ALLOPURINOL IN THE TREATMENT OF URAEMIC PATIENTS WITH GOUT*

BY

J. D. WILSON, H. A. SIMMONDS, AND J. D. K. NORTH

From the Medical Unit, Auckland Hospital, Auckland, New Zealand

Uricosuric drugs have provided considerable relief to many gouty patients. Lowering of serum uric acid by antagonizing reabsorption of urate in the renal tubule is usually followed within a few months by a decreased frequency of acute episodes of gout. Tophi can be reabsorbed and bones can recalcify (Velayos and Smyth, 1965). The effect of these drugs on gouty nephropathy is not impressive and cases of improved renal function after treatment with uricosuric drugs are rare (Phillips, 1955) while continued progression of nephropathy in spite of adequate treatment is common (Thompson, Duff, Robinson, Mikkelsen, and Galindez, 1962). Many gouty patients with renal impairment respond poorly or not at all to uricosuric drugs. Those in whom treatment is successful run the risk of urolithiasis because the increased concentration of uric acid in the urine approaches or even exceeds its maximum solubility (Fried and Vermeulen, 1964). Protection against this complication, by increasing urinary output and by alkalinizing the urine, is difficult in uraemic patients whose urine remains at a low pH.

Allopurinol (4-Hydroxypyrazolo (3,4-d) pyrimidine) provides a solution to these difficulties by decreasing the production of uric acid, resulting in a fall in the levels of uric acid in both serum and urine.

Uric acid is the chief end-product of purine metabolism in man. It is derived from the oxidation of hypoxanthine and xanthine by xanthine oxidase. Allopurinol is an analogue of hypoxanthine which inhibits the action of xanthine oxidase, resulting in a decreased production of uric acid and leaving greater amounts of hypoxanthine and xanthine available for excretion.

This paper describes the results of the use of allopurinol over many months in twelve uraemic patients with severe gout.

Methods

Patients were selected for this study because of the severity of their gout and the extent of renal impairment. All were admitted to hospital for control studies before starting treatment. Three patients had been taking diuretics. These drugs were stopped 4 weeks before admission and episodes of symptomatic gout persisted. The first five patients received a low purine diet for 2 weeks but this lowered their serum uric acid by only 0.5 to 1.0 mg/100ml. with no change in urinary urate. Because these patients were to be followed as out-patients on normal diets, the practice was discontinued.

Allopurinol was given in a dosage of 100 to 400 mg. per day, patients with the most severe renal disease receiving the least. Prophylactic daily colchicine 0.5 mg. was given to all patients.

Urea was measured by the autoanalyser, urinary protein by the biuret method, creatinine by Jaffe's reaction using Fuller's earth (Hare, 1950), osmolality with an osmometer (Advanced Instruments) and pH with a Radiometer pH meter (Model 27).

Uric acid was estimated in blood and urine by an improved enzymatic spectrophotometric method (Simmonds, 1966). Urinary oxypurines (xanthine + hypoxanthine) were specifically adsorbed on to an anion exchange resin and quantitatively eluted. They were then converted by the action of xanthine oxidase to uric acid. The amount of uric acid produced was measured by uricase. Results are expressed as mg. of uric acid produced (Simmonds and Wilson, 1966).

Urine was collected under toluene. Aliquots were taken after 24-hr specimens had been heated to 45° C. for 30 min. to dissolve any uric acid or xanthine that might have precipitated out during the day. All specimens if not analysed immediately were kept at -10° C. until required.

*Requests for reprints to: Dr J. D. K. North, Medical Unit, Auckland Hospital, Park Road, Auckland, N. Zealand.

Results

Control Studies

Gout was severe both in frequency and duration of acute attacks in all patients (Table I). Attacks occurred at intervals of 2 to 8 weeks, each lasting 7 to 10 days. Ten of the twelve patients had previously received uricosurics without benefit. Eleven of the twelve patients had raised blood pressures. Five patients had tophi, which were massive in three.

