TREATMENT OF GOUT WITH ALLOPURINOL AND SULPHINPYRAZONE IN COMBINATION AND WITH ALLOPURINOL ALONE*

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Successful long-term management of primary gout in the presence of normal renal function may be achieved in most instances by agents which diminish tubular reabsorption of urates, thus permitting increased urinary urate excretion. In recent years the two most widely used uricosuric agents have been probenecid and sulphinyprazole. The easiest long-term control of gout with the fewest untoward side-effects has been achieved with sulphinyprazole (Gutman and Yü, 1957a; Kersley, Cook, and Tovey, 1958; Ogryzlo and Harrison, 1957; Kuzell, Glover, Gibbs, and Blau, 1964).

In spite of the relative ease in controlling gout with sulphinyprazole, any large group of gouty patients will include some in whom the use of uricosuric agents may be impossible or inadvisable because of impairment of renal function or drug intolerance. Some patients, for reasons not yet understood, form tophi much more readily than others, and quite large dosages of uricosuric agents may arrest the formation of tophi without rapidly diminishing those already present. Some form urate stones in the urinary tract so readily that increasing the urinary output of urates may be hazardous. Finally, in secondary gout attended by excessive uric acid formation, the employment of uricosuric agents may be inadvisable because any increase in the already high excretion rate may lead to obstruction of the lower urinary tract by concretions of uric acid.

A novel approach in the control of gout is offered by allopurinol, 4-hydroxypyrazolo (3, 4-d) pyrimidine (4-HPP), an inhibitor of xanthine oxidase which prevents conversion of hypoxanthine to xanthine and of xanthine to uric acid (Rundles, Wyngaarden, Hitchings, Elion, and Silberman, 1963; Yü and Gutman, 1964; Rundles, Metz, and Silberman, 1966b). Uric acid available for excretion is diminished, and the relatively more soluble xanthines are readily excreted, thus permitting the use of

allopurinol in the presence of impaired renal function. It then appeared attractive to explore the possibility of hastening the mobilization of stored urates and regression of tophi by concurrently inhibiting uric acid formation while enhancing its urinary excretion. Several preliminary clinical studies have, in fact, indicated that the combined use of allopurinol and uricosuric agents promotes more rapid disappearance of tophi (Smyth, 1965; Houpt, 1965; Kuzell, Glover, Seebach, Gibbs, and Jackman, 1965; Rundles and others, 1966b; Rundles, Elion, and Hitchings, 1966a).

Material and Methods

The 48 patients selected for this clinical evaluation all, save two (Table II, Cases 5 and 19), been under treatment for variable periods from 1 month to 8 years. They were all seen by more than one physician.

Serum uric acid (SUA) and urinary uric acid (UUA) determinations were done by the enzymatic method (Feichtmeir and Wrenn, 1955). Urinary xanthine determinations were done by a modification of the method of Kalckar (1947) in which diluted urine was incubated in 0.1 M. tris buffer, pH 8.0, in the presence of milk xanthine oxidase* and the resulting excess of uric acid liberated was determined by the difference between the uric acid content of the treated sample and that of an untreated control. Although the substance measured is uric acid, the oxypurines are reported by calculation as mg. xanthine, with no attempt to identify the actual percentage derived from hypoxanthine.

Many of the patients were subjected to extensive laboratory testing before and during the clinical trial. The tests included complete blood count, erythrocyte sedimentation rate, urine analysis, serum uric acid, urinary uric acid, urinary oxypurines, serum glutamic oxaloacetic transaminase (SGOT), cephalin cholesterol flocculation, thymol turbidity, alkaline phosphatase, creatinine, bilirubin, cholesterol, alpha and beta cholesterol, serum protein electrophoresis, and blood urea nitrogen (BUN).

Observations were made at various intervals depending upon the seriousness of the clinical problem considered. Measurements were made of visible tophi metrically, photographically, and radiographically.

