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PATHOLOGIC CHANGES IN GOUT

SURVEY OF ELEVEN NECROPSIED CASES *

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Renewed interest has been manifested in gout in recent years and, while much still remains to be clarified, the advances of the past decade are impressive. Insight has been gained into the basic nature of this disorder of purine metabolism and this has had practical application in more effective treatment. Among the more significant observations brought forth by Gutman and Yü,[1] Stetten,[2] Talbott,[3] Stecher *et al.*,[4] and others, mention should be made of elucidation of the hereditary factor in gout.

Especially noteworthy is the demonstration, through new isotope techniques, that hyperuricemia in some gouty subjects reflects an augmented, metabolically active pool of uric acid in the body, fed apparently by abnormal diversion of dietary glycine and other readily available metabolites to direct uric acid synthesis (uricotelic tendency). It also has been shown that in gout secondary to various hematopoietic disorders the turnover of nucleic acids involved in hemopoiesis is accelerated, with excessive formation of uric acid. Whatever the mechanism, accumulation of uric acid in these circumstances is of potentially serious consequence in man (as distinct from lower mammalian species) because of enzymatic inability to convert uric acid to allantoin and physiologic resorption by the renal tubules of fully 80 per cent of the glomerular urate filtrate. These factors, along with the relatively low solubility of uric acid and its salts in the tissue fluids, obviously favor the insidious formation of urate deposits in certain skeletal and extra-skeletal sites of predilection, which will be indicated presently.

With reference to improved therapeutic measures, one may cite the

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proved effectiveness of phenylbutazone and corticotrophin as well as colchicine in terminating attacks of acute gout, the use of regular colchicine prophylaxis to reduce the incidence and severity of acute episodes, and the concomitant administration of new uricosuric agents, such as probenecid, with a view to preventing chronic gouty arthritis and perhaps even ameliorating established deformities and disability.

Some definition of essential terms seems indicated in the interest of clarity. The word "tophus" has been used to denote hard deposits or concretions of varying types, even salivary calculi and pararticular syphilitic nodes. In this paper it will have reference only to localized, visible urate deposits, wherever they may be found. The term "gout" has also been used rather loosely in the past and the older literature contains references to so-called calcium gout (calcinosis), lipid gout (xanthoma tuberosum multiplex), and even oxalic gout (oxalism). The use of the designation gout in this vague miscellaneous sense is obviously confusing and is to be deprecated.

The present discussion is concerned exclusively with classical gout, which dates back to antiquity. This may be defined for basic orientation as a hereditary disorder of intermediary purine metabolism characterized by hyperuricemia, irregularly recurring attacks of acute arthritic involvement, and, eventually, a tendency to urate deposition, leading oftentimes to more or less severe, chronic tophaceous arthritis. For further clarification, it should be added that many persons (the relatives of gouty patients especially) may have a latent tendency to gout manifested only by otherwise unexplained hyperuricemia, without ever developing clinical gout. The latter is commonly ushered in by acute gout, affecting not only the first metatarsophalangeal joint (podagra) but frequently other joints as well.[5] The incidence and severity of these sporadic, excruciatingly painful attacks vary considerably from case to case and their pathologic basis is still a matter of conjecture. Between attacks (the so-called intercritical period) gouty patients may be ostensibly well. In fact, many never develop significant tophaceous gout. Some, however, after years of recurring episodes of acute gout, go on to develop chronic deforming changes associated with progressive urate deposition. While this is ordinarily a relatively slow, gradual process, it may be remarkably accelerated at times.[6] To round out the concept of gout and its sequelae, it is essential to note that in some patients there is an associated tendency toward vascular disease of potentially serious import, reflected in a significantly high incidence of hypertension, severe nephrosclerosis with renal insufficiency, cardiac failure, and cerebral vascular acci-

dents. The significance of these cardiovascular and renal changes, as observed in our material as well as by others, will be considered subsequently.

It would appear that general interest in gout on the part of pathologists has not kept pace with recent biochemical and clinical advances, perhaps for lack of opportunity to study relevant material, as Sherman[7] has suggested. Although gout is a fairly common disease, not a few pathologists still have difficulty in unequivocally identifying urate deposits microscopically through unfamiliarity with the distinctive pattern of foreign body giant cell reaction. Only a limited number of papers dealing with certain of the pathologic findings in gout, notably those of Bunim and McEwen,[8] Sherman,[7] Spitz *et al.*,[6] Kersley *et al.*,[9] and Traut and his associates[10] have appeared since 1940. It seems worth-while, therefore, to present in some detail a necropsied case of chronic deforming gouty arthritis of unusual severity, characterized further by remarkable calcification and ossification of tophaceous deposits. For collateral study, the protocols and slides of 10 additional necropsied cases of proved gout from our files, dating back to 1948, were reviewed.

The inferences culled from this material, amplified from the pertinent literature, will serve as a basis for comprehensive discussion.

Report of Case

The patient was a white male, 56 years of age, who was admitted to the hospital on April 19, 1952, because of severe deforming arthritis, as well as increasing weakness and periods of mental confusion. He was known to have had gout for about 35 years, first manifested by occasional episodes of acute gouty arthritis affecting his toes and/or fingers. These recurred sporadically and he went on to develop large tophi about the peripheral joints. By 1928 (at age 32) his fingers were no longer movable, and his feet were already severely deformed. During this entire period and throughout the rest of his life the patient observed no dietary restrictions and took colchicine only rarely and, then, in small ineffective doses. Despite his handicap, he remained active in business until 1944 (age 48), although he had been obliged to use crutches during the preceding 3 years. It is pertinent that no history of gout and/or hyperuricemia in other members of his family was elicited, although it appears doubtful whether thorough investigation was made.

By 1940 (at age 44) the effects of chronic tophaceous gout necessitated his seeking hospital treatment (elsewhere), the details of which are not available. He was first treated at this hospital in 1944 for progressive deforming arthritis and discharging tophi. At that time he presented slight hypertension (170/90 mm. of Hg), some impairment of renal function, and moderately severe secondary anemia. The serum uric acid level was noted to be 8.6 mg. per 100 cc.

The patient was observed here again in 1951, with manifestations of what appeared to be hypertensive encephalopathy. His blood pressure had risen to 230/135, and there were indications of increasing renal insufficiency. The uric acid level was estimated as high as 13 mg. per cent. After his cerebral symptoms

cleared in response to treatment, it was noted that the patient had sustained a fracture through the neck of the right femur, presumably during a convulsive seizure. This fracture failed to unite but open reduction was not attempted because of his poor renal status. Roentgen skeletal survey showed widespread, severe, gouty arthritis and striking radiopacity of the prominent tophaceous deposits, especially in the hands and feet, suggesting unusual calcification of them. The patient left the hospital, only to return after some months, when he suffered another attack of acute gout affecting the left knee.

During his terminal hospital stay, he was obviously in uremia and the blood urea nitrogen level rose steadily to 126 mg. per cent, while the uric acid level was reported as high as 14.1 mg. Despite supportive measures, he gradually lapsed into coma and died on the seventh hospital day.

Post-Mortem Examination

Gross Findings

The body was that of a somewhat obese white male, measuring 68 inches in height (Fig. 1) and weighing approximately 175 lbs. The hair was thin and graying. A number of small tophi, measuring up to 2.0 mm., were observed on the ears. The hands were strikingly deformed, presenting sausage-like enlargement of all the fingers from firm subcutaneous deposits, as well as marked flexion deformity of the left wrist (Fig. 2). There was also a marked flexion deformity of the left elbow. Over both forearms there were multiple, rubbery, freely movable, subcutaneous nodules, measuring up to 2.0 cm. in diameter (Fig. 4). The anterior abdominal wall was flabby, and the muscles of the extremities appeared wasted from disuse. Examination of the right lower extremity indicated the presence of a fracture of the femoral neck. Both knees appeared swollen. The feet were of twice the usual thickness, apparently from the presence of widespread, firm, tophaceous deposits, resembling those seen in the hands (Fig. 3). There were two sinuses over the right first metatarsophalangeal joint, apparently related to discharging tophi, and there were also a number of small scars on the hands and over the left knee.

