing crust. Biopsies obtained from these skin lesions eventually resulted in a diagnosis of mycoses fungoides. Treatment with radiotherapy was planned to a total dose of 3000 roentgens but was discontinued after the dose had reached 1800 roentgens. This treatment produced considerable improvement in the appearance of the lesion.

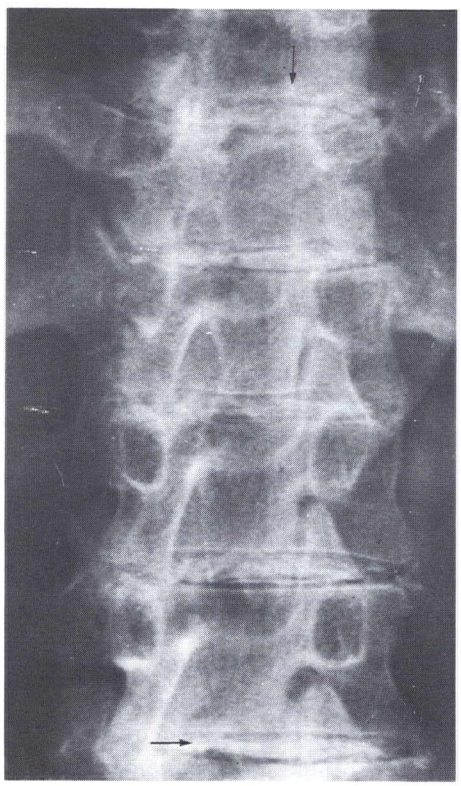

Figure 1

Radiograph of thoraco-lumbar vertebrae showing calcification of intervertebral discs (horizontal arrow) and increased density of the inferior margin of a vertebra (vertical arrow).

Diabetes mellitus was diagnosed in this patient 21 years earlier and apparently was controlled adequately by diet.

The patient had experienced recurrent mild low back pain for about 20 years. Three years prior to admission she reported bilateral shoulder pain. At that time a urine specimen became black shortly after being received in he laboratory. Her sclerae, nails and ear lobes had a bluish tint, of which she was unaware. More recently she had had pain in both knees.

Examination showed limited motion in the shoulders and some straightening and limitation of motion of the lumbar spine. Other joints had a normal range of motion. An effusion was detected in her right knee.

Hemoglobin was 8.8 gm per 100 ml and hematocrit 27%. There was 2+ albumin in the urine which contained 6 to 8 white blood cells and 5 to 7 red blood cells per high power field. One serum glucose measurement was 140 mg per 100 ml but several others were normal. Serum urea nitrogen was 50, 31 and 46 mg per 100 ml, serum

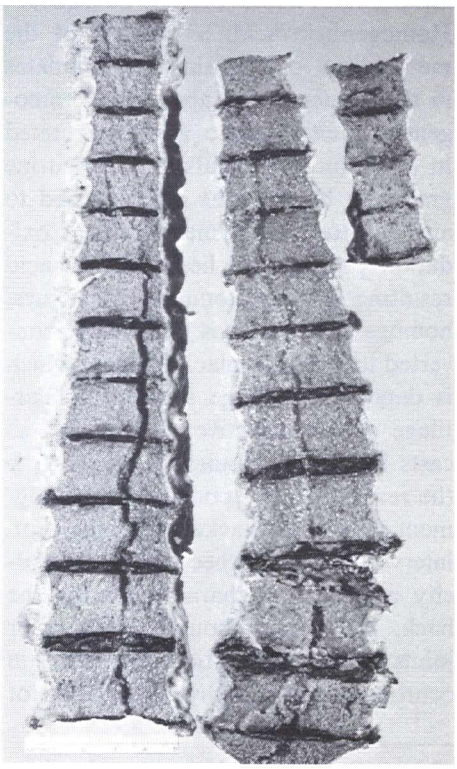

Figure 2

Intense black pigmentation of intervertebral discs is evident. The vertebral bodies contain no pigment. In vertebrae on the left the irregular dark vertical line is shadow.

creatinine was 2.3 mg per 100 ml and creatinine clearance 15 ml per minute. Examination of a urine specimen by a thin-layer chromatographic technic[2] revealed homogentisic acid. Radiographic studies of the lumbosacral spine (Fig 1), wrists, hands, knees and pelvis showed calcification of all intervertebral discs with narrowing of disc spaces and lucent clefts between discs and vertebral surfaces. Demineralization was described in other bones with erosive changes and loss of joint space in the shoulder joints.