All patients had renal disease, with an endogenous creatinine clearance below 68 ml./min. (average 33 ml./min.) and a serum urea above 44 mg./100 ml. Seven patients had proteinuria above 0.5 g./day. The pitressin concentration test showed impaired concentrating ability in all patients (average 507 mOsm./kg.). The extent of the depression was similar to that of patients without gout but with comparable degrees of renal damage as judged by the endogenous creatinine clearance. Urinary pH, determined on two fresh 3-hr specimens collected

TABLE I
EFFECT OF ALLOPURINOL ON CLINICAL GOUT AND ON RENAL FUNCTION

Case No.	Age (yrs)	Sex	Duration of Gout (yrs)	Allo-purinol (mg./day)	Duration of Treatment (wks)	Creatinine Clearance (ml./min.)	Serum Urea (mg./100 ml.)	Protein-uria (g./day)	Clinical Response	Complications
1	48	M	20	0		26	132	0.8	Greatly reduced frequency and severity of acute gout Much more mobile Off steroids	Diarrhoea
				300	48	17	221	0.01		
2	68	M	15	0		6	250	7.7	Little change Died terminal renal failure	—
				300	4	Died	350			
3	46	M	5	0		22	210	1.5	Greatly reduced frequency and severity of acute gout Tophi resorbing	Inguinal rash
				300	26					
				200	12	18	162	2.5		
4	40	M	24	0		10	260	2.7	Some reduction in frequency and severity of acute gout Died terminal renal failure	Reticulocytosis Inguinal rash
				300	16					
				100	8	Died	348			
5	43	M	18	0		52	47	2.0	Almost complete cessation of clinical gout	Eczematous rash on arms
				400	17					
				300	9	98	50	3.7		
6	32	M	8	0		30	82	1.5	Some reduction in severity and frequency of acute gout	—
				300	21	32	89	1.13		
7	54	F	4	0		67	76	—	Almost complete cessation of clinical gout	Persistent reticulocytosis
				300	34	60	61	0.26		
8	50	M	4	0		54	51	0	Great reduction in frequency and severity of acute gout More mobile Back at work	—
				300	13	45	73	1.4		
9	46	M	3	0		46	58	0.16	Some reduction in frequency and duration of clinical gout	Diarrhoea. Persistent reticulocytosis Inguinal rash
				300	17	51	70	0.42		
10	37	F	16	0		26	69	0.04	Greatly reduced frequency and severity of acute gout	Diarrhoea Eczematous ra
				300	17		152			
				200	4	20		1.5		
11	74	M	5	0		31	78	0.02	Greatly reduced frequency and severity of acute gout More mobile	—
				300	17	56	57	0.11		
12	37	M	7	0		41	110	1.2	Decreased frequency of clinical gout Back at work	—
				300	17	26	87	1.9		

Notes:

Duration of treatment is opposite the drug dosage given.

Creatinine clearance, proteinuria, and serum urea are recorded from the control period and from most recent values.

at 9. a.m. and 12 noon, was below 5.4 in all patients except one who had a urinary tract infection at the time.

Clinical Response

Acute attacks of gout decreased in frequency in eleven of the twelve patients, all of whom were followed for at least 3 months. In ten the severity of the attacks decreased dramatically and attacks were usually aborted in 24 hrs (Table I).

One patient (Case 1) with chronic tophaceous gout for 20 years had suffered from almost continuous clinical gout for the 18 months before treatment, but after starting allopurinol he had only two short attacks in 10 months. Whereas he was formerly confined to the house, he was able to resume outside activities. Mild chronic aches were not significantly improved.

A second patient (Case 5), in whom gout began 18 years ago, had to take 3 days off work every 3 to 4 weeks because of acute gout, episodes usually being precipitated by heavy work. In the 8 months since starting allopurinol he had only one attack of acute gout, and is now doing heavy work in a quarry.

A third patient (Case 3), in whom symptomatic gout started 5 years ago, was having acute attacks every 2 to 3 weeks, each episode lasting 7 to 10 days. The blood urea had risen to 150 mg./100 ml. With allopurinol the serum uric acid fell from 13.9 to 5.0 mg./100 ml. and remained below 6.0 mg./100 ml. for 9 months. His hands, which before therapy were stiffened, have become much freer and small tophi have been reabsorbed. He had only two short attacks of gout during the 9 months of treatment and each was precipitated by heavy drinking.

