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TREATMENT OF GOUT WITH ALLOPURINOL

A STUDY OF 106 CASES*

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As allopurinol appears to be the most interesting of drugs currently available for gout, we have been using it regularly for 2 years, and have collected a series of 106 gouty patients, whom we have kept under regular clinical and laboratory observation while under treatment with the drug.

All these patients had been having several acute attacks of gout each year; fifty of them had tophi and 26 had a previous history of renal colic. The aim of the treatment was to attain a "safe" serum uric acid (SUA) level—by this we mean a level of 6 to 7 mg./100 ml., below which precipitation of uric acid is unlikely. Indeed, one hopes that, at this level, tissue deposits of urate will be mobilized into the plasma and eventually excreted in the urine.

The effect of increasing doses of allopurinol on the serum uric acid level is shown in Fig. 1, a "safe" level being usually achieved by a dosage of 200 to 300 mg. allopurinol daily. This is the dosage range we usually employ, the average in the series being 261 mg. daily. The duration of treatment ranged from several days to 2 years (average 120 days). Doses in excess of 300 mg. have been given to some patients, and in these we have observed SUA levels below 5 mg./100 ml.

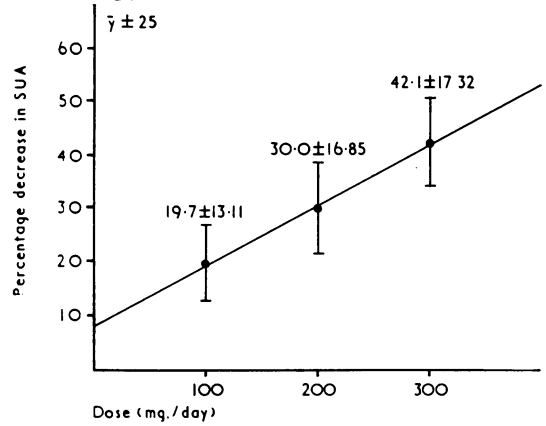

Fig. 1.—Effect of increasing doses of allopurinol on serum uric acid level.

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Method

The majority of the patients were initially treated in hospital, in a metabolic ward, and on a low purine diet containing 2,200 calories/day (320 g. carbohydrate, 70 g. fat, and 50 g. protein) with a liberal diuresis induced by drinking 2 l. of Evian water daily. The patients were also given colchicine, 1 mg. orally, in the evening. After some time the treatment was continued on an out-patient basis, with clinical and laboratory supervision.

The drug was, in general, very well tolerated (total number of days treatment 12,807; total 3·13 kg. prescribed). Six cases of intolerance to the drug, all occurring at the outset, which compelled treatment to be stopped, included four cases of cutaneous intolerance, among which there was one scarlatiniform rash, and three cases of prurigo on the anterior aspect of the wrists. There were also two instances of digestive upset (gastric pain in one patient and vomiting in another).

The laboratory tests consisted of regular measurements of liver function (flocculation test and serum transaminase levels), kidney function, blood count, and serum iron level. We found no abnormalities, except for a slight, insignificant fall of the white cell count in some patients.

Clinical Results

Effect of Allopurinol on the Inflammatory Element of Gout.—Acute attacks of gout may occur in some patients at the beginning of treatment, in spite of adequate colchicine prophylaxis, and the patients should be forewarned of this possibility. However, most of the gouty patients derived benefit from long-term treatment with the drug. This opinion is based on a study of 45 patients treated for 4 months or more:

(*a*) Eleven patients (25 per cent.) had an acute attack of gout at the onset of allopurinol treatment, but the majority have had no further trouble since.

(*b*) 34 patients (75 per cent.) had no further acute attack of gout after allopurinol therapy was started.

(*c*) Ten patients (20 per cent.) continued to have symptoms despite treatment; but they all considered that the acute attacks were less frequent, shorter, and less severe, and did not interfere with their work. The acute attacks often occurred while the serum uric acid was still raised