The patient was readmitted to the hospital three months later because her skin lesions had enlarged and become infected. She was given antibiotics systemically, they were also applied locally to the lesions as was an adrenal cortical steroid preparation. There was gradual improvement.

At time of admission, the serum urea nitrogen was 40 mg per 100 ml and creatinine 2.0 mg per 100 ml. Hemoglobin was 8.7 gm per 100 ml and white blood count 12,200 per cu mm. Urinalysis showed 2+ albumin, 4 to 6 red blood cells and 0 to 2 white blood cells per high power field, 3+ glucose and no acetone or diacetic acid. Serum sodium was 129 mEq per liter, potassium 5.4 mEq per liter, chloride 93 mEq per liter and CO_2 26 mEq per liter and serum glucose was 90 mg per cent. On the fifteenth hospital day, 2+ to 3+ pitting pedal, pretibial and presacral edema was first noted. A few bilateral basal rales were heard and the heart revealed a regular rhythm at 88 beats per minute with no gallop. Treatment was started with a diuretic and digitalization. Two days later, the edema was somewhat less. On the nineteenth hospital day the patient was lethargic and dyspneic with expiratory wheezing breath sounds. Serum glucose was 185 mg per 100 ml, urea nitrogen 180 mg per 100 ml, creatinine 8.0 mg per 100 ml, sodium 125 mEq per liter, potassium 6.8 mEq per liter, chloride 100 mEq per liter and CO_2 11 mEq per liter. On the following day these components were: glucose 330 mg per 100 ml, urea nitrogen 147 mg per 100 ml, sodium 121 mEq per liter, potassium 7.5 mEq per liter, chloride 102 mEq per liter and CO_2 4 mEq per liter. She became less responsive and died later in the evening of the twentieth hospital day.

Autopsy

The cut surfaces of intervertebral discs (Fig 2), costal cartilages and thyroid cartilage were inky black and had a friable quality. Disc spaces were narrow. The articular surfaces of the shoulder joints were light bluish gray in color. Irregularly distributed in the media and adventitia of the aorta were deposits of dark pigment which appeared through the intima as bluish to gray areas. These deposits were prominent in the aortic root and valve ring (Fig 3). The cerebral dura was bluish gray in patchy irregular areas.

The kidneys were symmetrical and normal in size and cortical surfaces were smooth except for scattered pitted scars. The cut surface showed a bluish gray color in the pyramids and a well demarcated cortical medullary junction. There were no calculi. Skin lesions were as described clinically. Other organs showed no significant pathologic change and a systemic lymphoreticular neoplasm was not found.

The descriptions of microscopic changes that follow are from sections

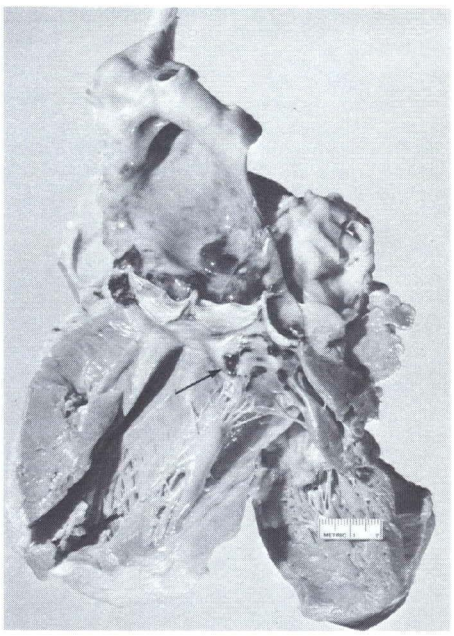

Figure 3

This view of the opened heart shows pigmentation of the supravalvular aorta, aortic annulus and aortic leaflet of mitral valve (arrow).