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TABLE I
COMBINED THERAPY OF GOUT WITH ALLOPURINOL AND SULPHINPYRAZONE
IN TWENTY MALE PATIENTS

Tophi	Case No.	Age (yrs)	Duration of Gout (yrs)	Previous Therapy		Combined Therapy			Serum Uric Acid (mg./100 ml.)		Result of Combined Therapy
				Dose (mg./day)	Duration (days)	Dose (mg./day)*		Duration (days)	Previous	Combined	
						Allopurinol	Sulphin-pyrazone				
(A) Not Visible	1	73	2	400-100 (S)	245	200	100	259	7.54	6.30	Less pain
	2	80	10	100 (S)	418	100	100	195	7.25	8.78	Dosage insufficient
	3	62	9	300-400 (S)	2,911	200	300	120	10.40	6.80	Cessation of urate stones
	4	60	8	400 (S)	2,190	100	200	264	6.88	6.14	Equal to 400 mg. (S)
	5	73	2	200 (S)	320	200	200	129	8.25	5.08	Less pain
	6	58	31	200 (S)	2,868	200	200	55	7.96	4.52	No urate stones
	7	47	1½	200 (S)	210	200	200	486	4.44	4.18	No urate stones
	8	51	1/12	400 (Ph) 1,000 (P)	30	600-1,000	300-400	92	10.70	8.10	Less pain
(B) Visible	9	54	15	200 (S)	2,920	200	200	204	10.40	6.80	Tophi smaller and softer
	10	57	30	300 (S)	1,882	300-200	400-200	455	7.78	4.96	Tophi smaller and softer
	11	46	12	400 (S)	1,042	200	400-200	211	4.10	4.00	Tophi smaller and softer
	12	71	10	600-800 (S)	55	300-400	600	389	5.90	3.35	Tophi smaller and softer
	13	69	12	400 (S) 200 (T)	2,555	300	300	446	8.62	5.78	Tophi smaller and softer
	14	39	15	400 (S)	104	200	400	235	4.48	3.52	Tophi smaller and softer
	15	50	18	400 (S) 1,000 (P)	2,565	400	400	475	5.92	3.55	Tophi smaller and softer No renal stones
	16	75	12	200 (S) 100 (T)	584	200	200	143	6.30	5.40	Tophi smaller and softer Passed one urate stone
	17	54	20	400 (S)	2,492	200	400	433	7.30	5.90	Tophi smaller and softer
	18	47	10	2,000 (P)	3,650	600	400	203	9.70	5.20	Tophi smaller and softer
	19	30	3	300 (S)	545	200	400	182	8.38	6.04	Less pain Tophi same
	20	80	40	200 (S) 1,000 (P)	1,989	200	200	347	6.40	5.40	Less pain Tophi smaller

*average maintenance dosage; (S) sulphinpyrazone; (P) probenecid; (Ph) phenylbutazone; (T) oxyphenbutazone.

Results

Combined Treatment

Allopurinol and sulphinpyrazone were given together to twenty male patients, who were divided into those with and those without visible tophi (Table I).

(A) *Patients without Visible Tophi*.—Eight patients (Cases 1-8) ranging in age from 47 to 80 years were treated for 5,323 patient-days (average

266.) Dosage of sulphinpyrazone ranged from 100 to 1,000 mg. daily, the most usual being 200 mg., and that of allopurinol from 100 to 400 mg./day, the most usual being 200 mg. Although all of the patients had previously been under treatment with uricosuric agents only Case 7 showed a normal SUA level at the beginning of the trial. Duration of treatment ranged from 55 to 486 days (average 200). The average SUA was 7.93 at the outset and 6.20 mg./100 ml. at the end of the trial; the level diminished in seven of the eight patients, and the eighth

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(Case 2) was taking only 100 mg. of each drug per day—obviously an insufficient dosage. Three patients who previously had passed frequent urate stones (Cases, 3, 6, 7) passed none during the trial. Three (Cases 1, 5, 8) had less pain than on previous treatment, and one taking 100 mg. allopurinol and 200 mg. sulphinyprazole had relief equivalent to that obtained by taking 400 mg. sulphinyprazole previously.