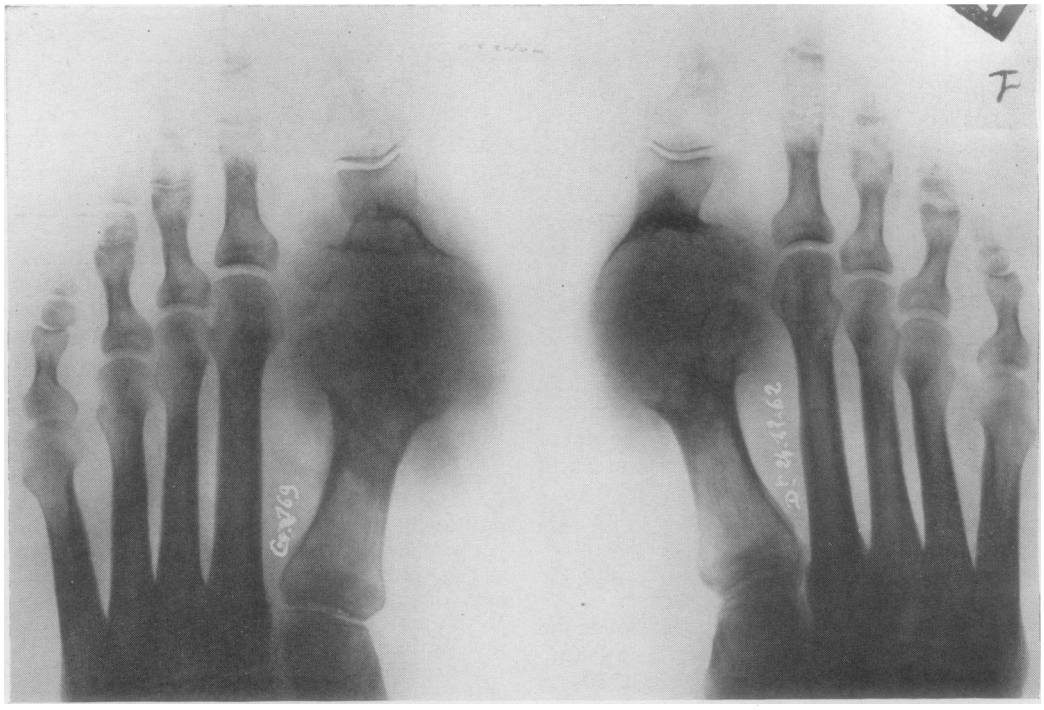

Fig. 2.—Massive tophi on great toe metatarsals in a 42-year-old patient.

because the dosage of the drug was inadequate, but three patients also had attacks while the SUA concentration was below the "safe" level.

(*d*) Only one patient did not improve and was unable to resume work.

The majority of our gouty patients complained of permanent discomfort as a background to their acute attacks, and it should be emphasized that they all believed themselves to be better in the weeks after allopurinol therapy was begun.

Effect of Allopurinol on Tophi.—It is too early to apply statistical methods, but we have already had some interesting results.

A striking example is that of a 42-year-old patient who had massive tophi on the metacarpals of the big toes. Radiography showed extensive destruction of the joint interspace and the epiphyses, the contours of which were no longer visible (Fig. 2). After 8 months of allopurinol therapy (400 mg./day) there was considerable improvement, with a 50 per cent. reduction in the size of the tophi and reconstruction of the bony extremities (Fig. 3, opposite).

Ten patients (20 per cent.) have been able to wear smaller shoes, even after treatment of quite short duration.

None of our 106 patients has had any symptoms attributable to renal stones during treatment, although ten of these were "hyper-excretors" of uric acid and 26 had previously had attacks of renal colic, either spontaneously or during treatment with uricosuric drugs. Two patients had urate gravel in the urine, but the microcrystalluria disappeared within 48 hours of starting treatment.

Laboratory Findings.—These are summarized in Table I. The serum uric acid was reduced by 34 per cent. on average, and this brought most patients within the "safe" range. The fall in urinary uric acid (UUA) excretion was 42 per cent, while the

TABLE I
BIOCHEMICAL CHANGES IN 106 PATIENTS TREATED WITH ALLOPURINOL
(average 261 mg./day for 120 days)

Time of Investigation	Mean Serum Uric Acid (mg./100 ml.)	Mean Urinary Urate Excretion (mg./day)	Mean Urinary Oxypurine Excretion* (mg./day)
Before Treatment	10·0	563·4	25·7
During Treatment	6·6 (−34%)	324·4 (−42%)	131·0 (+400%)

*Method of Jørgensen and Poulsen (1955) using xanthine oxidase and uricase.