stained with hematoxylin and eosin. Intervertebral discs and adjacent vertebrae showed diffuse brown pigmentation of cartilage unevenly distributed in the matrix. Granular pigment was present in macrophages in connective tissue between the bone and disc. Bony trabeculae adjacent to the disc were thickened with resulting reduction of marrow space. Costal cartilage was diffusely and heavily pigmented (Fig 4). There was essentially no pigment in sections of vertebrae, ribs and skull but there was hyperplasia of blood forming elements in vertebrae and ribs.

Every glomerulus in several sections of kidney showed nodular and/or diffuse lesions of diabetic glomerular disease (Fig 5). These consisted of marked thickening of intercapillary membranes which had a hyaline or finely fibrillar character. Adhesions of the glomerulus to Bowman's capsule were common as was hyaline thickening of the walls of glomerular arterioles. Segments of many glomeruli were necrotic with segmented neutrophils in these areas. Focal lesions of healed and chronic active pyelonephritis were present. Many distal tubules contained brown casts which were deeply colored centrally but faded peripherally to a pink hyaline appearance. Other tubules contained coarse deep brown pigment particles which were also present in the cytoplasm of some tubular epithel-

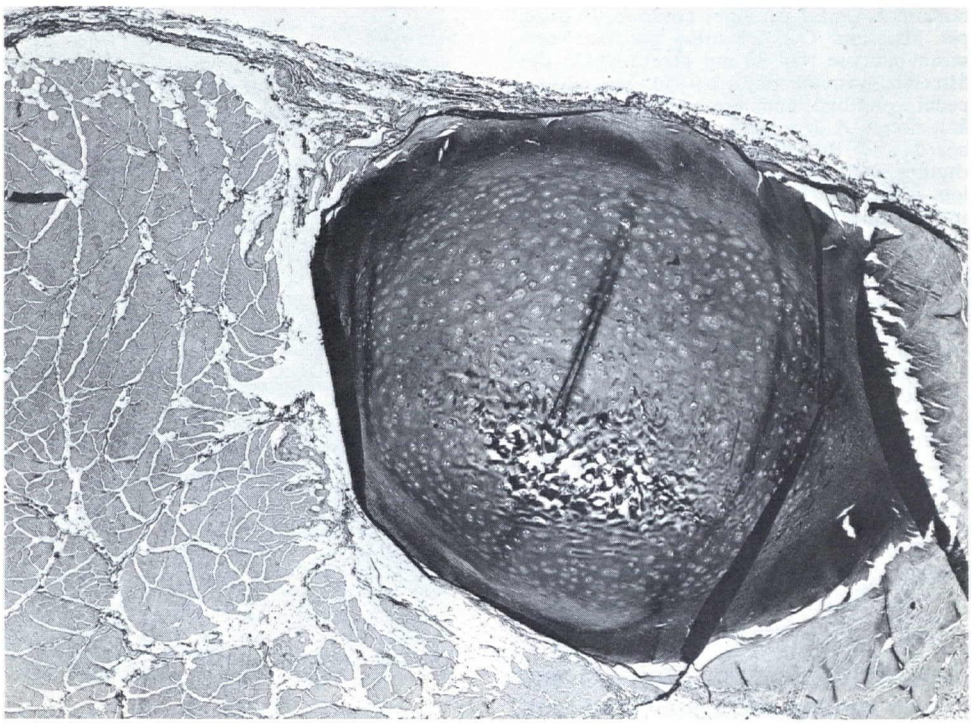

Figure 4

This costal cartilage is diffusely pigmented while the adjacent intercostal muscle contains no pigment. x 17. Hematoxylin and eosin.

ial cells (Fig 6). Large muscular arteries of the renal parenchyma frequently had brown granular pigment in the interstitial tissue of the outer media (Fig 7).

