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SESSION IV
GOUT WITH RENAL COMPLICATIONS

(*Chairman:* DR. F. DUDLEY HART)

BIOCHEMICAL CONSIDERATIONS OF THE RENAL DAMAGE OF GOUT

BY

J. E. SEEGMILLER AND PAUL D. FRAZIER

From the National Institute of Arthritis and Metabolic Diseases, and the National Institute of Dental Research, National Institutes of Health, Bethesda, Maryland, 20014, U.S.A.

The development of renal damage is one of the most common extra-articular complications of gout. Clinical evidence of proteinuria is seen in 20 to 40 per cent. of gout patients and hypertension in a similar proportion (Gutman and Yü, 1957b; Talbott and Terplan, 1960). Progressive renal failure leading to death is reported in about 25 per cent. of gout patients. The histological lesion characteristic of gout consists of crystalline deposits presumed to be urate which are mainly located in the parenchymal tissue of the renal pyramids (Sokoloff, 1957). Although these deposits are seldom if ever found within the tubular lumen and are primarily interstitial, many pathologists postulate a tubular location for the initial deposits, which are thought to give rise to local obstruction followed by tubular destruction. Additional less specific pathological changes include degeneration of renal tubules, vascular sclerosis, and glomerulosclerosis (Gonick, Rubini, Gleason, and Sommers, 1965). Varying degrees of interstitial inflammatory reaction are seen as a pyelonephritis which is often sterile, but the precise way by which these latter changes can be related to uric acid is not clear (Sokoloff, 1965).

I propose to discuss some chemical considerations of the lesion pathognomonic for gout—the crystalline deposits. The work to be described was performed with the collaboration of Dr. Leon Sokoloff of our National Institutes of Health. The nature of the crystalline deposits has been determined by *x*-ray diffraction, and they bear certain implications for the clinical management at least of this aspect of the renal damage seen in gout patients.

Previous work has shown that the abnormalities of uric acid metabolism associated with gout result in the deposition of two types of crystalline deposits. Monosodium urate monohydrate has been identified by *x*-ray diffraction in gouty tophi and free uric acid has been similarly identified in renal calculi (Prien and Frondel, 1947; Howell, Eanes, and Seegmiller, 1963). The type of crystal deposited is determined by the *p*H of the supersaturated solution of urate. The primary physical property of uric acid to which this can be related is the first acid dissociation constant. The pKa of uric acid is 5·75. Consequently, at the *p*H of body fluids, over 98 per cent. of the molecules are present in the dissociated form of urate ions (Peters and Van Slyke, 1946). This fact, coupled with the high sodium concentration of extra-cellular fluids, leads to the deposition of monosodium urate crystals in those regions of the body bathed by vascular fluids that are supersaturated with respect to urate (Seegmiller, 1965a). At the lower *p*H encountered in urine, a greater portion of the molecules is present as undissociated uric acid so that free uric acid is the least soluble component and can precipitate from the supersaturated solution in the urinary tract.

Terminology commonly used in pathological descriptions makes no distinction between these two types of crystalline deposits. As a result the nature of the deposit occurring in kidney tissue in gouty nephropathy is somewhat confused. Knowledge of the precise nature of such deposits could be of help in clarifying the pathogenetic mechanism by which they arise and in identifying the body fluid, whether it be plasma or urine, with which these crystals are in equilibrium. Such considerations could also provide a rational approach to the resolution of such deposits and their prevention in the gouty patient.

Another clinical condition in which the identity of crystals might be of similar help is the acute renal blockade encountered during therapy of various types of leukaemia (Rieselbach, Bentzel, Cotlove, Frei, and Freireich, 1964).

X-ray diffraction provides a definitive means for distinguishing between different crystalline substances. We have therefore used this technique to identify the crystals found in alcohol-fixed blocks of renal tissue obtained at autopsy from gout patients and from patients with acute leukaemia (Frazier and Seegmiller, 1966; in preparation). Thick sections were cut from paraffin blocks and cleared to remove all traces of liquid and paraffin which give interfering diffraction lines. Areas of the tissue containing birefringent crystals were removed from the slide and mounted in an *x*-ray diffraction camera. The resulting patterns were compared with those obtained from well-characterized primary standards.

An adequate quantity of crystals for *x*-ray diffraction was obtained from six of eleven gout patients studied. *X*-ray diffraction patterns identical to that of monosodium urate monohydrate present in gouty tophi were obtained from four of the gout patients (Table I), and patterns identical to calcium oxalate monohydrate from the remaining two. Diffraction patterns identical to that of uric acid were obtained in five of twelve patients who had acute leukaemia; all five had acute lymphocytic leukaemia.