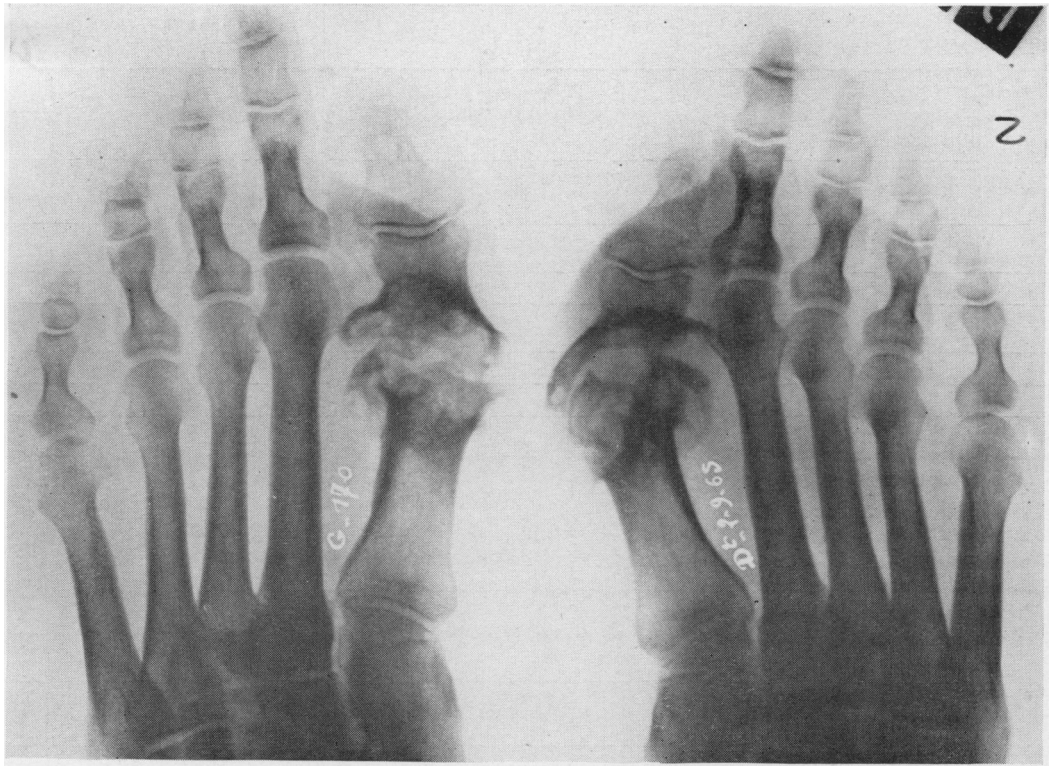

Fig. 3.—Reduction of tophi after 8 months' allopurinol therapy.

increase in oxypurine excretion exceeded 400 per cent. This increase in oxypurines was, however, inferior in absolute terms to the decrease in uric acid, with the net result that the total (oxypurine + urate) excretion fell by 133 mg./day. The risk of urinary stone formation is thus presumably less during allopurinol treatment.

A detailed study of the purine balance has shown, however, that these results are only true in a general sense, and that there are wide individual differences. Regular systematic measurement of the SUA and UUA and of the serum and urinary oxypurine concentration in 28 gouty patients showed that the results of treatment differ, according to whether the patients are "hyper-excretors" (uric acid output above 700 mg./day), "normo-excretors" (output 350 to 700 mg./day), or "hypo-excretors" (output less than 350 mg./day). The patients having been divided into three groups on the basis of whether they were hyper-, normo-, or hypo-excretors of uric acid, these three groups were then further subdivided according to whether, during allopurinol treatment, total urinary purine excretion (hypoxanthine + xanthine + uric acid) was reduced or increased relative to the control level.

(*i*) *Gouty hyper-excretors.*—All five patients in this group had suffered bouts of renal colic, but none had renal impairment. The fall in SUA and UUA was always of importance in this group, but the essential finding was a consistent fall in the total purine output during allopurinol therapy (uric acid + oxypurine excretion 1·89 mM/day). The deficit ranged from 20 to 53 per cent. of the control level (mean 36·7 per cent.). The serum xanthine level was moderately raised from 144 to 334 γ/100 ml., an increase of 131 per cent. Details are given in Table II (overleaf).