Sections of aorta showed heavy concentrations in some areas of coarse granular pigment in the outer half of the media. Others contained practically no pigment. Atherosclerotic plaques sometimes showed diffuse pigment in the media and intima adjacent to deposits of cholesterol and amorphous material.

Several sections of the skin lesions showed features of the indurative or plaque stage of mycosis fungoides. The striking finding was a continuous, rather loose, collection of cells with dark nuclei in the upper part of the dermis (Fig 8). These cells were of all types with atypical histiocytes having hyperchromatic irregular or wrinkled nuclei predominant. Other cells were lymphocytes, neutrophils, rare eosinophils and a few plasma cells. The pleomorphic cellular infiltrate extended focally into the lower dermis and occasionally into the subcutaneous fat. Small blood vessels were numerous, congested and dilated in the upper dermis.

The major final diagnoses were: 1) Ochronosis with ochronotic arthropathy involving vertebrae, shoulders and knees and ochronotic nephrosis. 2) Diabetes mellitus with diabetic glomerulonephropathy. 3) Mycosis

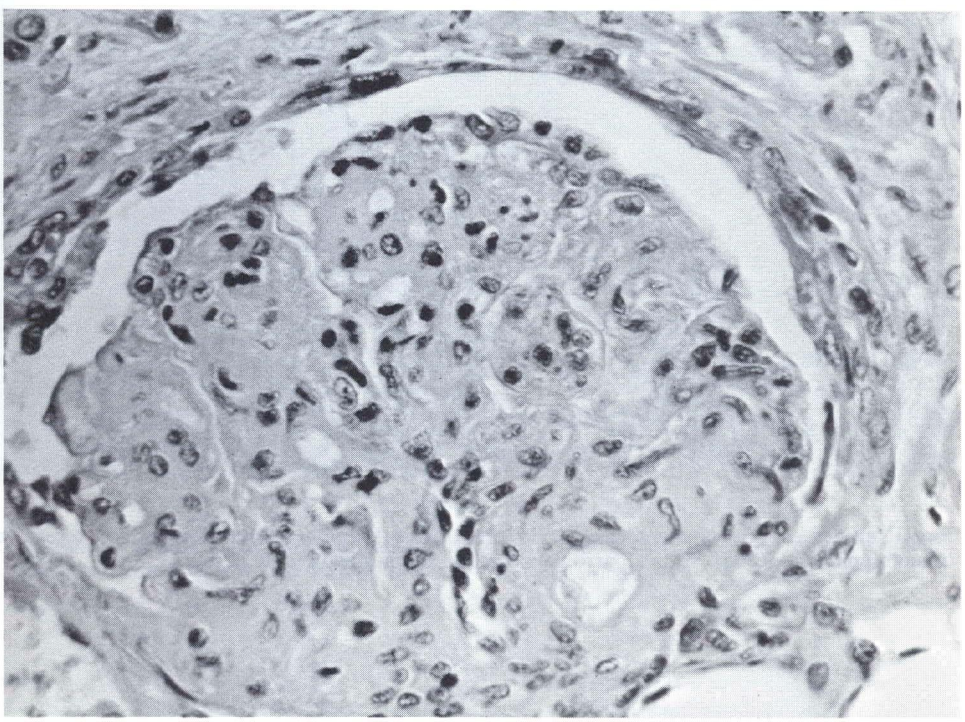

Figure 5

The nodular diabetic lesion is seen in this glomerulus. Intercapillary material is increased resulting in the formation of indistinct nodules of hyaline material containing a few cell bodies. x 390. Hematoxylin and eosin.

