The Effect of Allopurinol (HPP) in the Treatment of Gout

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A study has been made of the therapeutic effect of HPP (allopurinol)† in 20 male patients with primary gout, one female patient with primary tophaceous gout, one female patient with myelofibrosis, and one male patient with azotemia due to polycystic kidney disease who was maintained with dialysis through a small intestinal loop (Roux-en-Y). The drug has been given for periods up to eight months. Fifteen patients have been treated for over four weeks.

Figure 126 shows a typical response in a patient with nontophaceous gout. The serum uric acid dropped slowly over 48 hours, perhaps a little slower than in patients treated with uricosuric drugs. The urine uric acid decreased

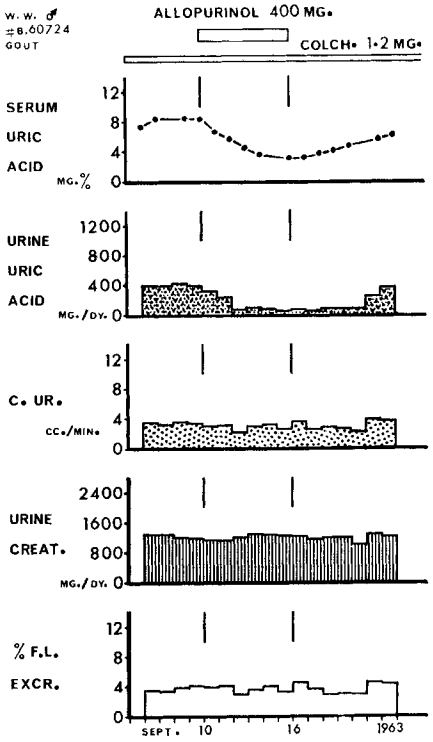

Fig. 126.—Results of balance study in patient with nontophaceous gout treated with allopurinol (HPP) for six days.

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†Zyloprim-Burroughs Wellcome & Co. brand of allopurinol (4-hydroxypyrazolo(3,4-d) pyrimidine).

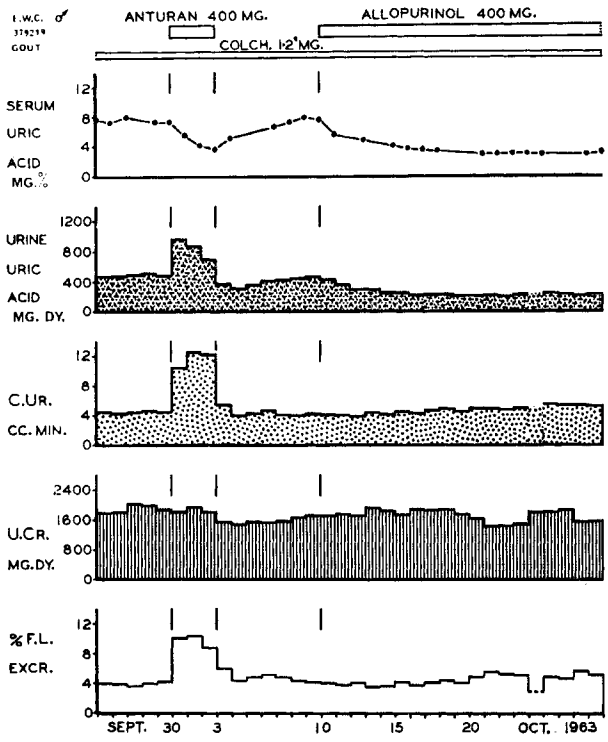

Fig. 127.—Comparison of effects of Anturane and allopurinol (HPP). Observe similar lowering of serum uric acid with marked difference between urine uric acid excretion, clearance of uric acid and per cent of filtered uric acid load excreted.

from a control level of 400 mg./24 hours to 130 mg./24 hours by the fifth day. The clearance of uric acid and the ratio of uric acid clearance to creatinine clearance (arithmetically equal to the percentage of the filtered urate load which is excreted) did not change appreciably.

Figure 127 shows the typical response to the drug in a patient with tophaceous gout. (Six patients had tophaceous deposits and the serum uric acid levels fell more slowly in this group). This man required 19 days for his serum uric acid to drop from 12 mg. per cent to below 6 mg. per cent. It was of interest to hear the comments of Dr. Wyngaarden and others that the urine uric acid does not change appreciably in patients with tophaceous deposits, presumably due to mobilization of uric acid from the tophi. The urate excretion in this patient decreased only slightly from a control level of 340 mg./24 hours to approximately 250 mg./24 hours. The clearance of uric acid and the ratio of urate clearance to creatinine clearance did not change appreciably, although there appeared to be a slight increase after 10 days of therapy.