The panniculus adiposus was 4 cm. in thickness and there was abundant fat in the omentum and mesentery. The liver extended 2.0 cm. below the right costal margin. Inspection of the abdomen showed nothing noteworthy, otherwise. The serous cavities contained no free fluid. The pleural surfaces were smooth and glistening.

The *heart* weighed 375 gm. and the pericardial sac was rather fatty. The noteworthy changes were dilatation of the right auricle and ventricle, moderate hypertrophy of the left ventricle, and calcification of the mitral ring, as well as of one of the aortic cusps. The coronary arteries were thin-walled and widely patent, while the aorta showed relatively little atheromatous change.

The *thyroid gland* showed nothing unusual.

Three *parathyroid glands* of normal size were identified.

Lungs. The tracheobronchial tree contained a large amount of viscid brown sputum and the mucosa of the larger bronchi appeared hyperemic. The lungs weighed 800 gm. each and, on section, showed slight congestion and edema.

The *liver* weighed 2,100 gm. and its surface was yellow-brown, smooth, and glistening. Its architecture appeared unaltered.

The *gallbladder* contained 10 cc. of brown bile and presented a thickened wall, in which there were focal submucosal deposits of calcareous gravel. The bile ducts were not remarkable.

The *spleen* weighed 150 gm. and presented a firm, reddish purple pulp.

The *pancreas* was heavily infiltrated by fat, but was not unusual otherwise.

The *adrenal glands* showed thin cortices, somewhat depleted of lipid.

The *kidneys* were appreciably reduced in size and presented irregular, coarsely granular cortical surfaces, pitted by retention cysts, ranging in size up to 1.5 cm. in diameter. There were also a number of small yellow-white, slightly elevated nodules resembling cortical adenomas. On section, the kidneys were pale gray-brown and the markings of cortex and medulla could not be clearly distinguished (Fig. 21). Also noted were several chalky, yellow-white deposits within the medulla, resembling tophaceous material. The pelves and calyces appeared slightly dilated and thickened, and contained creamy yellowish fluid. The ureters also appeared thick-walled, but were of normal caliber.

The *urinary bladder* was thickened and trabeculated, and contained creamy, inspissated urine. Its mucosa appeared hyperemic and somewhat edematous. The *prostate* was nodular and contained tiny calcific concretions. The *seminal vesicles* appeared normal, as did the testes.

The *gastro-intestinal tract* showed nothing noteworthy.

Brain. The calvarium, dura, and leptomeninges were not unusual. The brain weighed 1,400 gm. and, on serial coronal section, presented no gross abnormalities. The vessels at the base were thin-walled and patent.

Skeletal System. Inspection of a ventral slice of the lower dorsal and lumbar vertebral column showed chalky deposits within the intervertebral disks and the contiguous spongy bone; the bodies, otherwise, were not altered (Fig. 11).

Examination of the right hip joint showed a rent in the capsule, allowing thick, creamy, blood-stained material to exude into the adjacent muscles and fascial planes. The acetabulum was extensively modified. The head of the femur constituted a loose fracture fragment; its articular surface was partially denuded and irregularly coated by yellow-white urate deposits suggesting drops of paint. There was non-union at the fracture site in the femoral neck, and at the bone ends one observed fibrous tissue coated by a creamy white paste (Fig. 12). Chemical assay of this material indicated a concentration of calcium as high as 4.0 per cent and of urate, exceeding 11.0 per cent.

Inspection of the left knee joint disclosed a thin, irregularly dispersed spattering of chalky white material on the articular surfaces of the femur and tibia. This was most prominent around the edges of the articular bone ends and was generally absent at contact points. The cartilage was almost completely destroyed. The articular surface of the patella was likewise extensively denuded of cartilage and coated by heavy deposits of whitish urate material. Sections through the articular bone ends revealed several, comparatively soft, chalky white deposits within the femur and tibia, just beneath their articular ends. Within the lower end of the femur, some 4 cm. proximal to its articular surface, there were additional localized urate deposits surrounded by fibrous tissue and apparently condensed spongiosa (Fig. 9). The synovial membrane of the knee joint showed villous hypertrophy in places, as well as chalky granular deposits in the vicinity of the patellar ligament (Fig. 10). Within the ligament also, there were a number of similar foci ranging up to 1.0 cm. in greatest diameter.

The feet were remarkably swollen and deformed, as noted (Fig. 3). At the level of the head of the third metatarsal, they measured as much as 6 cm. in their supero-inferior dimension. Beneath the skin and extending to the modified atrophic remnants of the foot bones, there was a thick layer of gray-yellow, granular, calcareous material and chalky firmer deposits, interspersed by tracts of fibrous tissue (Fig. 13). In the perionychial spaces also, there was a layer of chalky material extending into the nail beds. The right foot was sectioned sagittally in the plane of the middle ray. On section, the head of the third metatarsal bone presented as a thin shell containing pinkish gray mucoid material and irregular deposits of chalky white paste. The discernible phalanges appeared to be partially destroyed and similarly replaced by chalky deposits. The interphalangeal joint spaces, too, appeared virtually obliterated by calcareously impregnated urate deposits.

Microscopic Findings

The significant findings have been incorporated in the anatomical diagnosis and will not be described in detail here with exception of those relating to the manifestations of gout and its sequelae.

Skeletal Tissues. Sections of the foot showed the presence in the deeper layers of the skin and subcutis, as well as in the underlying fascia, of extensive, conglomerate, smaller and larger urate deposits. These were ringed in characteristic fashion by foreign body giant cells, as well as mononuclear histiocytes (Fig. 15), and presented, as an added feature, prominent and often heavy calcium deposition within urate material. Also in evidence were trabeculae of reactive new bone around the periphery of some of the urate deposits (Figs. 16 and 17). The latter appeared amorphous for the most part, and only in the alcohol-fixed preparations could one discern crystalline structure. The connective tissue between the focally calcified urate deposits contained fibroblasts, adventitial reticular cells mobilizing as macrophages, and a scattering of small mononuclear cells.

Sections of the femoral head (constituting the proximal fracture fragment) showed the articular cartilage to be eroded in places and replaced by urate-containing pannus. Urate deposits were present also within the subchondral bone and marrow. As noted grossly, there were prominent urate deposits at the site of pseudo-arthrosis in the femoral neck (Fig. 12), as well as numerous polymorphonuclear leukocytes indicative of localized infection.

Sections of the knee joint capsule showed pronounced villous hypertrophy of the synovium and focal deposits of urate material within the synovial lining and subjacent tissue. Here, too, calcification of urate deposits was a conspicuous feature (Fig. 19).

Sections of the vertebral column showed conglomerate urate deposits within the intervertebral disk tissue, as well as in the contiguous spongiosa of the bodies. Within the vertebrae, at sites of urate deposition, were observed interstitial fibrosis and slight reactive osteosclerosis.

Sections of both *kidneys* showed widespread cortical scarring and interstitial inflammation, apparently indicative of chronic pyelonephritis. There were also polymorphonuclear leukocytes within the areas of fibrosis, as well as in some of the tubules. Also noted were partial or complete obliteration of many glomeruli, dilation of tubules, and moderate thickening and narrowing of the small arterial branches. Multiple small cortical adenomas were dispersed through both kidneys. Within the tubules there were many small calcific concretions. Deep

in the parenchyma there were a number of spaces (without distinct lining) which contained urate material admixed with calcium. There was leukocytic reaction about them, as well as in the surrounding interstitial connective tissue. The latter also contained occasional small, focal, urate deposits ringed by small histiocytes. The renal pelves showed chronic inflammation of the fat tissue and mucosa, which also presented focal erosions.