(*ii*) *Gouty hypo-excretors.*—This second group contained seven patients, none of whom had a history of urinary stones, though six had signs of renal impairment. During allopurinol treatment the fall in serum uric acid was 35 per cent. The changes in urinary purine excretion induced by the treatment were trivial, but showed a general tendency to increase. This group, therefore, showed opposite effects to the first, in which the total urinary purine output always tended to fall. Details are given in Table III (overleaf).

The data are too few to give a clear indication of the changes in the blood xanthine levels induced by allopurinol therapy, but the increase seemed greater in this second group than in the first.

FINDINGS IN

Case No.	Clinical Particulars					U
	Previous Uric Acid Excretion (mg./day)	Renal Stones	Renal Damage	Dosage of Allopurinol (mg./day)	Duration of Medication (days)	Previous Level (mM/day)
1	740	+	—	200 300	14 60	4·59 4·59
2	730	+	—	200 + 300	60 + 17	4·53
3	976	+	—	200 400	8 100	6·02 6·02
4	820	+	—	150	80	5·14
5	1,128	+	—	200	18	6·71
Mean	872					5·37

FINDINGS IN S

Case No.	Clinical Particulars					U
	Previous Uric Acid Excretion (mg./day)	Renal Stones	Renal Damage	Dosage of Allopurinol (mg./day)	Duration of Medication (days)	Previous Level (mM/day)
6	330			200	8	2·04
7	210		+	200	9	1·31
8	253		+	200	16	1·58
9	200		+	200 200	10 42	1·28 1·28
10	303		+	300	57	1·92
11	239		+	200	30	1·53
12	330		+	200	70	2·08
Mean	265			210	30	1·62

(*iii*) *Gouty normo-excretors.*—This third group of sixteen comprised the majority of our patients. In Table IV (overleaf) they are listed in order of the change in (uric acid + oxypurine) excretion induced by allopurinol. Sixteen of the 22 studies revealed a fall of up to 43·4 per cent. in total urinary purine excretion; eight of these patients had a history of renal colic, but had no impairment of renal function. The blood xanthine level rose to 183 per cent. during treatment.

Three patients (Cases 26, 27, 28), none of whom had a previous history of renal stone, showed a change in the opposite direction, that is, an increase in total purine excretion during treatment. A significant rise in blood xanthine also occurred.

One can therefore separate these "normo-excretors into two types:

(*a*) Those in whom total urinary purine output **falls** during allopurinol therapy, who have a history of renal stones, and in whom the blood xanthine level rises relatively little. Everything points to this being due to long-standing over-excretion of uric acid in the urine.

(*b*) Those in whom the total urinary purine output **rises** during allopurinol therapy. These include some with renal insufficiency but none with renal stones. The blood xanthine level generally rises further, and these patients resemble, in general, those in the second ("hypo-excretor") group.

YPER-EXCRETORS

ypurines		Uric Acid (mg./day)	Serum Levels			
			Xanthine (γ/100 ml.)		Uric Acid (mg./100 ml.)	
ith rinol day)	Percentage Variation	With Allopurinol	Previous Level	With Allopurinol	Previous Level	With Allopurinol
6	− 53	280	159	222	9·68	7·80
2	− 38·6	360	159	254	9·68	5·42
2	− 37·7	350			10·52	6·36
6	− 37·5	570	127		10·40	6·76
1	− 33·3	340	127	180	10·40	5·20
8	− 36·9	430	148	265	11·64	7·78
4	− 20·5	420	158	752	11·20	7·50
8	− 36·7	392	144	334	10·50	6·68

YPO-EXCRETORS

purines		Uric Acid (mg./day)	Serum Levels			
			Xanthine (γ/100 ml.)		Uric Acid (mg./100 ml.)	
ith rinol day)	Percentage Variation	With Allopurinol	Previous Level	With Allopurinol	Previous Level	With Allopurinol
2	− 5·9	270			10·88	7·00
9	− 2·3	160			9·48	6·84
7	+ 5·7	213	180	466	9·52	8·20
2	+ 18·8	180			10·36	7·40
0	+ 9·4	140			10·36	7·80
1	+ 25·6	216		540	10·36	6·04
5	+ 0·9	138		380	11·04	6·04
3	− 12·0	207	106	212	8·56	5·60
9		189		399	10·56	6·84

It is difficult to explain these differences and the division of gouty patients into several groups. We can, as a first approximation, group them according to their response to allopurinol, and thus distinguish the "hyper-excretors", who respond with a reduction in purine output and only a slight elevation of blood xanthine, from the "hypo-excretors", who more often show an increase in total urinary purine output and an increased blood xanthine level.