Biochemical Studies

Serum uric acid levels fell in all patients (Table II) and each of the ten patients now alive has a serum uric acid below 6.5 mg./100 ml. The minimum level was reached between 4 and 14 days after starting allopurinol, and a plateau was then usually established at about 0.5 mg./100 ml. above the minimum figure. One patient who died of terminal renal failure had a serum uric acid of 7.9 mg./100 ml. one week before death.

TABLE II
RESULTS OF TREATMENT

Tests	Allopurinol			
	Before	2-4 wks	2-3 mths	Recent
Serum Uric Acid (mg. per 100 ml.)	9.6 (6.5-13.2)	5.6 (3.4-7.4)	5.3 (2.8-7.3)	5.3 (2.5-7.9)
Urinary Uric Acid (mg. per day)	318.9 (175-444)	195 (92-328)	205 (100-368)	201 (105-368)
Urinary Oxypurines (mg. per day)	3.5 (1.0-9.0)	72 (4-150)	68 (7-150)	74 (27-215)

Mean values and range given for all patients, excluding Case 2 in whom treatment was discontinued after 1 month.

The mean daily urinary excretion of uric acid fell by 37 per cent. from 319 to 201 mg. (Table II), except for one patient in whom no fall occurred despite a satisfactory decrease in the serum levels of uric acid. All patients were advised to increase their fluid intake, and this, together with the above decrease in urate excretion, resulted in a reduction of the concentration of uric acid in the urine by more than 50 per cent., which may well protect them from possible intratubular deposition of uric acid.

Urinary oxypurines (hypoxanthine plus xanthine) after 4 weeks' treatment reached an average of 72 mg./day and have remained steady in most patients over the months. One patient (Case 9) with a creatinine clearance of 46 ml./min. excreted up to 215 mg./day.

Total urinary purine excretion, which is almost entirely represented by the sum of uric acid, hypoxanthine, and xanthine, was not much altered by allopurinol therapy (Table III, opposite). There was a mean fall in purine excretion (expressed as mg. uric acid) of 35.9 mg./day, 11 per cent. lower than the average control figures. However, four patients have actually excreted more purines while on treatment than before, although two of them have had some improvement in renal function. In seven of the ten patients whose results are given in Table III, the total urinary purine excretion on allopurinol exceeded the average control level on at least one occasion. In only one patient did the 24-hr total purine excretion on allopurinol not once exceed the minimum level before treatment.

Renal Function and Urate Clearances

Significant improvement in renal function which can certainly be attributed to allopurinol did not occur. In two patients (Cases 5 and 11) there was an increase in creatinine clearance from 52 to 98 and from 31 to 56 ml./min. respectively (Table I).

Case 5, 11 months before starting allopurinol, had an episode of the nephrotic syndrome with proteinuria above 20 g./day. It is possible that the improved glomerular filtration was related to his slow recovery from this syndrome.

Case 11 had suffered a myocardial infarction 5 weeks before starting allopurinol and some of his renal improvement might be ascribed to his changed myocardial state. However, allopurinol may have contributed to these improved clearances.

The serum urea was not altered significantly. The average control level of the ten patients now alive was 91.3 mg./100 ml. and the average of their most recent levels was 102.2 mg./100 ml. Six of the ten patients showed a rise in serum urea levels (Table I).

No significant change was observed in the urinary sediment. Some patients showed decreased red cell

TABLE III
EFFECT OF ALLOPURINOL ON DAILY TOTAL URINARY PURINES*

Case No.†	Control (mg. per day)		Allopurinol (mg. per day)		Mean Change
	Mean	Range	Mean	Range	
1	305	211-416	178	129-211	-127
3	230	155-298	234	186-313	+ 4
4	300	279-523	226	141-343	-74
5	229	229	309	258-350	+80
6	293	251-336	267	226-307	-26
7	419	297-486	308	220-400	-111
8	342	342	373	296-452	+31
9	449	401-499	335	308-375	-114
11	303	267-338	347	306-395	+44
12	349	261-436	283	182-385	-66
Mean	321.9		286.0		-35.9

*Total urinary purines are the sum of xanthine + hypoxanthine + uric acid, expressed as mg. of uric acid.

†Case 2 was excluded because of too short a duration of treatment. Case 10 was excluded because of unreliability of tablet ingestion.

and cast excretion, but in others there was an increased excretion of the formed elements.