Sections of the *prostate* showed fibro-adenomatous hyperplasia and chronic inflammation of the larger ducts. Many of the smaller ducts and acini contained inspissated secretion and within the lumina in one group of dilated ducts there were yellow-brown needle-like crystals resembling those of urate deposits. They were surrounded by foreign body giant cells and were associated also with intense focal calcium deposition (Fig. 23).

While the *parathyroid glands* were not appreciably enlarged, they showed significant chief-cell hyperplasia, apparently reflecting long-standing chronic renal insufficiency.

The remaining sections showed nothing remarkable, except as indicated in the anatomical diagnosis.

Anatomical Diagnosis

Far advanced, chronic tophaceous gout: chronic gouty arthritis of long standing, involving almost all joints, with severe deformity; extensive subcutaneous tophi in hands, feet, forearms, ears, with pronounced calcification and regional heterotopic ossification; urate deposits within fascia, tendons, ligaments, periosteum, articular bone ends, at fracture site (femoral neck), and in intervertebral disks; urate deposits within renal tubules; prostatic concretions, apparently containing urates. Severe chronic and acute pyelonephritis, with extensive alteration of renal architecture; uremia; hypertensive encephalopathy (clinical); old fracture of right femoral neck, with non-union; generalized osteoporosis; chief-cell hyperplasia of parathyroid glands (microscopic). Generalized arteriosclerosis; lipomatosis and intralobular fibrosis of pancreas; cholelithiasis.

Discussion

Hereditary Character of Gout

The familial incidence of gout has long been recognized. Recent investigations[11,12,4] of the pedigrees of numerous gouty families have shown that many members apparently free of symptomatic gout nevertheless manifest hyperuricemia. If one accepts the reasonable premise that hyperuricemia in these circumstances represents an expression

of latent gout, it becomes possible to study the full genetic pattern of familial inheritance. According to Stecher, Hersh, and Solomon,[4] the available data strongly suggest that the tendency to gout is transmitted as an autosomal dominant genotype having a much lower penetrance in the female than in the male (approximately 1:20). The *modus operandi* of this genetic defect in biochemical terms is still obscure and its clarification would seem to hinge upon better understanding of the essential enzyme reactions in the intermediary metabolism of purine derivatives, a field which is now being explored profitably.[13]

The Nature of Acute Gout

There has been much speculation in regard to the pathogenesis of acute gout. However, apart from a keener awareness of numerous precipitating "stress" factors, we have no better insight actually than did Sydenham[14] in 1683, when he rendered his classical description of the torture he endured during gouty attacks. For that matter, the basis for the specific action of colchicine in alleviating these attacks is still not understood, although the drug has been in use for some 1400 years. It is quite conceivable that elucidation of the biochemical action of this remarkable alkaloid (used also in plant breeding and genetics) may yet furnish the key to solution of the problem. As for direct pathologic observation, according to Talbott[3] not a single report of the gross or microscopic examination of the interior of an affected joint during an acute attack has appeared, apparently because no one has had the temerity to secure material for biopsy in these circumstances. Nor has the condition ever been reproduced or simulated experimentally by any means whatsoever. For reasons which have been cogently marshalled elsewhere,[15] urate deposition *per se* cannot be held responsible plausibly for acute gouty attacks. As Gutman[16] has tentatively suggested, however, it is possible that acute gout is provoked by some precursor of uric acid, perhaps an intermediary purine metabolite as yet unidentified. Although the concept also has been advanced[17] that temporary adrenocortical deficiency may be the trigger mechanism, the observations of Levin, Rivo, and Bassett[18] would seem to cast serious doubt upon the soundness of this view. In any event, this factor in itself would hardly account altogether for the acute gouty episode.

Urate Deposition in Chronic Gout

In contrast to acute gout, there is every indication that chronic gout results from very gradual, but appreciable deposition of urates, especially within and about the joints, and that no other essential etiologic

factors need be invoked. Even in birds (which, unlike man, are well equipped to dispose of uric acid as the normal nitrogenous waste product of ordinary protein, as well as of purine catabolism), a condition resembling chronic tophaceous gout, so-called avian gout, may be induced experimentally by prolonged forced feeding of protein, by ligation of both ureters, or by the use of renal poisons. Under these conditions, as Bauer and Klemperer[19] have cited, urate deposition takes place in the joint cartilages and large tophi appear in the extremities.

Fortunately, according to Talbott[3] and other experienced clinicians, chronic deforming gouty arthritis is the ultimate fate of only a limited number of patients afflicted with gout and particularly of those who suffer frequent attacks of acute gout while still comparatively young. While most patients with gout are middle-aged when they first experience arthritic attacks, the latter may occur in younger persons, and have been noted even in children. Incidentally, the subject in the case reported sustained his initial bout of acute gout at age 21, and at the comparatively early age of 32 already presented severe deformity and limitation of motion of his hands and feet. His prolonged neglect of prophylactic treatment may well have contributed to the extensiveness of the urate deposits observed at necropsy.

In chronic tophaceous gout the characteristic tissue response to urate deposits, wherever they may be encountered, is essentially that of a peculiar foreign-body reaction (Fig. 15). As noted, the urate material usually appears rather amorphous in formalin-fixed specimens, and only in alcohol-fixed preparations does one regularly discern crystalline structure. This apparently depends upon the presence of sodium biurate,[9] with an admixture also of protein and, occasionally, of a small quantity of cholesterol. On microscopic examination, as indicated, one characteristically observes smaller or larger, discrete or conglomerate deposits, ringed peripherally by foreign body giant cells and/or mononuclear histiocytes. This reaction pattern is sufficiently distinctive, so that blackening with silver[20] is scarcely required for confirmation. The inflammatory response otherwise usually is rather inconspicuous provided that there has not been ulceration or complicating infection, although one may note slight interstitial fibrosis and occasional macrophages or small mononuclear cells.

The finding of striking widespread calcification of urate deposits in our major case merits brief comment. Localized calcification of tophi in gout, while noteworthy, is apparently not too uncommon. A number of writers[21,22] have remarked, for example, that sizeable tophi

of long standing in olecranon or prepatellar bursae may occasionally become sufficiently impregnated with calcium to render them radiopaque. Also, in one of our other cases tophaceous deposits in a toe were found to be calcified. Massive widespread calcification of tophaceous material, however, appears to be distinctly unusual. In the necropsied case of gout reported by Kersley, Mandel, and Jeffrey,[9] pronounced calcification in the tophaceous soft parts of the hand was demonstrated. Similarly, Talbott[3] illustrated heavy calcium deposits associated with urate tophi within the bones and soft parts of the foot, although he referred to the observation as being almost unique. By the same token, the finding of conspicuous heterotopic ossification within tophaceous deposits in our case (Figs. 16 and 17) likewise is remarkable, and it may well be that the presence of abundant calcium was a significant predisposing factor.

Calcification of urate deposits seems clearly to represent a secondary change in point of time. Furthermore, in our case at least, it did not appear to be an expression of secondary hyperparathyroidism associated with chronic renal insufficiency. It is true that the parathyroid glands showed hyperplasia microscopically. On the other hand, the evidence of skeletal resorption apart from disuse atrophy was minimal, and appreciable calcium deposition was observed only within tophaceous material.