(B) *Patients with Visible Tophi.*—Twelve patients (Cases 9 to 20) previously treated with uricosuric agents showed visible tophi which had not increased in size or which had regressed slightly. They were treated with allopurinol 200 to 600 mg./day, usually between 200 and 400 mg. Sulphinyprazole dosage varied from 200 mg. to 600 mg./day, the most usual being 200 to 400 mg. The extent of the treatment was 3,723 patient-days (average 310), and the duration of treatment ranged from 143 to 455 days. The average SUA level was 7.12 mg./100 ml. at the beginning of treatment and 5.59 at the end. At the start of the trial four of the twelve patients (Cases 11, 12, 14, 15) showed a level below 6.00 mg./100 ml., and at the end only two (Cases 9 and 19) were just above 6.00 mg./100 ml. All except Case 19 showed softening and regression of tophi. Cases 15 and 16 were previously troubled occasionally by passing urate stones, but only Case 16 passed a single stone during the treatment period.

Treatment with Allopurinol Alone

28 patients (including eleven females) were treated for 5,680 patient-days with allopurinol alone (average 203 days), the duration of treatment ranging from 42 to 486 days. These patients were divided into seven categories (Table II).

(A) *Impaired Renal Function* (4).—Cases 1 and 2 had previously been unable to take uricosuric agents because of severely impaired renal function; each had multiple tophi ranging from 2 mm. to several centimetres in diameter, which tophi had been steadily increasing in size.

Case 1 (aged 85) was able to tolerate from 400 to 600 mg./day allopurinol for 270 days, during which the SUA level fell from 11.35 to 5.40 mg./100 ml., the tophi became smaller and softer, and his range of general physical activity increased. Unfortunately, he died from cerebral haemorrhage at a time when the gout was under control.

Case 2 continued to take 300 to 500 mg./day allopurinol for 486 days; the SUA has fallen from 8.98 to 5.74 mg./100 ml., the tophi have not increased in number, and some of them have become softer and smaller. She has experienced less pain and the renal function has remained unchanged.

Cases 3 and 4 had previously passed urate stones. In Case 3, sulphinyprazole had previously prevented attacks of acute gout, but stones continued to form, and

ALLOPURINOL TREATMENT

Category	Case No.	Sex	Age (yrs)	Duration (yrs)	Clinical Situation	Effect of Previous Therapy (mg./day)
A. Impaired Renal Function	1	M	85	45	Multiple tophi	Unable to take uricosuric agents Colchicine helped acute attacks
	2	F	73	30	Multiple tophi One kidney Psoriasis Multiple drug sensitivities	Only able tolerate colchicine 0.5 to 1 Tophi increasing
	3	M	59	15	Occasionally passed urate stones	(S) prevented attacks but stones continuing
	4	M	58	3	One kidney Urate stones Paget's disease Parkinsonism	200 mg. (S) markedly reduced uric acid
B. Duodenal Ulcer	5	F	59	4	Frequent persistent acute gouty arthritis	Uricosuric agents not used because of ulcer
	6	M	58	16	Ulcer aggravated by (S), (Ph), and (T) Frequent severe acute gout	(S) 400 mg./day reduced uric acid but aggravated ulcer
	7	F	63	3	Ulcer with haemorrhage on (S) Obesity and hypertension Taking (Th)	Uric acid not lowered enough by (S) which aggravated ulcer

(contd)

Case 4 had shown a marked reduction of SUA on sulphinpyrazone therapy but continued to pass stones. During the trial of allopurinol neither passed any stones.

(B) *Duodenal Ulcer* (5).—Allopurinol was given for from 91 to 335 days. The ulcers were quiescent in all five patients, but Case 8 also had a hiatus hernia which continued to trouble him symptomatically. Four of them received 200 mg./day allopurinol and Case 6 received 300 mg. Although the SUA became normal only in Case 5, only Case 6 occasionally had some joint pain. Cases 7 and 9 were also receiving thiazide diuretics concurrently. In this group Cases 6 to 9 had previously been unable to tolerate sulphinpyrazone because of ulcer aggravation, and in Case 5 uricosuric therapy had not been attempted because of the severity of the ulcer.

(C) *Toxic Reactions to Sulphinpyrazone* (3).—Cases 10 to 12 had been unable to tolerate sulphinpyrazone because of vertigo (Case 10), rash (Case 11), and rash, nausea, and transient leucopenia (Case 12). They were treated with allopurinol from 42 to 181 days, and the SUA became normal in all of them. The medication was well tolerated by Cases 10 and 11, but Case 12 was forced to discontinue it after 42 days because of nausea, diarrhoea, and furunculosis of the nose.