Four patients showed a rise in proteinuria of more than 1.0 g./day after starting treatment with allopurinol, but the daily variation was such that these changes are of doubtful significance. Uric acid clearances were not altered by allopurinol.

Two patients (Cases 2 and 4) died of terminal renal failure after 4 and 24 weeks' treatment; the serum urea in both was above 240 mg./100 ml. before treatment.

In Case 4, autopsy showed bilateral contracted kidneys with visible streaks of sodium biurate in the medulla. Histologically there was almost complete absence of normal glomeruli, considerable interstitial fibrosis and lymphocytic infiltration, and needle shaped crystals of sodium biurate in the medulla and in some tubules. Occasional afferent arterioles showed hyaline thickening and large arteries had medial coat thickening and reduplication of internal elastic lamina.

Complications

Allopurinol therapy was followed by an acute attack of gout within one month in three of the twelve patients, and in two of these the drug appeared to precipitate the episode. After the first 3 weeks of treatment, no patient had an increased frequency of attacks of acute gout.

A mild eczematous rash appeared in the groin in three patients (Cases 3, 4, and 9) but settled. A rash of similar appearance but more troublesome appeared on the arms of two other patients (Cases 5

and 10). Transient diarrhoea occurred in three patients (Case 1, 9, and 10), each of whom was on colchicine together with Ismelin or a broad-spectrum antibiotic at the time.

A persistent reticulocytosis of 3 to 4 per cent. occurred during treatment in three patients (Cases 4, 7, and 9).

One patient had a rise in serum transaminase to 72 units/ml. accompanied by an increased zinc sulphate turbidity; both resolved without alteration of the dosage. No changes were noted in white blood cells or platelets.

Discussion

In contrast to other workers we have found a dramatic clinical improvement in our gouty patients treated with allopurinol. Acute attacks of gout have been less severe and much less frequent than before. Reports on the use of allopurinol from other centres have not indicated this degree of clinical improvement (Rundles, Wyngaarden, Hitchings, Elion and Silberman, 1963; Yü and Gutman, 1964; Klinenberg, Goldfinger, and Seegmiller, 1965). Many of their patients may have had mild or infrequent attacks of gout so that insufficient time had elapsed before publication to assess an altered pattern of their attacks. Our patients were all having frequent attacks of acute gout so that an effect from treatment was obvious within 4 months. These results are even more gratifying when the extent of each patient's renal disease is considered. Renal damage was a major factor in the resistance of most

of our patients to uricosuric drugs, for their kidneys were unable to excrete increased amounts of uric acid. Allopurinol has broken the cycle of hyperuricaemia made worse by the inadequate urinary excretion of uric acid, and the clinical response has followed this fall in serum uric acid.

Allopurinol in our experience effectively lowers serum and urinary uric acid levels in the presence of renal failure. One of our patients was maintained for 4 months on allopurinol with a serum uric acid of 5 to 7 mg./100 ml. when his serum urea was above 300 mg./100 ml. Most patients showed a fairly constant urinary excretion of uric acid, but in a few there were wide daily fluctuations, as noted by Smyth (1965).

The method for measuring oxypurines which we developed is specific for hypoxanthine together with xanthine because the non-specific enzyme xanthine oxidase is followed by the specific enzyme uricase. Thus only the contribution of uric acid produced by the action of xanthine oxidase is measured in the ultraviolet absorption at $292.5 \text{ m}\mu$. The method for measuring oxypurines described by Rundles and others (1963) is used in most other studies. This method assumes a fixed ratio of hypoxanthine to xanthine in the urine and estimates oxypurines as mg. hypoxanthine, using a constant $\Delta E 292/\mu\text{g./ml.}$ extinction value after the concentrated eluate from a cation-exchange resin has been incubated with xanthine oxidase. No uricase is used. We have found widely differing proportions of hypoxanthine and xanthine in the urine of our patients both before and after allopurinol, so that a fixed extinction value would give erroneous results. In addition, some interfering compounds react with xanthine oxidase but not with uricase which makes our method more specific.