Skeletal Alterations. That the skeletal connective tissues, particularly the joints and periarticular structures, bear the brunt of urate deposition in tophaceous gout is common knowledge. For a detailed account of these skeletal alterations one may turn to the article by Lang,[23] which is useful also for its compilation of the pertinent German literature. It may be worth-while, however, to emphasize the essential changes for convenient orientation. Within an affected joint (be it a metatarsophalangeal, metacarpophalangeal, or interphalangeal joint, a knee, a hip, a shoulder, or any other) focal, chalky white or yellow, tophaceous deposits are observed on the articular surfaces (appearing oftentimes as though painted). They are also found in the deeper layers of the cartilage. The articular cartilage tends gradually to be destroyed and replaced by pannus (Fig. 20). Eventually, in severe instances with attendant deformity and immobilization, fibrous ankylosis may ensue,[24] as well as the usual changes of secondary osteo-arthritis. The latter are often reflected in the appearance of roentgenographically discernible subchondral rarefactions, although these in themselves are by no means pathognomonic of gout, as is sometimes assumed. Concomitantly, the synovial lining and the sub-

lining connective tissue of the affected joint capsule likewise exhibit focal impregnation by urates and, eventually, more or less extensive, reactive, chronic villous synovitis ensues (Fig. 19). The articular bone ends frequently manifest urate deposits within their periosteal covering, as well as in the subchondral spongy bone (Figs. 9 and 18). The ligaments and tendons, too, may be more or less heavily impregnated (Figs. 16 and 17). Similarly, certain of the pararticular bursae, especially the olecranon and prepatellar bursae, are often predilected. In the vertebral column, as seen in our case, the intervertebral disks and the contiguous portions of the bodies may be the sites of appreciable urate deposition (Fig. 11). In the noteworthy case meticulously recorded by Kersley and his associates,[9] tophaceous involvement of the first cervical vertebra (among other sites) was so extensive as to bring about subluxation of the upper cervical spine and impending compression of the cord.

Extraskeletal Urate Deposits. As noted by numerous investigators,[25,26] the deposition of urates in gouty subjects may be encountered in certain extraskeletal sites as well, with greater or lesser frequency. Tophaceous involvement of the skin and subcutis, especially of the hands and feet and occasionally of the ear, is, of course, commonly observed in instances of moderate severity. Involvement of the eyelids, the cornea, and the sclera has also been noted, although this is comparatively unusual and we have not observed it in our own material. More important, urate deposits frequently are encountered at necropsy in the kidneys and occasionally in the lower urinary tract as stones or gravel. Also noteworthy is deposition in the heart and blood vessels, observations of which will be cited in the following section. The literature also contains casual reference[25] to the finding of urate deposits within the cartilages of the upper and lower airways (nose, epiglottis, vocal cords, arytenoid cartilages, and the bronchi), as well as in other rare sites, specifically the tongue, prepuce and corpus cavernosus of the penis, testis, pleura, and meninges. These latter references (which we were unable to verify) are to be found mainly in the older German literature and date back to a period when inordinately severe, tophaceous gout apparently was more common than it is today. Among the findings mentioned, the cardiovascular and renal changes are of sufficient interest to merit further consideration.

Cardiovascular Lesions. Specific involvement of the heart in tophaceous gout is comparatively rare and was not noted in our material, although there are a limited number of pertinent observations on

record. The finding of urate deposits in the pericardium has been cited by Kaufmann.[26] With reference to myocardial involvement, Hench and Darnall[27] have called attention to a remarkable case in which complete heart block was caused by a large (urate) tophus affecting the conduction bundle. Also noteworthy is the observation by Bunim and McEwen[8] of urate deposition in the posterior leaflet of the mitral valve of a 63-year-old man with long-standing, chronic tophaceous gout. This tophus was sharply circumscribed, about 4.0 cm. long and 0.5 cm. thick, and was associated with little, if any, inflammatory change. In this connection, mention should be made of another pertinent instance recently described by Traut and his associates[10] in which urate deposition was noted likewise in a mitral valve leaflet extending down over the endocardium of the left ventricle, and apparently in the aortic cusps as well. The same authors reported another instance of gout in which urate crystals were believed to be present within the wall of a coronary artery and within several of the intra-abdominal arteries. Positive identification was lacking, however, and the possibility that the crystals observed were of the nature of cholesterol cannot be dismissed. In surveying our own 11 necropsied cases of gout, careful search was made for urate deposits within blood vessels, but none was found.

Renal Changes in Gout. It has been stated[3] with apparent justification that renal failure is the single most important cause of death in gouty patients irrespective of age, and the only important cause of premature death. It is noteworthy that the primary cause of death was uremia in 5 of the 11 necropsied cases of proved gout studied by us. All but one of these patients were men in their fifties. This experience, while limited, is essentially in accord with the clinical observations of Schnitker and Richter[28] on 55 patients with gout, 17 of whom (approximately one third) presented evidence of renal insufficiency. As Talbott[29] has indicated, chronic renal impairment need not necessarily go hand in hand with advanced joint disease and may, in fact, completely overshadow what appears clinically to be minimal arthritic involvement. In any event, once renal insufficiency develops, it tends to aggravate the manifestations of tophaceous gout through uric acid retention and further elevation of the plasma urate.

Collaterally, another serious hazard of many gouty patients apparently is their tendency to develop hypertension and significant arteriosclerosis, for reasons which are not yet altogether clear. This trend also is reflected in our material in that another 5 of the 11 patients succumbed to coronary thrombosis, congestive heart failure, or intra-

cranial hemorrhage. These findings are in harmony with those of Brown and Mallory,[30] among others. Although Fishberg[31] has expressed the view that there is no convincing evidence to indicate that gout plays a rôle in the pathogenesis of essential hypertension, their positive association cannot be dismissed readily as fortuitous. Specifically, the systolic and diastolic blood pressures were noted to be moderately or markedly elevated in 7 of our 11 gouty subjects. The corresponding weights of these hearts at necropsy ranged from 450 to 650 gm., with the majority about 500 gm. While the number of cases surveyed is not highly significant statistically, it is perhaps noteworthy that all but one of the gouty subjects necropsied here within the past several years died of cardiovascular or renal complications.

The concept of "gouty nephritis" or of "gout kidney" has long been a rather vague one[32] and it seems questionable whether it is advantageous to retain these old designations, except perhaps for convenient reference to the specific instances in which appreciable urate deposition is demonstrated in the renal parenchyma. The general opinion[30,33] at present is that the kidneys of gouty patients suffering from renal insufficiency present a variety of changes characterized by more or less severe arteriosclerotic contraction, chronic pyelonephritis, and frequently, though not invariably, the presence of urate deposits. As Brown and Mallory[30] have emphasized, the latter are encountered mainly within the lumina of collecting tubules and in their vicinity, where they tend to obstruct, to destroy the tubular epithelium and, in general, to set up a focus of subacute or chronic pyelonephritis. Occasionally, the presence of uric acid stones or gravel in the renal pelvis may be another predisposing factor favoring the development of pyelonephritis, although this is not very common and was observed in only one of our cases. On the other hand, urate deposition within the renal pyramids and associated with significant pyelonephritis was noted in 4 of the 5 cases terminating in uremia. When these urate deposits are comparatively small and surrounded by small macrophages rather than conspicuous foreign body giant cells, their significance may be readily overlooked by an inexperienced observer.

Summary

This paper deals with the pathologic changes in gout, as indicated by the findings in 11 necropsied cases and by collateral study of the pertinent literature. A detailed account is given of the findings in one of these cases, an instance of chronic deforming gouty arthritis of unusual severity, characterized by remarkable calcification and

ossification of tophaceous deposits. While emphasis has been placed upon the pathologic changes observed in fully developed chronic tophaceous gout, particularly the skeletal, cardiovascular, and renal alterations, an attempt has been made also to bring the condition as a whole into sharper focus in the light of recent clinical and biochemical advances.