Figure 127 and the next two compare the effects of allopurinol and Anturane (sulfinpyrazone). With the uricosuric drug Anturane (Fig. 127), the serum uric acid dropped rapidly with the expected increase in urine uric acid, and

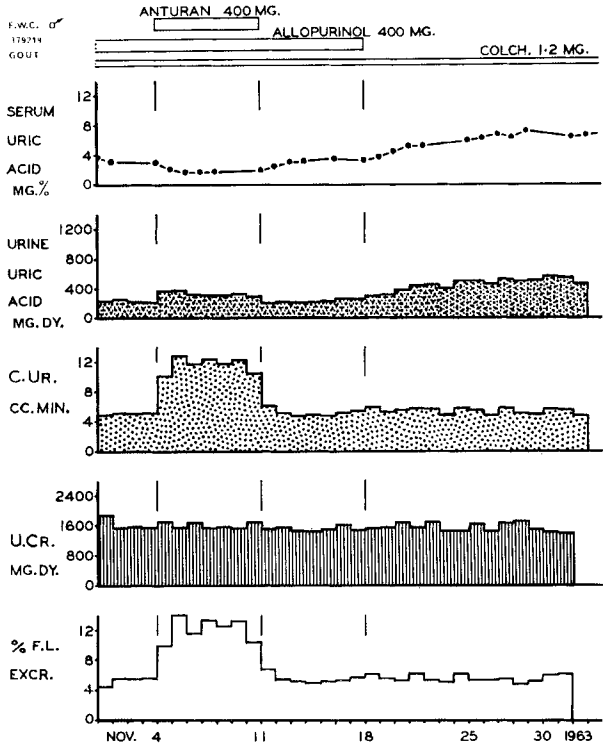

Fig. 128.—Comparison of effects of Anturane and allopurinol (HPP). With addition of Anturane, noted marked rise in clearance of uric acid and per cent of filtered uric acid load excreted.

C_{Ur}/C_{Cr} ratio (per cent filtered urate load excreted) increased. When the Anturane was stopped the serum uric acid returned rapidly to pretreatment levels. The patient was then given allopurinol, 100 mg., 4 times daily. The serum uric acid fell from 9.5 mg. per cent to 4.9 mg. per cent in 3 days. There was a decrease in the urine uric acid excretion but little change in clearance of uric acid or in the C_{Ur}/C_{Cr} ratio. After 24 days (Fig. 128) Anturane, 400 mg. daily was added. The serum uric acid fell even further, from 3.0 mg. per cent to 1.8 mg. per cent with a slight increase in the urine uric acid. However, this resulted in a marked rise in clearance of uric acid from 5.2 cc./min. to 13 cc./min. and a marked rise in the C_{Ur}/C_{Cr} ratio. When the Anturane was stopped, the serum uric acid rose again to 3.4 mg. per cent and the urate excretion and clearance returned to levels previously attained with HPP alone (Figs. 128, 129).

Figure 130 shows the cumulative data of the first 19 patients treated with this agent. The serum uric acid levels fell from a mean of 8.9 mg. per cent to a mean of 4.3 mg. per cent within 5 days of therapy with 400 mg. of HPP daily. The urine uric acid also fell from a mean of 556 mg./24 hours to a mean of 266 mg./24 hours. I would like to point out that as a group, pa-

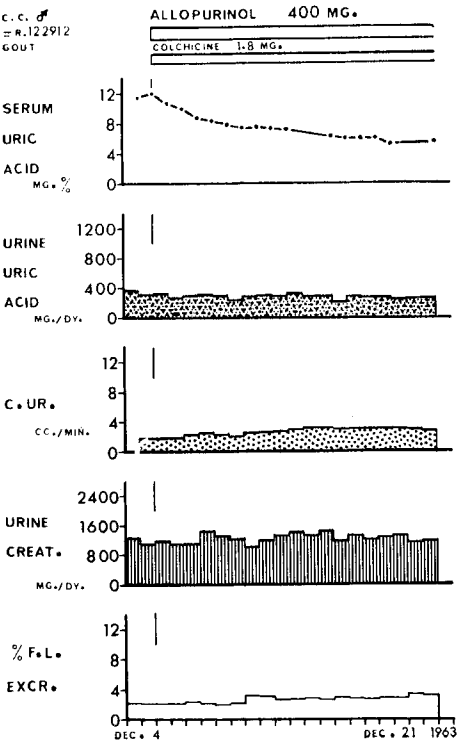

Fig. 129.—Results of balance study in patient with tophaceous gout treated with allopurinol (HPP). Note slow fall in serum uric acid and slight decrease in urine uric acid.

tients treated with HPP excrete less uric acid/24 hours although their serum levels were comparable to the normal controls.