(D) *Hyperuricaemia with Rheumatoid Arthritis* (3).—Cases 13 to 15, hyperuricaemic patients who occasionally experienced gout-like pains during treatment for rheumatoid arthritis, were given 200 mg. allopurinol daily for from 122 to 232 days. Cases 14 and 15 were also receiving thiazide diuretics concurrently. All three had less joint pain and swelling during treatment. Case 15, who had previously been treated with 200 mg./day sulphinpyrazone, experienced similar relief with 200 mg./day allopurinol.

(E) *Psoriasis and Psoriatic Arthropathy* (2).—Cases 16 and 17 were treated with 200 mg./day allopurinol and the SUA level became normal.

Case 16 experienced marked diminution of pain and swelling of the involved joints, and Case 17 showed a 75 per cent. reduction in the skin area affected by psoriasis after 74 days. This was the first instance of marked improvement in the skin in 12 years. Her hip pain was unchanged, but was thought to be largely due to marked deformity of the femoral heads from previous disease.

(F) *Secondary Gout* (1).—Case 18, who had secondary gout associated with chronic myelogenous leukaemia, had been unable to tolerate

UT IN 28 PATIENTS

Effect of Allopurinol				
Dosage (mg./day)	Duration (days)	Serum Uric Acid (mg./100 ml.)		Result of Treatment
		Initial	Final	
400-600	270	11.35	5.40	Tophi smaller and softer Physical activity increased Died of cerebral haemorrhage
300-500	486	8.98	5.74	Tophi smaller and softer Less pain Renal function same
200	149	7.82	5.82	Cessation of urate stones
200	327	3.33	4.48	Serum uric acid higher but no stones
200	91	7.88	3.58	Relief of subacute gouty arthritis Ulcer quiescent
300	335	6.64	7.36	Insufficient dosage Occasional acute gout Ulcer quiescent
200	236	8.00	7.70	Irregular medication Dosage to be increased No pain Ulcer quiescent

(contin.)

TABLE II (contin.)

Category	Case No.	Sex	Age (yrs)	Duration (yrs)	Clinical Situation	Effect of Previous Therapy (mg./day)
B. (contin.)	8	M	58	6	Hiatus hernia Frequent trochanteric bursitis	(S) 300 to 400 mg. lowered uric acid gave gastrointestinal irritation
	9	F	60	3	Hypertension, myocardial infarction Occasional painful joints Taking (Th)	(S) caused vertigo and gastrointestinal distress
C. Toxic Reactions Sulphinpyrazone	10	M	48	1	Occasional joint pain Carcinoma of larynx excised	(S) caused vertigo
	11	M	63	16	Recurrent joint pains	(S) caused rash
	12	M	69	1	Severe tophaceous gout with many acute attacks	(P) caused nausea (S) caused rash and transient leucopenia
D. Hyperuricaemia with Rheumatoid Arthritis	13	M	54	3	Gout-like attacks No tophi	(B) 1·2 mg. relieved rash
	14	F	56	12	Wrist joint pain and synovial swelling	Chloroquine, (T), (Th) gave moderate pain relief
	15	F	65	12	Hypertension Persistent joint pain and swelling	Steroids, (Th) gave moderate relief (S) 200 mg. effective
E. Psoriasis and Psoriatic Arthropathy	16	M	45	3	Hyperuricaemia with chronic pain and swelling	Indomethacin and glucocorticoids gave moderate relief
	17	F	66	14	Bilateral hip involvement Taking (Th)	(S) lowered serum uric acid but psoriasis unchanged
F. Secondary Gout	18	M	61	7	Chronic myelogenous leukaemia with marked hyperuricaemia Duodenal ulcer	(S) caused "flushing" and nausea
G. Miscellaneous	19	F	68	2	Osteoporosis of spine Old myocardial infarction Severe pains back and legs	Limited to analgesics because of cardiac status
	20	M	58	4	Diabetes mellitus Gout Osteo-arthritis Arteriosclerotic heart disease	(S) 400 mg. well tolerated
	21	F	74	7	Malum coxae senilis Gout	(S) 100 mg. well tolerated
	22	F	80	2	Diabetes Cholelithiasis Duodenal ulcer Arteriosclerotic heart disease Gout	(S) 200 mg. did not lower uric acid (Th)
	23	M	67	5	Cardiac insufficiency Mitral stenosis (inoperable) Gout	(S) 400 mg. well tolerated (Th)
	24	M	62	2	Residua of cerebro-vascular accident Hypertension Gout	Occasional joint pain on (Th) and reserpine (S) 200 mg. did not lower uric acid
	25	F	72	10	Hypertension Gout "Pre-diabetes"	(S) 100 mg. caused bitter taste (chewing) but effective
	26	M	61	12	Obesity Recurrent gout Migraine	(S) 400 mg. well tolerated for 5 yrs No attacks
	27	M	48	5	Tophi Chronic trochanteric bursitis	(S) 300 to 600 mg. well tolerated for 5 yrs, but pain increased
	28	M	70	10	Recurrent joint pains No tophi	(T) relieved joint pain but gave muscle pains in legs