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LEGENDS FOR FIGURES

FIG. 1. The patient in the case reported in detail, showing widespread prominent tophi and the effects of deforming arthritis.

FIG. 2. A hand of this patient, showing flexion deformity at the wrist and sausage-like expansion and deformity of the fingers, reflecting extensive tophaceous deposits. This may be compared with the roentgenogram in Figure 7.

FIG. 3. Comparable changes in the foot of this patient, illustrated also in Figure 8.

FIG. 4. Multiple tophi in the elbow region and forearm.

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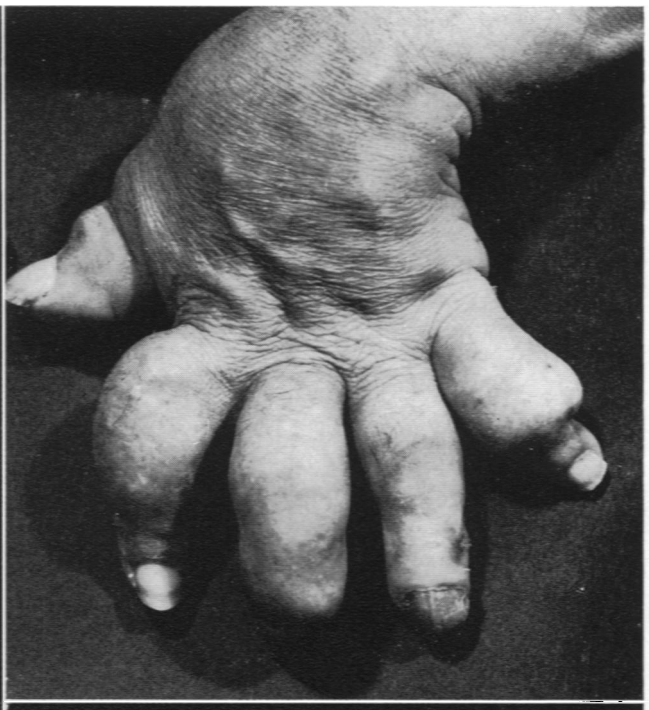

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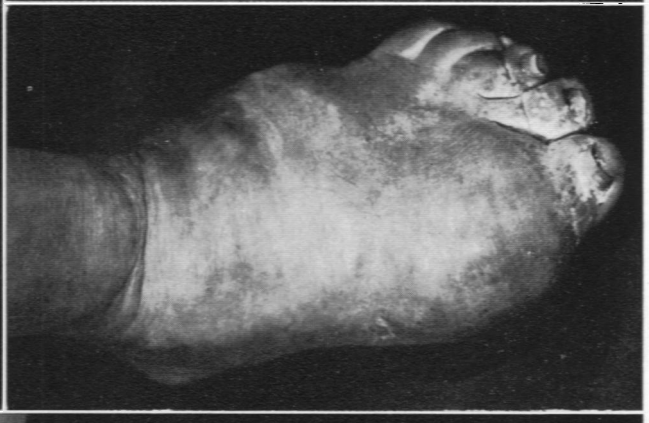

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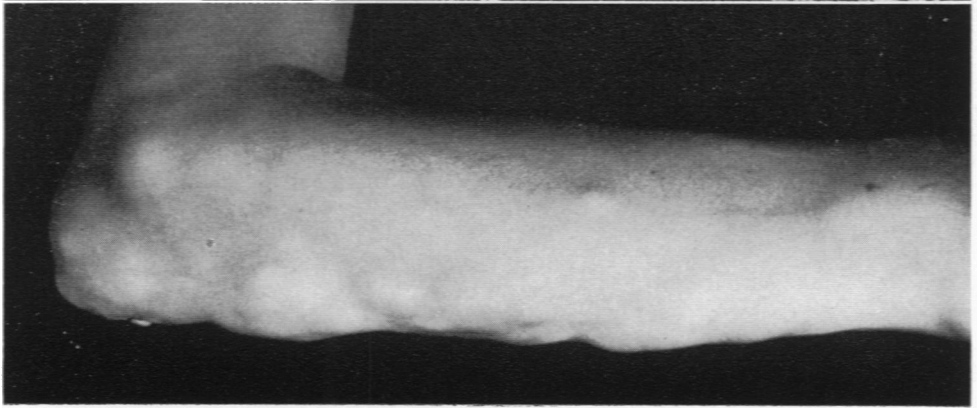

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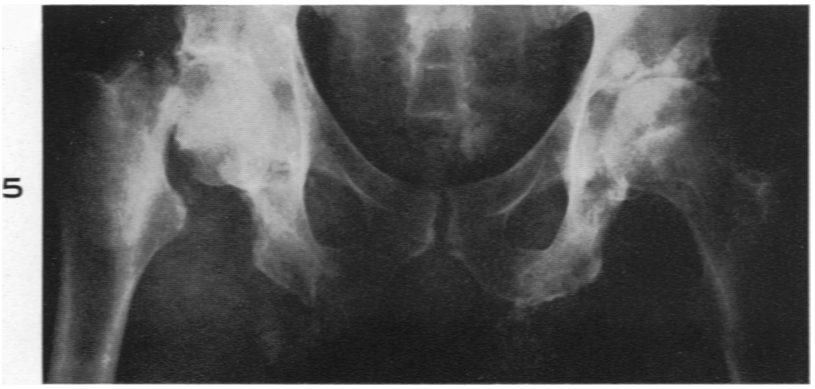


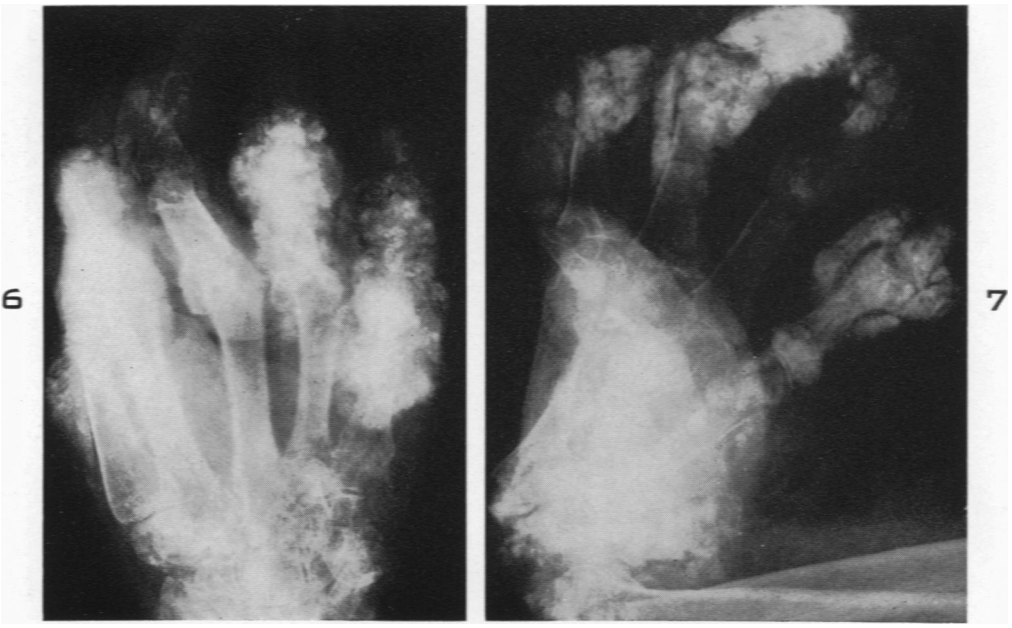
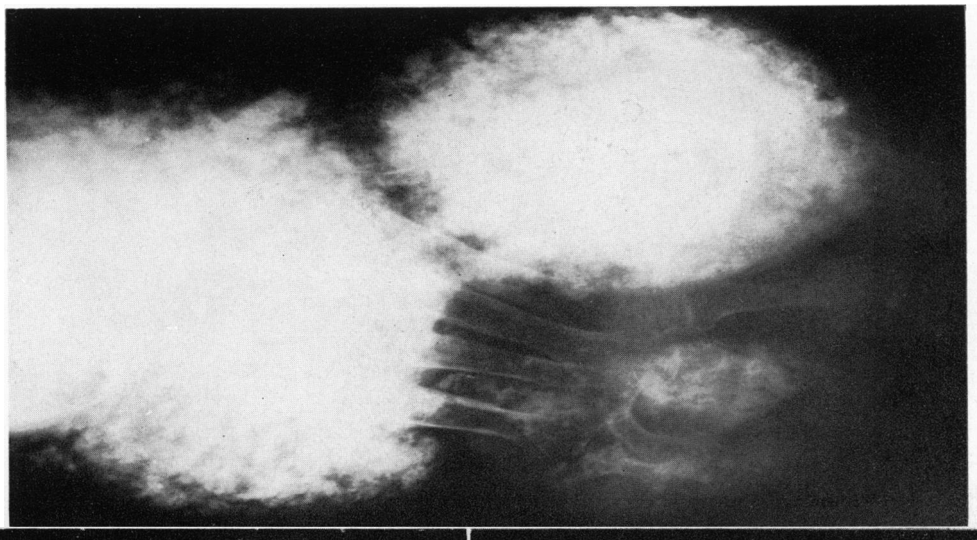