Using the formula of Rundles and others (1963), we calculated the oxypurines produced after xanthine oxidase and compared these results with values obtained by our method after uricase. The differences in the results with the two methods were significant. In some the result calculated as hypoxanthine and corrected to millimoles after xanthine oxidase exceeded the final result by 50 per cent. In others, the reverse occurred, and results after xanthine oxidase, corrected to millimoles, were 25 per cent. lower than the final result. Petersen, Jørni, and Jørgensen (1965a, b) noted a wide range in the ratio of hypoxanthine to xanthine in six normal subjects. We believe, for these reasons, that a fixed ratio of hypoxanthine to xanthine cannot be assumed for patients and that measurement of oxypurines should include the use of uricase following incubation with xanthine oxidase.

Rundles and others (1963) described a fall in

urinary excretion of the sum of uric acid plus hypoxanthine plus xanthine in their patients during treatment with allopurinol compared with control levels. This discrepancy in "total" urinary purine excretion was confirmed by Yü and Gutman (1964) and Hall, Holloway, and Scott (1964).

Using our method for estimating oxypurines, we have not observed this substantial fall in excretion of total urinary purines. We have in fact seen a rise in the purine excretion in four patients on allopurinol while a great overlap occurred in the daily excretion before and during treatment with allopurinol. The average fall of only 11 per cent. in "total" urinary purines per day in our series is much less than that previously reported. Differences in method and the extent of the renal damage in our patients might explain these observations. However, Wyngaarden (1965) observed the greatest fall in urinary purine excretion after allopurinol in patients with renal damage or with tophaceous gout, in whom a decrease of up to 50 per cent. was seen. Klinenberg and others (1965), using a method for estimating oxypurines which employs uricase after xanthine oxidase, found no significant fall in urinary purines in a small group of patients treated with allopurinol for 40 days. It seems probable that the methods used play a major part in explaining these differences.

No clear explanation is available for the reported fall in purine excretion with allopurinol. A reduction in purine biosynthesis was suggested (Rundles and others, 1963), because the ribonucleotide derivative of allopurinol is a potent inhibitor of the first enzyme of purine synthesis (Wyngaarden, Rundles, Silberman, and Hunter, 1963). Krakoff and Meyer (1965) review the suggestion that purines could be "recycled" in the purine metabolic pool. In patients with renal impairment, the kidney becomes a less important pathway of uric acid excretion than the gastrointestinal tract, and as little as 33 per cent. of the daily uric acid excretion may be excreted by the kidneys in patients with advanced renal damage (Sorensen, 1960). Thus no conclusions can be drawn from our patients about total purine synthesis. Considerable falls in total purine production could occur without necessarily being reflected in the urinary excretion of our uraemic patients. Oxypurines are cleared by the kidneys six to sixteen times more effectively than uric acid (Goldfinger, Klinenberg, and Seegmiller, 1965). This should be a great advantage particularly in patients with renal damage though it adds to the difficulties in interpreting urinary purine excretion in relation to purine metabolism.

Serum iron levels were followed because of the possible relationship of xanthine oxidase to intestinal absorption of iron and in mobilization of iron from

the liver, but no changes were noted. Ayvazian (1964) reported a case with both xanthinuria and haemochromatosis and suggested the latter condition was also related to the lack of xanthine oxidase. Engelman's xanthinuric patient had evidence of neither haemochromatosis nor defective iron absorption (Engelman, Watts, Klinenberg, Sjoerdsma, and Seegmiller, 1964). However, possible disturbances of iron metabolism must be watched with long-term allopurinol therapy. The persistent reticulocytosis seen in some of our patients has also been noted by Rundles and others (1963), yet chromium survival times are reportedly normal (Emmerson, 1965). Further studies are required to evaluate this finding.

Most of the kidney damage in gouty patients is not due to massive urate deposition but consists rather of glomerular changes, hyalinization of the intima, thickening of arterial walls, tubular atrophy, and interstitial fibrosis (Gonick, Rubini, Gleason, and Sommers, 1965). Until the relationship of uric acid metabolism to these changes is clarified, it is not possible to predict accurately the effect of allopurinol upon renal damage in gouty patients. Uric acid deposition in the kidneys will almost certainly be halted, but it is possible that in most patients established renal damage will continue to progress. Long-term studies with allopurinol will be needed to establish its usefulness in this aspect of the gout syndrome. The improvement in renal function in two of our patients is possibly related to allopurinol therapy.