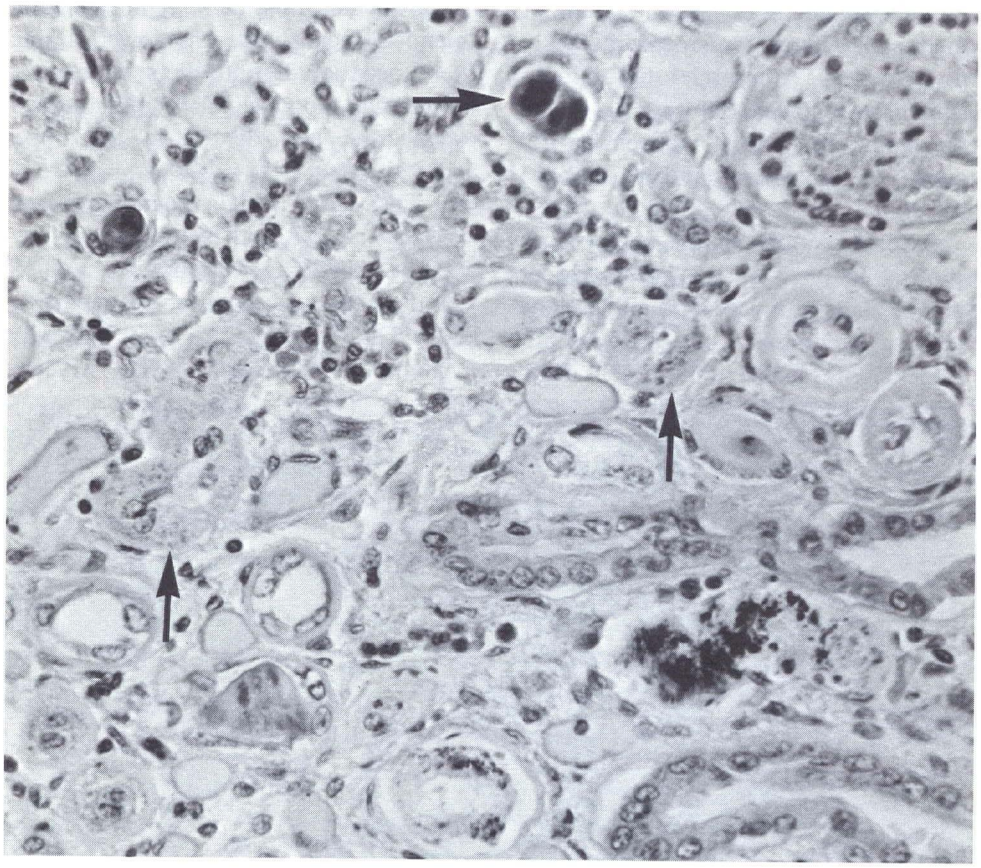

Figure 6

Renal tubules contain pigment casts (horizontal arrow) and granular pigment is present in tubular epithelial cells (vertical arrows). x 300. Hematoxylin and eosin.