The theoretical side of the problem merits a few comments. Should one postulate, for the first group, a re-utilization of xanthine bases derived from allopurinol—perhaps resulting from an accumulation of nucleotides, which are capable of inhibiting purine synthesis by a feedback mechanism? Or is the difference due to an effect on the intestinal excretion of purines? It is possible (but remains to be proven) that xanthine is excreted better than uric acid by the digestive tract, and that the purine deficit arises in this way.

Points of Practical Importance

Allopurinol is specially indicated for the treatment of gouty patients who synthesize excessive amounts

FINDINGS IN SIXT

Case No.	Clinical Particulars					Ur
	Previous Uric Acid Excretion (mg./day)	Renal Stones	Renal Damage	Dosage of Allopurinol (mg./day)	Duration of Medication (days)	Previous Level (mM/day)
13	661			200	22	4·15
14	586			300 400	7 8	3·72 3·72
15	530	+ +		200 200 + 300	60 54 + 31	3·37 3·37
16	460	+		200	17	2·82
17	580	+		200	8	3·73
18	550	+		200	60	3·48
19	580	+		200	10	3·69
20	365	+		200	15	2·26
21	440	+		200	375	2·79
22	552			200 500	45 150	3·44 3·44
23	515			200	8	3·25
24	490			300	120	3·10
25	390		+	200	54	2·40
26	550			500 500	13 65	3·38 3·38
27	540		+	200 300	14 150	3·39 3·39
28	416			300 400	52 18	2·67 2·67
Mean	512					

of uric acid, *i.e.* those in whom UUA excretion exceeds 700 mg./day, or who have a history of renal stones. In these the drug has a spectacular effect, not so much on the SUA, which changes equally whatever the urate excretion, but on UUA excretion, which is more profoundly affected, and above all on the urinary oxypurine excretion. The urinary oxypurine excretion is always less than 30 per cent. during treatment, and early fears that patients previously troubled by stones in the urinary tract might form xanthine deposits during allopurinol therapy have not been realized.

Allopurinol is just as suitable for patients with low urate excretion as for the hyper-excretors, but it is necessary to take some precautions with this group, as total urinary purine excretion can be increased after treatment, with a somewhat increased risk. Although tissue deposits might be feared on theoretical grounds, because the blood xanthine level may be materially raised, the actual changes have not given cause for alarm. The risk of deposits forming in the urinary tract is slight, because the excess of purine bases which augments urinary purine excretion in some patients consists largely of oxypurines, and these are ten times more soluble than uric acid.

Summary

Allopurinol is a useful drug, which can apparently be given without risk to the majority of gouty patients, if not to all. It is prudent, in all patients, to maintain a diuresis.

UTY NORMO-EXCRETORS

:retion			Serum Levels			
d + Oxypurines		Uric Acid (mg./day)	Xanthine (γ/100 ml.)		Uric Acid (mg./100 ml.)	
Level with Allopurinol (mM/day)	Percentage Variation	With Allopurinol	Previous Level	With Allopurinol	Previous Level	With Allopurinol
2·35	−43·4	313	138	244	10·20	6·20
2·96 2·50	−36·5 −32·8	250 220			10·36 10·36	6·48 6·32
2·66 2·53	−21·5 −25·4	370		264 307	10·08 10·08	7·92 6·68
2·13	−24·5	250			10·68	7·64
2·96	−20·8		138	127	8·52	7·08
2·80	−19·5	340		233	10·08	5·84
3·11	−15·7	430	158	191	10·44	7·60
1·90	−16·0	250	191	328	10·44	6·96
2·51	−10·0	340		254	9·32	6·76
2·42 3·16	− 2·9 − 8·1	308 340	191 191	424	10·40 10·40	7·64 6·28
2·99	− 8·0		159	244	10·24	8·56
3·08	− 0·6	330		562	12·40	6·92
2·38	− 0·5	290	116	297	9·96	6·84
3·71 3·56	+ 9·8 + 5·6	380		 509	12·44 12·44	6·20 6·20
3·75 4·88	+11·5 +43·0	100 170	180 180	1,800 1,400	12·24 12·24	6·68 5·52
3·13 3·13	+17·2 +17·2	360 430		403 350	10·12 10·12	7·44 6·84
		314				