TABLE I
IDENTIFICATION OF CRYSTALS DEPOSITED IN RENAL TISSUE BY *X*-RAY CRYSTALLOGRAPHY

Crystals Found	No. of Patients	
	Gout	Acute Leukaemia
Monosodium Urate Monohydrate	4	0
Uric Acid	0	5
Calcium Oxalate	2	0

The location of the crystals in the histological section was also in accord with the physical chemical considerations that determine deposition of these two crystal types. In patients with acute lymphocytic leukaemia, crystals of uric acid were found only within the lumen of the renal tubule (Fig. 1), and so were in equilibrium with urine components flowing

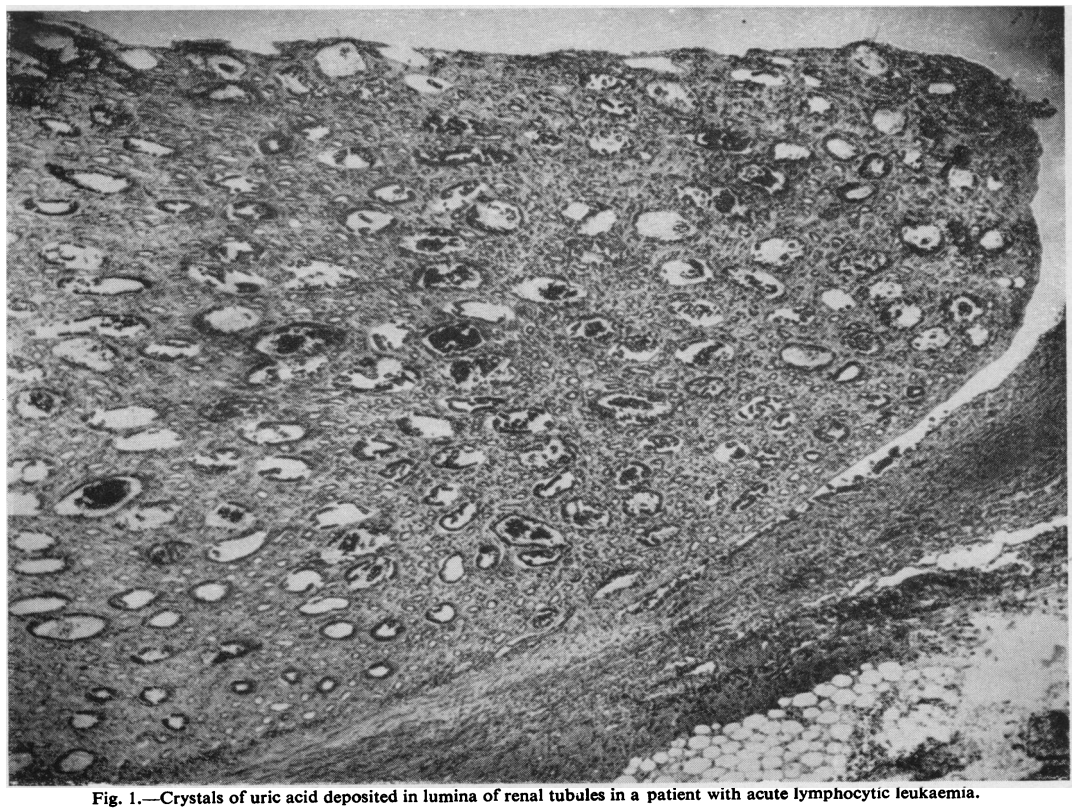

Fig. 1.—Crystals of uric acid deposited in lumina of renal tubules in a patient with acute lymphocytic leukaemia.

through the tubules. As would be expected, the converse situation was found in the gout patients, in whom none of the crystals of monosodium urate monohydrate were found within the tubular lumen but rather in the parenchymal tissue of the renal pyramids (Fig. 2), where they were surrounded by collagen with varying degrees of inflammatory reaction similar to that found around gouty tophi. Furthermore, there was no evidence of a basement membrane of the tubular lumen surrounding the deposits. The fact that monosodium urate monohydrate found in the gouty kidney is also found in gouty tophi leads to the conclusion that the deposits are in equilibrium with vascular fluids rather than with fluids of the urinary tract. Recent studies of the distribution of infused urate within various portions of the dog kidney have shown that the renal pyramid is the site of the highest concentration of urate, with values often greater than the concentration of urate in urine (Epstein and Pigeon, 1964). The high concentration of sodium normally present in the renal pyramid during excretion of maximally co centrated urine (Levitin, Goodman, Pigeon, a Epstein, 1962) may contribute to the precipitation the monosodium urate monohydrate.