FIG. 5. Roentgenogram of the pelvis and upper femora in the case illustrated in Figures 1 to 4, showing radiopaque tophaceous deposits in the hips and ischial tuberosities, and an un-united fracture in the neck of the right femur.

FIGS. 6 and 7. Roentgenograms of the hands in the same case, showing striking radiopacity of tophaceous deposits, reflecting heavy calcification. Of note also are the skeletal alterations associated with advanced chronic gouty arthritis.

FIG. 8. Comparable changes to those in the hands are shown in a foot of the same patient.



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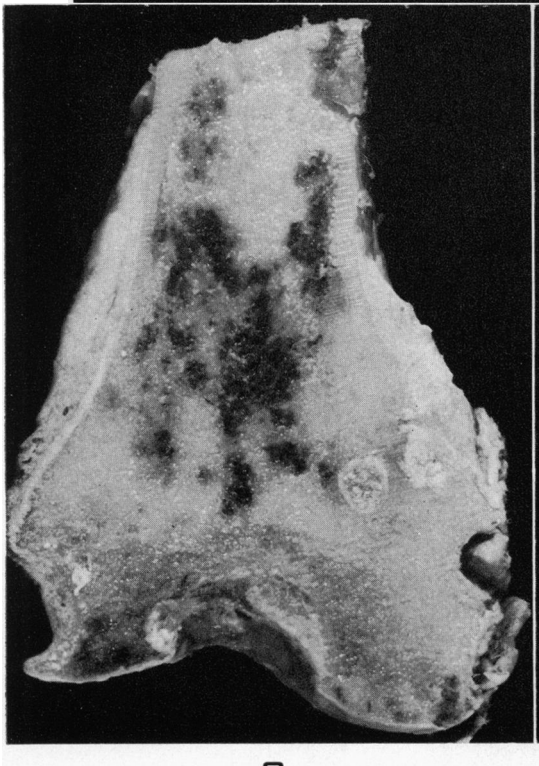

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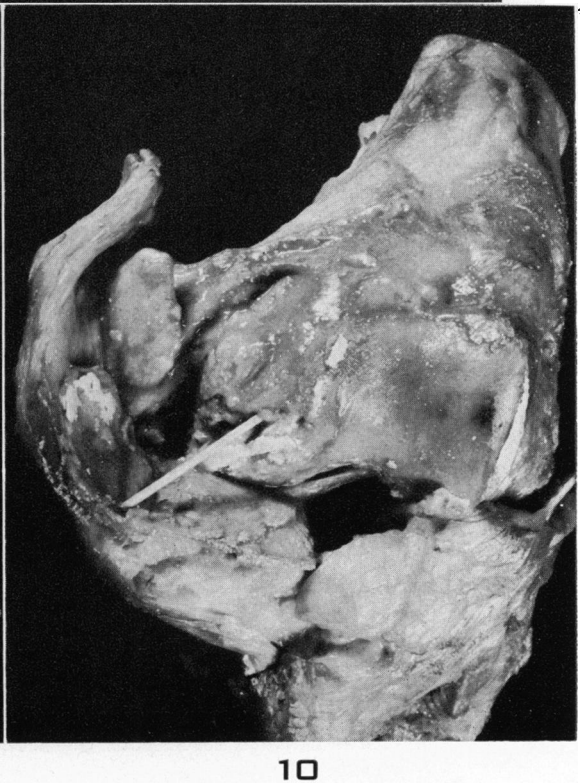

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FIG. 9. A frontal section of the lower femur in the necropsied case reported in detail, showing focal urate deposits subchondrally and also deep to the joint surface. See also Figure 18.

FIG. 10. Photograph of the lining surface of the capsule of the knee joint, showing chalky (yellow-white) flecks of urate deposit within the synovial membrane and on the articular cartilage of the patella, especially around its periphery. This may be compared with Figures 19 and 20.

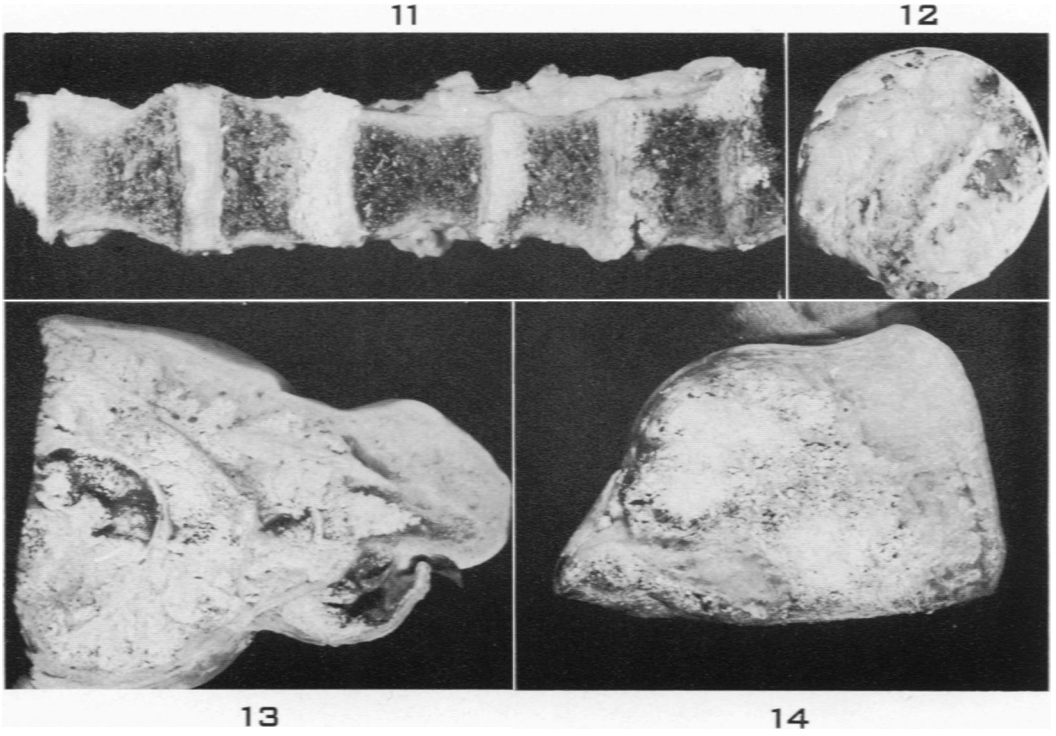


FIG. 11. Ventral slice of a segment of the vertebral column showing heavy urate deposits within most of the intervertebral disks and extending into the contiguous bodies.