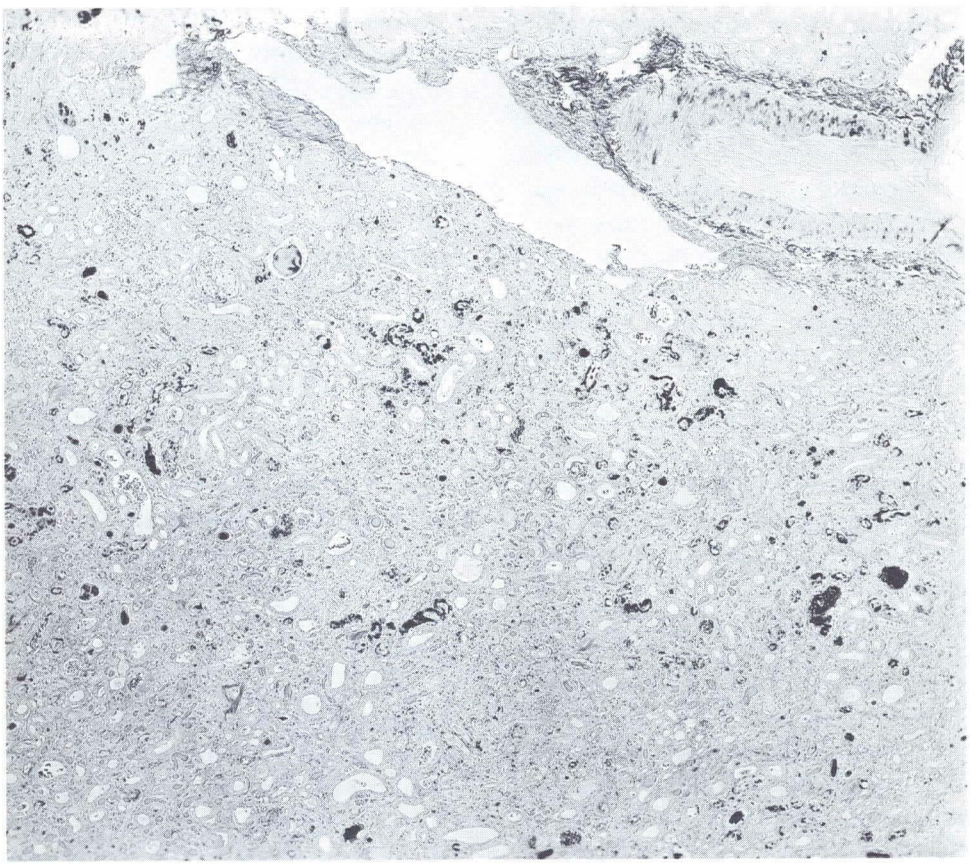

Figure 7

Renal tubules contain casts many of which are black. Hyaline casts are also present. Pigment is present in the media of the artery in the upper right. x 45. Fontana silver stain.

fungoides involving forehead, abdomen, inner thighs, hands and feet.

Comments

The course and results of ochronosis in this patient were like those described in most patients with this disease. Our patient, however, had diabetes mellitus and mycosis fungoides. Diabetes has been reported[1] in patients with ochronosis; the occurrence of these two metabolic diseases in the same patient is apparently only coincidental. Mycosis fungoides was also probably unrelated to ochronosis in the patient here described.

In ochronosis the typical pigment is frequently present as casts in renal tubules and as cytoplasmic granules in tubular epithelial cells. Stones composed of calcium salts and ochronotic pigment have frequently been described in the upper urinary tract and in the prostate.[1] Even so, renal failure is rarely found in patients with ochronosis. When these two conditions occur together O'Brien et al[1] believe that they are not related. Cooper and Moran[3] ascribed death in their patient to ochronotic nephrosis even though the patient had a history of hypertension and the kidneys showed gross and microscopic evidence of nephrosclerosis.

Putschar[4] reported autopsy findings in an ochronotic patient who had gastrointestinal hemorrhage and acute renal failure. There were many pigment casts in renal tubules and a diagnosis of ochronotic nephrosis was made. The kidneys also showed evidence of pyelonephritis and glomerular basement membrane disease.

In our patient pigment casts filled many renal tubules (Fig 6) and granules of pigment were numerous in the cytoplasm of tubular epithelial cells. Glomeruli, however, without exception showed the lesion of diabetic glomerulosclerosis; glomerular arterioles were thickened with luminal compromise. Thus, we attributed the renal disease primarily to diabetes.

In these three patients renal failure was abrupt in onset and of short duration and in all there was an underlying renal lesion independent of ochronosis. We feel that the large number of tubules blocked by ochronotic pigment casts contributed significantly to the renal failure in these patients. In ochronosis renal failure accelerates pigment deposition in tissue because homogentisic acid excretion by the kidney is impaired. This would lead to the formation of more pigment casts, further reducing the functional capacity of the kidney, so a cycle results of increasing renal impairment. It is appropriate to designate this condition as ochronotic nephrosis.