The clinical success in the control and resoluti of the more obvious tophaceous deposits in t gouty patient through control of the serum ur (Bishop, Rand, and Talbott, 1951; Yü and Gutm 1951) suggests that the renal deposits of monosodiu urate monohydrate of gouty nephrosis may similarly controlled and prevented. These co siderations provide additional reason for maintainin the serum urate of the gouty patient within t normal range and for providing a high fluid intak

Since allopurinol provides one of the most effe tive drugs for lowering serum urate, it is appropria that we consider the consequences to the kidney the use of this drug to inhibit uric acid synthesis fro xanthine and hypoxanthine (Klinenberg, Gol finger, and Seegmiller, 1965). The relative solubil ties of these metabolites in plasma and urine

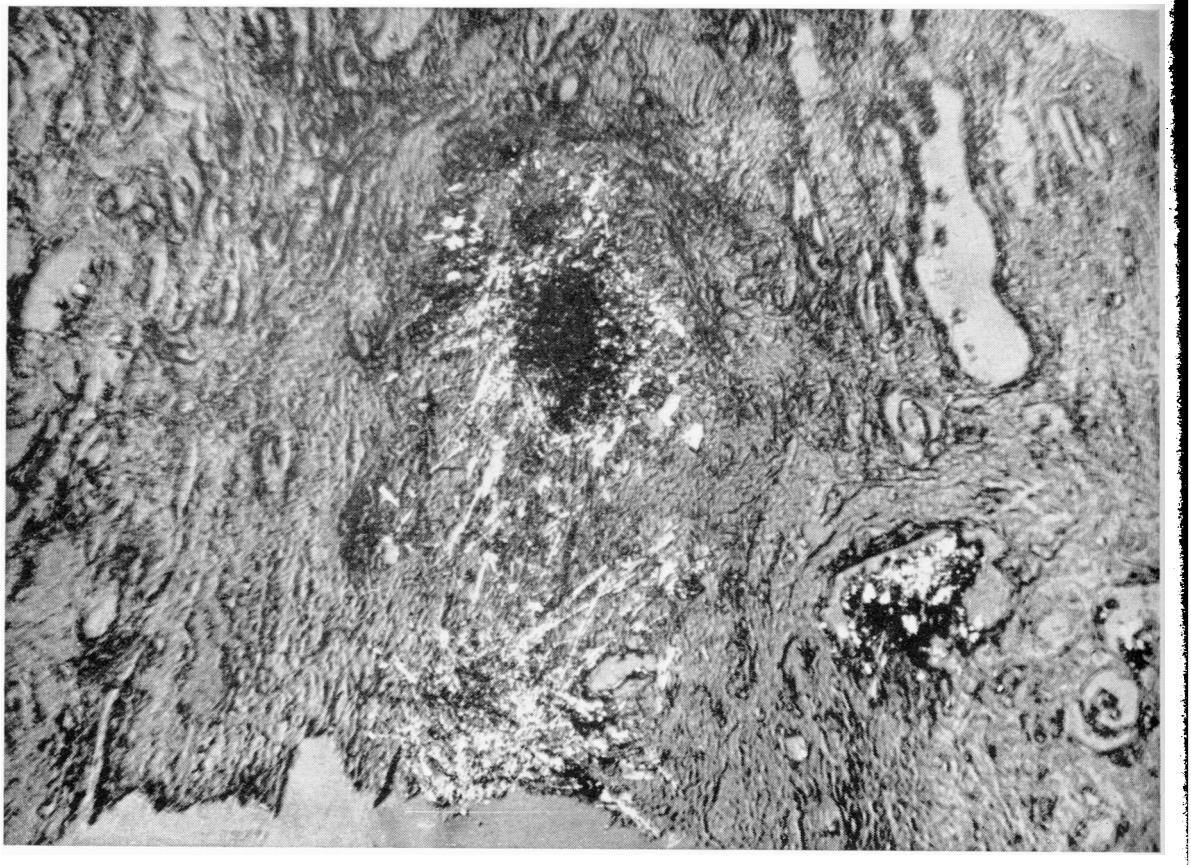

Fig. 2.—Crystals of monosodium urate monohydrate deposited diffusely in interstitial renal tissue of a patient with gout. Birefringent crystals in unstained tissue are shown under polarized light.

shown in Table II. Xanthine is less soluble than uric acid in urine, even at neutral *p*H, while hypoxanthine is much more soluble. However, there is an obvious advantage in distributing the load of purine to be excreted among three different species of molecules, each with its independent solubility, rather than in carrying all the material in the form of one sparingly-soluble molecular species—uric acid.

TABLE II
SOLUBILITY OF PURINES IN SERUM AND URINE

Purine (mg./100 ml.)		Uric Acid	Xanthine	Hypoxanthine
Serum	*p*H 7·4	7	10	115
Urine	*p*H 5	15	5	140
	*p*H 7	200	13	150

An experiment of nature shows us the consequence of exposure of the human body throughout life to the oxypurines xanthine and hypoxanthine. This is seen in the inborn metabolic disorder xanthinuria (Dent and Philpot, 1954), which results from the hereditary deletion of xanthine oxidase activity (Engelman, Watts, Klinenberg, Sjoerdsma, and Seegmiller, 1964). The principal pathological consequence of this deletion has been the formation of xanthine stones in the urinary tract in three of the seven patients known to have this disorder. Evidently the absence of uric acid *per se* poses no serious handicap to survival.