FIG. 12. The under surface of the femoral head (constituting a proximal fracture fragment) heavily coated in places by a streaky layer of urate deposit. This site was bathed in a thick, white, creamy paste rich in calcium and in urates (determined by chemical assay).

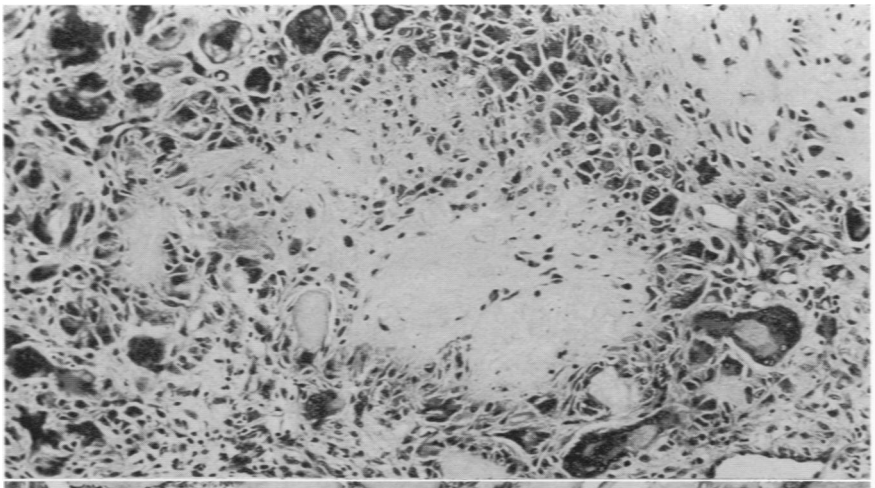
FIG. 13. Sagittal section through the middle ray of the right foot demonstrating substantial destruction of the bones and diffuse deposition of chalky urate material. Sections showed the latter to be calcified and ossified in places. See Figure 17.

FIG. 14. Another field comparable to that of Figure 13, and likewise showing abundant calcified tophaceous deposits.

FIG. 15. A representative field, showing urate deposits characteristically ringed by foreign body giant cells, as well as smaller macrophages. This block was fixed in formalin, rather than alcohol, and crystalline structure is lacking. × 250.

FIG. 16. Conglomerate urate deposits within the plantar fascia. There is a tendency to new bone formation at the periphery of some of these deposits. × 55.

FIG. 17. Calcification and appreciable ossification of tophaceous material within the skin and subcutis of a foot. × 55.



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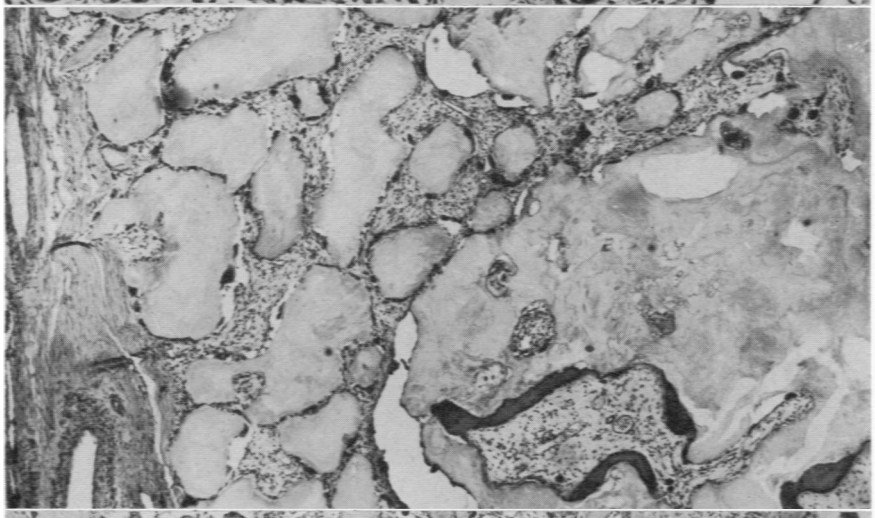

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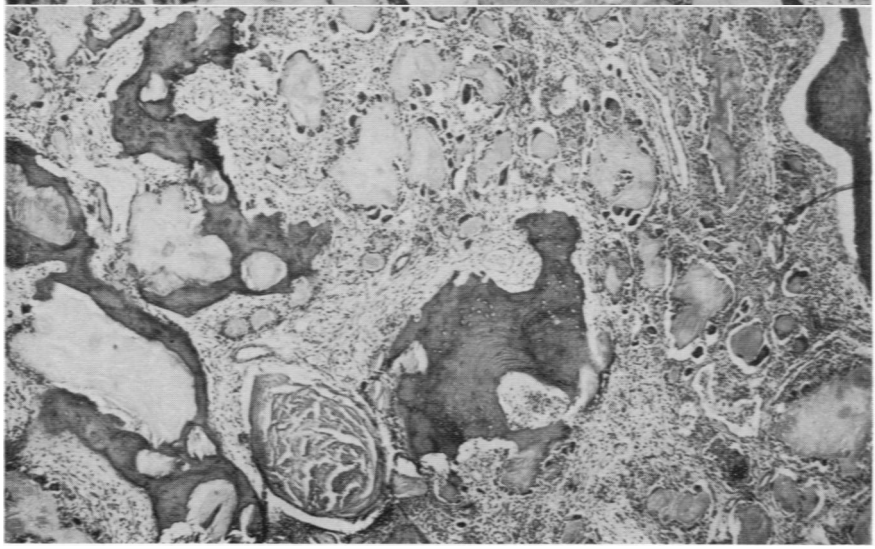

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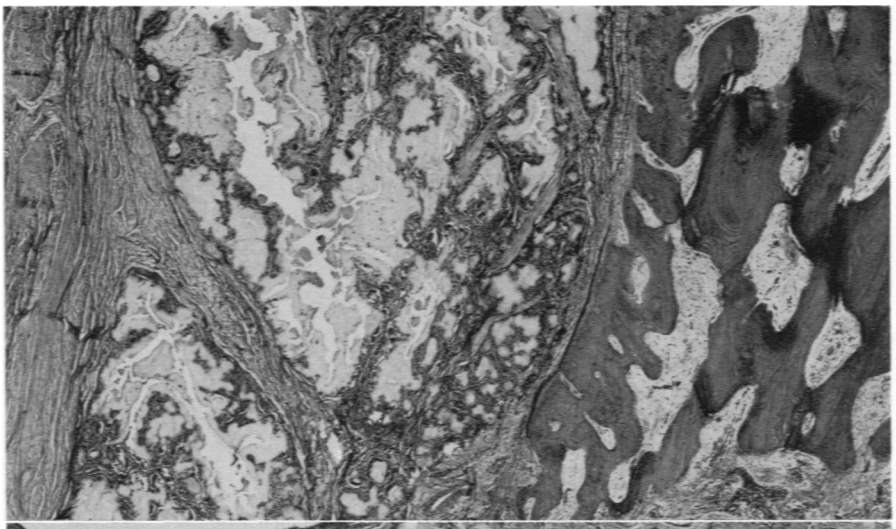
FIG. 18. Photomicrograph showing the general appearance of urate deposits within bone. × 55.