Even if allopurinol is shown eventually to have little effect on renal damage in gouty patients, its

impressive control of clinical gout and its beneficial effect on tophi will still justify its use in the therapy of gout, particularly in patients unresponsive to uricosuric drugs.

Summary

Allopurinol was given for up to 11 months to twelve uraemic patients with severe gout. A dramatic clinical improvement occurred with a decreased frequency and severity of acute gout in all but one patient. Serum uric acid levels are at present below 6.5 mg./100 ml. in the ten patients now alive, who have a mean serum urea of 102 mg./100 ml. Daily urinary uric acid excretion has fallen by 37 per cent. Using a new method for estimating oxypurines which employs xanthine oxidase followed by uricase, the mean urinary 24-hr oxypurine excretion has risen from 3.5 to 72 mg./day. Daily "total" urinary purines (being the sum of uric acid, hypoxanthine, and xanthine) have fallen only slightly with treatment and there is an overlap in daily levels of excretion before and during allopurinol therapy. Two patients died of renal failure, but a significant improvement in renal function occurred in two other patients. Transient diarrhoea, rashes, and a persistent reticulocytosis were minor side-effects.

This work was supported by the New Zealand Medical Research Council. We wish to thank Sister S. Cooper for in-patient care, Dr. E. A. Bowie for assistance in the later stages of the trial, and Mrs. E. Smith for secretarial aid. We thank Burroughs Wellcome, Ltd., for supplies of allopurinol.

REFERENCES

- Ayvazian, J. H. (1964). *New Engl. J. Med.*, **270**, 18 (Xanthinuria and hemochromatosis).
- Emmerson, B. T. (1965). Personal communication.
- Engelman, K., Watts, R. W. E., Klinenberg, J. R., Sjoerdsma, A., and Seegmiller, J. E. (1964). *Amer. J. Med.*, **37**, 839 (Clinical, physiological and biochemical studies of a patient with xanthinuria and phaeochromocytoma).
- Fried, F. A., and Vermeulen, C. W. (1964). *Invest. Urol.*, **2**, 131 (Artificial uric acid concretions and observations on uric acid solubility and supersaturation).
- Goldfinger, S., Klinenberg, J. R., and Seegmiller, J. E. (1965). *J. clin. Invest.*, **44**, 623 (Renal excretion of oxypurines).
- Gonick, H. C., Rubini, M. E., Gleason, I. O., and Sommers, S. C. (1965). *Ann. intern. Med.*, **62**, 667 (Renal lesion in gout).
- Hall, A. P., Holloway, V. P., and Scott, J. T. (1964). *Ann. rheum. Dis.*, **23**, 439 (4-hydroxypyrazolo (3,4-d) pyrimidine (HPP) in the treatment of gout).
- Hare, R. S. (1950). *Proc. Soc. exp. Biol. (N. Y.)*, **74**, 148 (Endogenous creatinine in serum and urine).
- Klinenberg, J. R., Goldfinger, S. E., and Seegmiller, J. E. (1965). *Ann. intern. Med.*, **62**, 639 (Effectiveness of the xanthine oxidase inhibitor allopurinol in the treatment of gout).
- Krakoff, I. H., and Meyer, R. L. (1965). *J. Amer. med. Ass.*, **193**, 1 (Prevention of hyperuricemia in leukemia and lymphoma).