(S) Sulphinpyrazone; (P) Probenecid; (Ph) Phenylbutazone; (T) Oxyphenbutazone; (Th) Thiazide diuretics; (B) Betamethasone.

TABLE II (contin.)

Effect of Allopurinol				
Dosage (mg./day)	Duration (days)	Serum Uric Acid (mg./100 ml.)		Result of Treatment
		Initial	Final	
200	211	8.52	6.52	Pain relieved Ulcer quiescent Hiatus hernia troublesome
200	268	7.02	6.42	No pain Well tolerated
200	70	6.48	4.40	No joint pain Well tolerated
200	181	8.55	5.62	No pain Well tolerated
200	42	8.70	5.72	Discontinued because of nausea, diarrhoea, and furunculosis of nose
200	232	7.74	6.12	Less pain (B) reduced to 0.6 mg.
200	122	7.40	4.40	Less swelling and pain in joints
200	186	5.80	5.48	Less swelling and pain in joints
200	108	6.88	4.85	Less swelling and pain in joints
200	74	8.40	5.65	About 75 per cent. regression in extensive skin lesions Pain unchanged
200	418	9.02	9.20	Gastrointestinal haemorrhage requiring transfusions Nausea unless allopurinol is given in capsules
100	130	8.58	5.04	All pain gone Tolerates (Th)
400	83	4.80	4.35	Less neck and back pain
100	266	5.78	5.14	No change from (S) regarding pain
100	273	7.46	5.66	No attacks of gout Well tolerated
200	391	7.64	5.08	General condition improved since more (Th) can be taken
200	67	7.38	6.0	Well tolerated Less frequent joint pain
100	74	5.15	5.52	No change from (S)
200	114	5.56	4.60	Well tolerated No attacks
200	340	8.60	5.52	Well tolerated Trochanteric bursitis almost painless
100	136	6.72	5.6	Well tolerated Muscle pains gone

sulphinpyrazone because of "flushing sensations" and nausea.

He was given 50 to 300 mg./day allopurinol, but experienced nausea and a massive gastro-intestinal haemorrhage presumably associated with a chronic duodenal ulcer. After receiving appropriate transfusions and therapy for the ulcer he was given P³² with good effect and was then able to resume allopurinol in gelatin capsules. On the low dosage he was able to tolerate, the SUA did not decrease, but he suffered no attacks of acute gout.

(G) *Miscellaneous* (10).—Cases 19 to 28, with various disorders additional to gout were given 100-400 mg./day allopurinol, for periods ranging from 67 to 391 days.

At the outset four patients (Cases 20, 21, 25, 26) showed a normal SUA level due to previous treatment with sulphinpyrazone, and at the end of the trial all ten patients showed normal levels.

Case 19, a cardiac patient with osteoporosis and gout, not previously treated, experienced marked reduction in SUA and was able to tolerate thiazide diuretics when taking only 100 mg. day allopurinol.

Case 28 had suffered from leg muscle pains when taking oxyphenbutazone, but on 100 mg. day allopurinol the pains subsided.

Cases 22, 23, and 24 had had no gouty attacks when taking sulphinpyrazone previously but since they were also taking thiazide diuretics the SUA remained high. When they took allopurinol the gout remained under control and the SUA became normal.

Cases 20, 21, and 27, previously controlled on sulphinpyrazone, remained symptom-free on allopurinol.

Case 25, who had difficulty swallowing pills, objected to the "bitter taste" of sulphinpyrazone but was able to chew allopurinol tablets without complaint.