FIG. 19. Conspicuous calcification of urate deposits within the synovial lining and sublining connective tissue of a knee joint. × 55.

FIG. 20. From an articular surface (patella), showing loss of the articular cartilage (toward the left of the illustration) and replacement by urate-containing, vascularized connective tissue. × 180.



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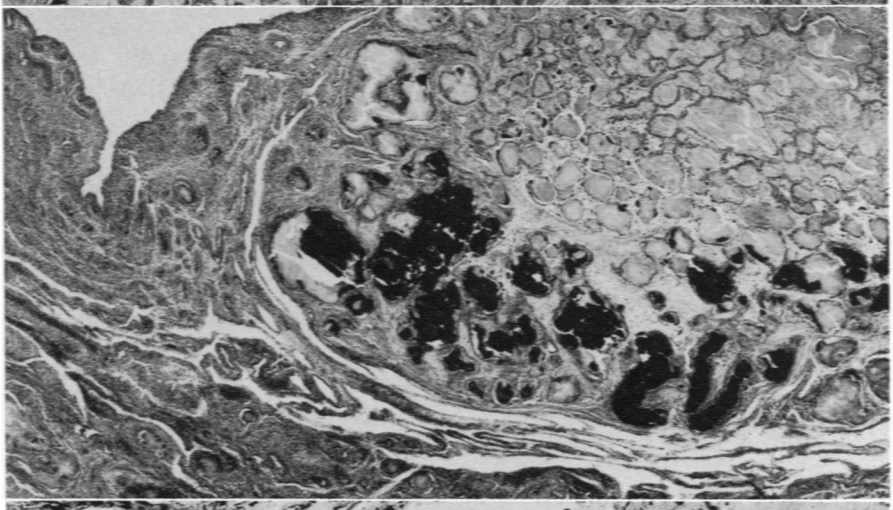

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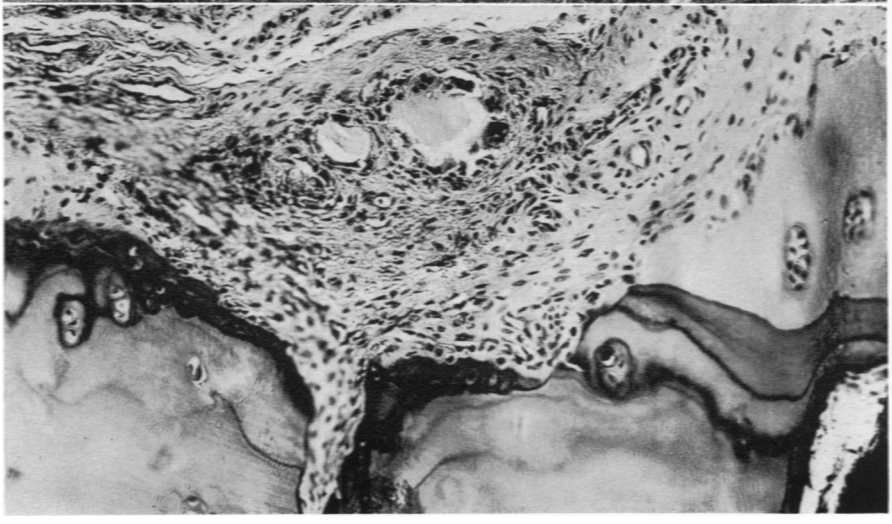

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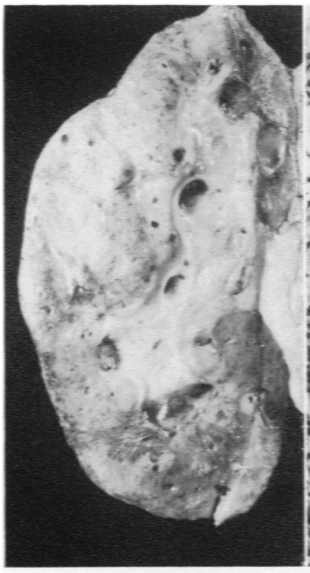
FIG. 21. Cut surface of the pale, scarred, and contracted kidney. Tophi were recognized within the medulla in the fresh state, but these are no longer clearly discernible in the preserved specimen.

FIG. 22. Urate deposition within a renal pyramid, in proximity to the pelvic mucosa. × 110.

FIG. 23. Crystalline deposits resembling urates within distended acini of the prostate. There is a foreign body reaction about them. The associated blackish deposits in the print represent calcium. × 125.



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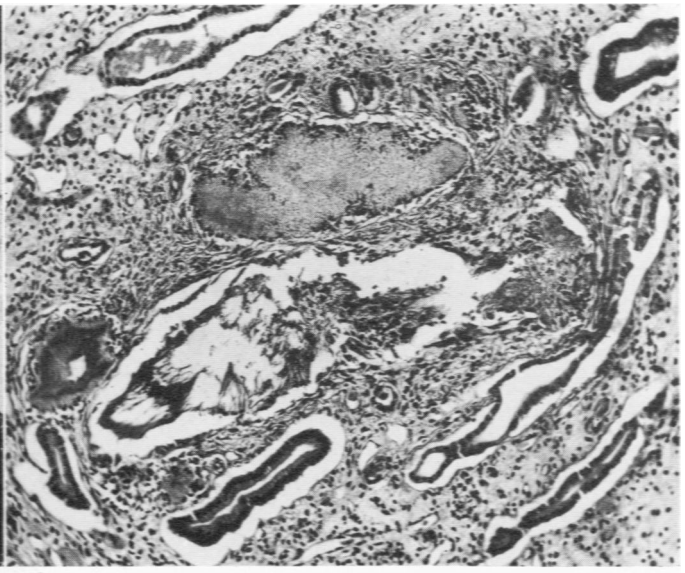

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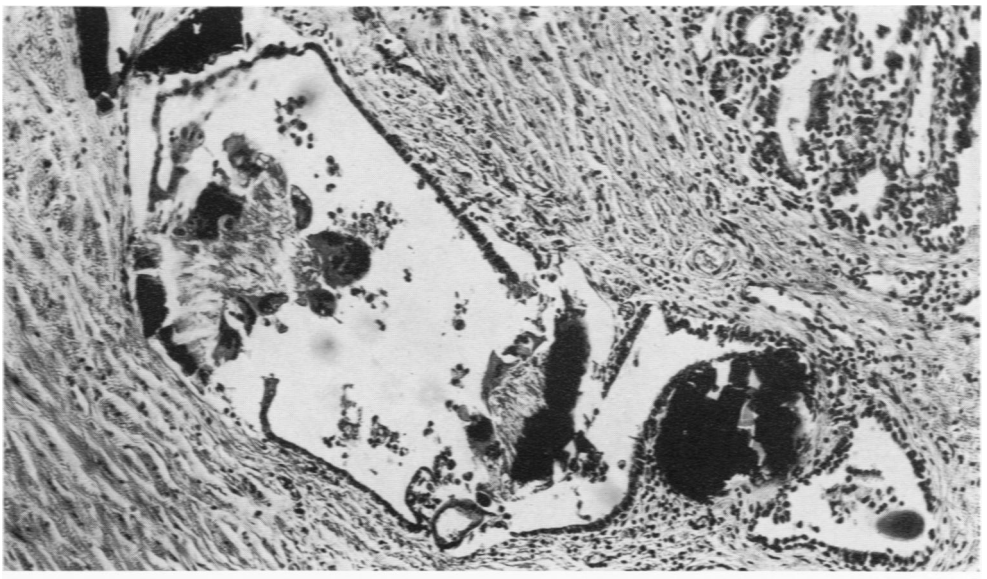

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