- Petersen, B. B., Jørni, J., and Jørgensen, S. (1965a). *Scand. J. clin. Lab. Invest.*, **17**, 454. (Separate enzymatic determination of hypoxanthine and xanthine in human urine).
- , —, — (1965b). *Ibid.*, **17**, 460 (Hypoxanthine, xanthine and uric acid in human urine and in decomposed blood).
- Phillips, R. W. (1955). *Arch. intern. Med.*, **96**, 823 (Reversal of renal insufficiency in gout).
- Rundles, R. W., Wyngaarden, J. B., Hitchings, G. H., Elion, G. B., and Silberman, H. R. (1963). *Trans. Ass. Amer. Phycns*, **76**, 126 (Effects of a xanthine oxidase inhibitor on thiopurine metabolism, hyperuricemia and gout).
- Simmonds, H. A. (1966). *Clin. chim. Acta*, in press. (A method of estimation of uric acid in urine and other body fluids).
- and Wilson, J. D. (1966). *Ibid.*, in press. (Method for the determination of xanthine and hypoxanthine in biological fluids).
- Smyth, C. J. (1965). *Arthr. and Rheum.*, **8**, 907 (Studies with allopurinol (HPP) in patients with tophaceous gout).
- Sorensen, L. B. (1960). *Scand. J. clin. Lab. Invest.*, **12**, Suppl. 54 (Elimination of uric acid in man).
- Thompson, G. R., Duff, I. F., Robinson, W. D., Mikkelsen, W. M., and Galindez, H. (1962). *Arthr. and Rheum.*, **5**, 384 (Long-term uricosuric therapy in gout).
- Velayos, E. E., and Smyth, C. J. (1965). *Arch. intern. Med.*, **116**, 212 (Urate diuretic therapy in chronic gout).
- Wyngaarden, J. B. (1965). *Arthr. and Rheum.*, **8**, 883 (Xanthine oxidase inhibitors in the management of gout).
- , Rundles, R. W., Silberman, H. R., and Hunter, S. (1963). *Ibid.*, **6**, 306 (Control of hyperuricemia with hydroxy-pyrazolopyrimidine, a purine analogue which inhibits uric acid synthesis).
- Yü, T., and Gutman, A. B. (1964). *Amer. J. Med.*, **37**, 885 (Effect of allopurinol on serum and urinary uric acid in primary and secondary gout).

L'allopurinol dans le traitement des patients urémiques atteints de goutte

RÉSUMÉ

On administra de l'allopurinol à douze sujets urémiques et présentant une goutte sévère pendant une période allant jusqu'à 11 mois. Une amélioration clinique radicale fut observée chez tous les malades sauf un, avec diminution de la fréquence et de la sévérité des accès de goutte aiguë. Le taux sérique de l'acide urique est à l'heure actuelle inférieur à 6,5 mg. pour 100 ml. chez les dix malades encore en vie; la valeur moyenne de l'urée sanguine chez ceux-ci est de 102 mg. pour 100 ml. L'élimination urinaire quotidienne de l'acide urique a chuté de 37 pour cent. L'élimination urinaire journalière moyenne des oxypurines, déterminées à l'aide d'une nouvelle méthode, utilisant la xanthine oxydase suivie d'uricase, s'est élevée de 3,5 à 72 mg. par jour. L'élimination quotidienne totale des purines urinaires (somme de l'acide urique, de l'hypoxanthine et de la xanthine) n'a diminué que d'une façon légère sous l'influence du traitement et il y a un chevauchement entre les taux d'élimination avant et pendant le traitement par l'allopurinol. Deux malades moururent d'insuffisance rénale mais une amélioration significative de la fonction des reins survint chez deux autres sujets. Comme effets secondaires mineurs on observa de la diarrhée éphémère, des rashes et une réticulocytose persistante.

Alopurinol en el tratamiento de pacientes urémicos con gota

SUMARIO

Alopurinol fué administrado a doce sujetos urémicos con gota grave por un periodo de hasta 11 meses. Una mejoría clínica espectacular ocurrió en todos pacientes menos uno, con una disminución de la frecuencia y gravedad de los ataques agudos de gota. Las cifras séricas de ácido úrico son actualmente menores de 6,5 mg. por 100 ml. en los diez enfermos que aún viven; la cifra media de la urea sérica en estos es de 102 mg. por 100 ml. La excreción diaria de ácido úrico ha disminuido en un 37 por ciento. La excreción urinaria diaria media de oxipurinas, determinadas por un nuevo método que emplea la xantina oxidasa seguida de uricase, se ha elevado de 3,5 a 72 mg. por día. La eliminación diaria total de las purinas urinarias (siendo estas la suma de ácido úrico hipoxantina y xantina) ha bajado sólo un poco con el tratamiento y hay un engranaje entre las cifras de excreción antes y durante el tratamiento con alopurinol. Doce enfermos murieron de insuficiencia renal pero una mejoría marcada de la función renal sobrevino en otros dos sujetos. Diarrea transitoria, erupciones y una reticulocitosis persistente fueron efectos secundarios de menor importancia.