Toxic Manifestations

In only two instances was allopurinol discontinued because of undesirable side-effects.

A 62-year-old man (Table I, Case 3) with gout, chronic pyelonephritis, and chronic lymphatic leukaemia, while taking allopurinol 200 mg. and sulphinpyrazone 300 mg./day for 120 days, experienced headache, nausea, and vertigo. These symptoms were related to taking allopurinol, and he has been able to take sulphinpyrazone subsequently without difficulty.

A 69-year-old male (Table II, Case 12) with severe gout, who had previously experienced a transient leucopenia on sulphinpyrazone, was forced to discontinue medication after 42 days on 200 mg./day allopurinol because of nausea, diarrhoea, and a severe furunculosis of the nose.

An 85-year-old male (Table II, Case 1), with severe tophaceous gout and impaired renal function, was able to

take 400 to 600 mg./day allopurinol for 270 days; the SUA fell from 11.5 to 5.4 mg./100 ml. with marked softening and diminution in size of multiple tophi. This patient died from a cerebral haemorrhage after a 2-day illness. The day before he died the leucocyte count fell to 2,800 with 28 per cent. neutrophils, 1 metamelocyte, 10 lymphocytes, and 5 per cent. monocytes. Occasional Döhle bodies were seen in the leucocytes. The serum creatinine varied between 2.5 and 4.5 mg./100 ml. before and during treatment with allopurinol. The diminution in leucocytes in this aged man could have been due to overwhelming infection. Permission for autopsy was not granted. We cannot with certainty attribute the blood changes to allopurinol.

Six other patients experienced undesirable side-effects:

(1) A man aged 61 (Case 18, Table II) with chronic myelogenous leukaemia, probable duodenal ulcer, and secondary gout, had nausea directly related to allopurinol. This was prevented by placing crushed tablets in gelatin capsules. While on allopurinol he experienced a severe gastro-intestinal haemorrhage and had to be given a blood transfusion. Subsequently he was treated with P³² and has successfully resumed treatment with allopurinol in capsules together with appropriate treatment for duodenal ulcer.

(2) A man aged 54 (Case 13, Table II) with rheumatoid arthritis and probable gout, complained that his smoking tobacco had an "acid taste" when he was taking allopurinol, but he has successfully continued treatment.

(3) A woman aged 73 (Case 2, Table II), with severe tophaceous gout, one kidney, impaired renal function, psoriasis, and multiple drug sensitivities, developed a transitory fine maculo-papular rash after beginning treatment with allopurinol. She was subsequently able to continue treatment without difficulty.

(4) A man aged 67 (Case 23, Table II), with probable gout, atrial fibrillation, mitral stenosis (inoperable), and cardiac insufficiency, experienced diarrhoea for several weeks, but successfully continued treatment with allopurinol.

(5) A man aged 51 (Case 8, Table I), with severe gout, experienced moderately severe diarrhoea, but as treatment was continued the diarrhoea lessened.

(6) A man aged 69 (Case 13, Table I), with severe tophaceous gout and old ankylosing spondylitis, experienced severe nausea whenever the daily dosage of allopurinol exceeded 400 mg.

Previous investigators have reported that allopurinol tended to bring on acute gouty arthritis with increased frequency during the first few weeks of treatment, but this was not observed in our study,

doubtless because of prolonged previous medication with uricosuric agents and perhaps also because of our practice of employing smaller average daily doses of allopurinol.

Laboratory Results

During this study numerous laboratory examinations were made of the blood and urine. No abnormality was noted other than the single instance of leucopenia (Case 1, Table II) described above. No hepatic abnormality was seen. Oxypurines were recovered from the urine uniformly in patients receiving allopurinol alone or in combination with sulphinyprazole.

Discussion

The use of allopurinol, a structural analogue of hypoxanthine, as an inhibitor of xanthine oxidase activity in gout has extended the scope of treatment to include several groups of patients previously beyond the reach of therapy.

Since impairment of renal function has been a contraindication to the use of uricosuric agents, the availability of allopurinol for such patients has been a great advance in the therapy of gout. Although they are relatively few in relation to the total gouty population, their previous inexorable progression has been witnessed with helplessness and chagrin by the physician. Our favorable results in patients with impaired renal function (Cases 1 and 2, Table II) have confirmed the observations of Rundles and others (1963), and Yü and Gutman (1964).