An additional advantage to the metabolic substitution of oxypurines for uric acid is found in the high renal clearance of oxypurines observed in patients with xanthinuria as well as in normal and gouty individuals in whom the plasma concentration of oxypurines has been increased by treatment with allopurinol (Goldfinger, Klinenberg, and Seegmiller, 1965). In some individuals the oxypurine excretion exceeded the glomerular filtration rate, indicating that tubular secretion of the oxypurine may have been occurring. The clinically significant consequence of such efficient elimination of the oxypurines from the body is the very low plasma concentration of oxypurines. The highest plasma concentration of oxypurines that we have encountered in our patients has been equivalent to 0·52 mg. xanthine/100 ml. plasma, which is far below the saturation limit of xanthine in plasma of 10 mg./100 ml. that has been determined experimentally.

An additional advantage of allopurinol observed in some but not all patients is the suppression of total purine synthesis (Fig. 3). The magnitude of this suppression varies greatly from one patient to another and may reflect individual metabolic differences that influence the rate-controlling step of purine synthesis. The possibility that allopurinol might by itself be inhibiting purine biosynthesis has been proposed (Rundles, Wyngaarden, Hitchings, Elion, and Silberman, 1963; Wyngaarden, 1966), but evidence against such an hypothesis was obtained from studies of a patient with xanthinuria.

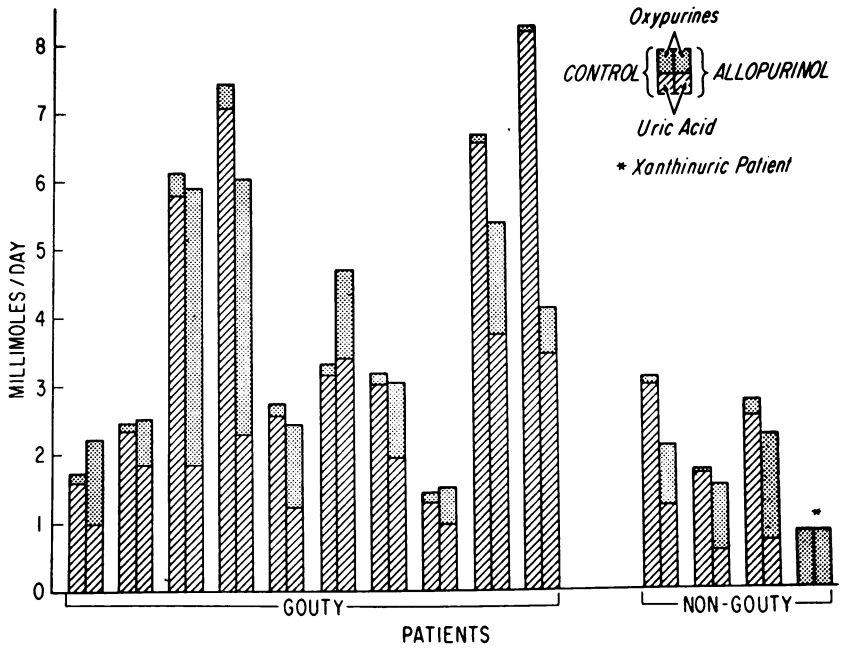

Fig. 3.—Effects of allopurinol administration on urinary purines in ten gouty and four non-gouty subjects (the last having xanthinuria).

The absence of xanthine oxidase in this patient permitted a study of the direct effect of allopurinol on purine biosynthesis independent of secondary effects that might be mediated through its action on xanthine oxidase. Administration of allopurinol to this xanthinuric patient produced no inhibition of total purine synthesis, suggesting that allopurinol had no direct effect on purine biosynthesis (Fig. 3).

Summary

X-ray diffraction has been used to identify the crystalline deposits seen in kidney tissue of patients with gout and in patients with acute leukaemia. The deposit in patients with gouty nephrosis is monosodium urate monohydrate, the same crystalline substance as is found in gouty tophi. The crystals are found in the parenchyma of the renal pyramid, outside the tubule. In patients with acute lymphocytic leukaemia in whom some degree of uric acid renal blockade has been observed clinically, deposits consisted of crystals of free uric acid deposited within the tubular lumen.

The oxypurines produced by the clinical use of allopurinol are excreted by the human kidney with much greater facility than uric acid, and the distribution of the uric acid load among three different molecular species decreases the chance of crystallization within the urinary tract. An added advantage noted in some patients who overproduce uric acid is the diminution of total purine synthesis induced by the administration of allopurinol.