Histologic stains of sections from formalin-fixed and paraffin-embedded tissue included hematoxylin and eosin, Fontana silver, Nile blue sulfate, ferrous iron uptake, alcian blue, Masson trichrome, periodic acid Schiff and Prussian blue reaction. In summary, these showed that ochronotic pigment is not a lipofucsin and does not give the Prussian blue reaction for iron and that melanin and ochronotic pigment were alike in their stain affinities. The alcian blue stain of cartilage indicated a reduction in the amount of sulfated acid mucopolysaccharides in this tissue.

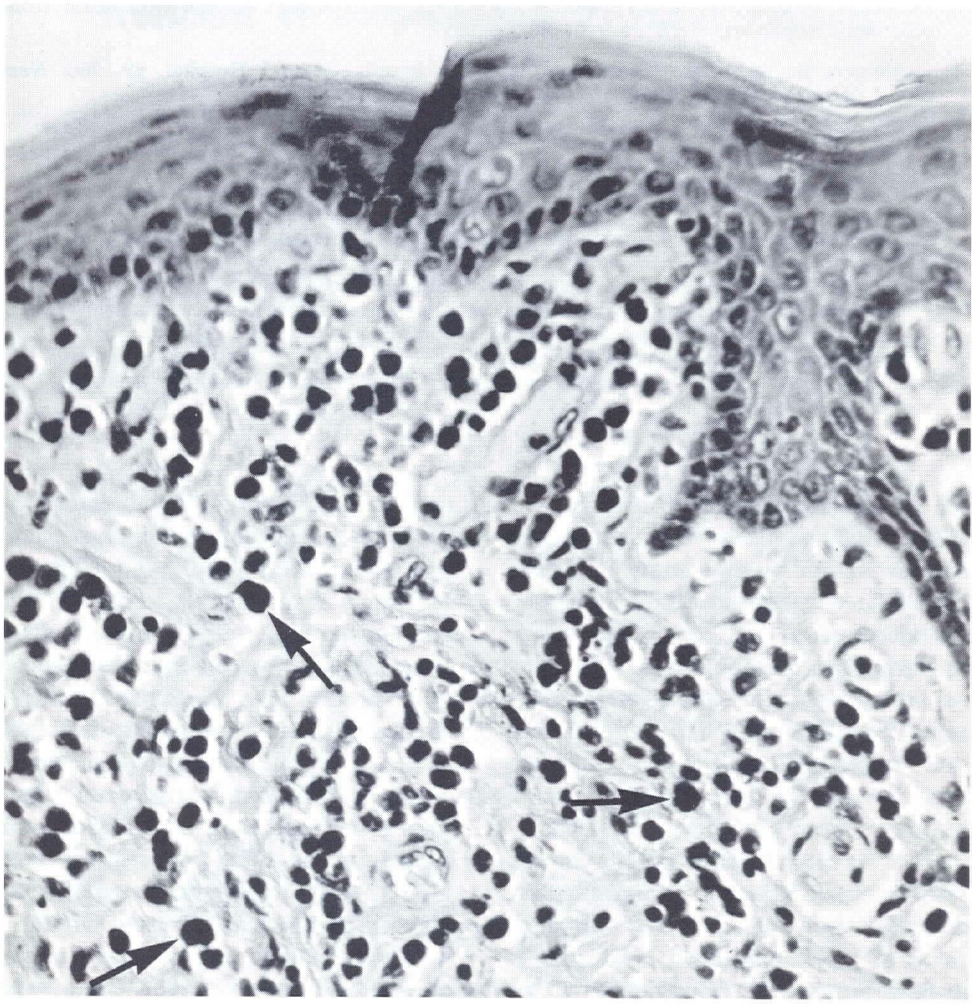

Figure 8

The skin shows a diffuse pleomorphic cellular infiltrate in the dermis. Cells indicated by arrows are atypical reticulum (mycosis) cells. x 375. Hematoxylin and eosin.

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