Since allopurinol diminishes uric acid formation, the concentration of uric acid in the renal tubular filtrate falls to levels not readily conducive to stone formation. This observation has led to the use of allopurinol in those gouty patients who form urate stones quickly and frequently particularly when treated with uricosuric agents. Our experience in Cases 3, 6, 7, 15, 16 (Table I) and 3, 4 (Table II) emphasizes the importance of using allopurinol—only one of the seven passed a single stone during the period of this study.

While it is generally accepted that most gouty patients can be controlled effectively with uricosuric agents (particularly sulphinyprazole), the addition of allopurinol to the treatment of patients with massive tophi has hastened their softening and resolution (Table I). Combined therapy diminishes the increment in uric acid production while augmenting output of UUA. This combined therapeutic approach may be expected to "pull out" stored uric acid, making it available for excretion thus accelerating the rate of resolution of tophi. This idea was

substantiated by the rapid softening and shrinking of tophi in eleven of twelve patients with tophi who received the combined treatment; with sulphinyprazole alone, the tophi decreased only slowly or not at all.

There are other special problems in cases of gout in which allopurinol may be used alone:

- (i) Active peptic ulcer aggravated by uricosuric agents.
- (ii) Toxic side-effects of uricosuric agents.
- (iii) Hyperuricaemia with rheumatoid arthritis, particularly when thiazide diuretics are concurrently employed.
- (iv) Psoriasis, in which the formation of uric acid is augmented in proportion to the area of skin involvement.
- (v) Secondary gout, in which the formation of uric acid is often massive secondary to disorders of haematopoiesis or to the use of cytotoxic agents.

Since thiazide diuretics reduce the excretion of uric acid, when their use is essential in the gouty patient, our studies have demonstrated that small doses of allopurinol—usually 100 to 200 mg./day—suffice to reduce SUA levels to normal. This is an area of therapeutic usefulness of allopurinol which deserves further study because of the widespread use of these diuretics.

The toxicity of allopurinol in our hands has not been alarming; only two of 48 patients were obliged to discontinue its use, and six other patients, in whom toxic manifestations included nausea, diarrhoea, and rash, have been able to continue treatment with subsidence of symptoms.

In one instance of leucopenia, as part of the terminal episode in an 85-year-old man with cerebral haemorrhage, the diminution in leucocytes could not with certainty be ascribed to allopurinol. Our patients have been able to achieve clinical control of gout in most instances using daily doses of 200 to 400 mg. which are lower than those often employed. Admittedly, the treatment with allopurinol could have been more vigorous; but since the patients were doing well clinically this did not appear to be necessary, and we feel that the use of low dosage schedules accounts for our relatively low incidence of diarrhoea and of the augmented attack rate of acute gout previously reported (Yü and Gutman, 1964; Rundles and others, 1966b).

Until more clinical studies are available, it should be emphasized that almost all gouty patients can be safely and effectively controlled by the uricosuric agent sulphinyprazole (Kuzell and others, 1965).

Summary

(1) Twenty male patients were treated with allopurinol and sulphinpyrazone in combination during 5,323 patient-days.

Combined treatment of patients previously treated with uricosuric agents resulted in diminution of serum uric acid, accelerated softening and regression of tophi, and cessation of renal stone formation.

(2) 28 gouty patients presenting special treatment problems were treated with allopurinol alone during 5,680 patient-days.

Treatment with allopurinol alone controlled gout in patients with impaired renal function, in the presence of duodenal ulcer previously aggravated by

uricosuric agents, in cases of psoriasis or rheumatoid arthritis with hyperuricaemia, in patients who had previous toxic reactions to uricosuric agents, in secondary gout, and in the presence of concurrent use of thiazide diuretics.

(3) Toxic reactions necessitated the cessation of allopurinol therapy in only two of the 48 patients. Nine patients exhibited toxic manifestations, including nausea, diarrhoea, and one instance each of headache, leucopenia, furunculosis, and rash.

(4) As a consequence of low dosage schedules of allopurinol (usually 200 to 400 mg./day) our patients did not experience the high incidence of diarrhoea and flare-up of acute gout previously reported.