Six patients had acute attacks of gout while on therapy, although all were taking colchicine. Two continued to have acute attacks up to three months after starting HPP and one patient is continuing to have acute attacks six months after starting therapy. Skin rashes were encountered in two patients treated with HPP. One man was treated initially for six weeks with HPP when we were temporarily interrupted. Three days after restarting the drug he developed a very severe, diffuse, erythematous maculopapular eruption. The HPP had to be discontinued three days later because of the severity of the eruption. No attempt was made to restart the agent in this man.

One other patient developed a pruritic eruption but the HPP was continued and his rash gradually disappeared. Four patients complained of pruritus but it was suspected that this was due to the hot, dry atmosphere in the Clinical Investigation Unit during the summer months.

I would like to raise a question here, because of our experience with one patient with azotemia due to polycystic kidney disease who had been maintained for the previous year and a half with intestinal dialysis through a small intestinal Roux-en-Y loop. He had serum uric acid values of 9 and

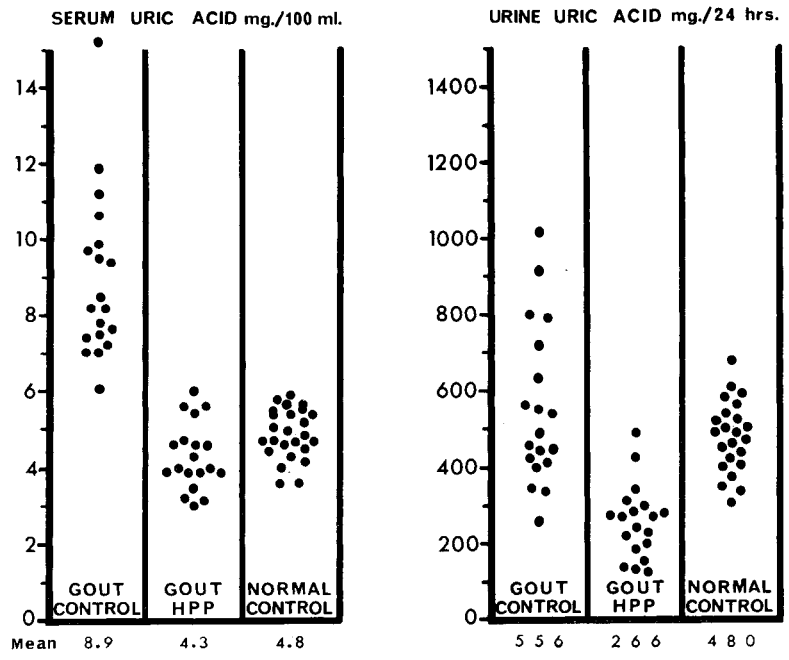

Fig. 130.—Serum uric acid and urine uric acid results in 19 gout patients treated with allopurinol (HPP), 400 mg. per day.

10 mg. per cent and because of the reported association of urate myocarditis in these patients, treatment with HPP was selected. He was given up to 800 mg. daily with no effect on his serum uric acid. It was suspected that he was probably not absorbing the agent, since the urinary oxypurines were unmeasurable. I would like to ask if anyone knows where this agent is absorbed? He was obviously absorbing other nutriments because he was maintained for a year and a half on this regimen and showed no other evidence of malabsorption.

Three patients with tophaceous gout have been maintained on high doses of Anturane and relatively high doses of HPP; 600 mg. of Anturane and 400 mg. of allopurinol daily. These patients previously required up to a gram of Anturane daily and as far as can be ascertained are reliable in regard to taking medications.

I would like to introduce one other concept for consideration. We have heard of the limitations and theoretical complications of treating patients with uricosuric agents. When patients are treated with uricosuric agents, the serum uric acid is reduced by increasing the uric acid excretion and clearance markedly. When patients are treated with HPP, their serum uric acid is reduced by decreasing the overall production of uric acid. Uric acid clearance remains unchanged but as a result of the reduced filtered load the amount of uric acid excretion is also reduced. The long term effects of allopurinol administration are not known although it appears to be a very

effective drug with very few side effects. In view of the often suggested dual etiology of primary gout it is suggested that uncomplicated (non-tophaceous) cases of primary gout might be treated more effectively with small doses of each agent, thus avoiding the undesirable effects of uricosuric therapy alone. In the few patients treated in this manner, giving them approximately 200 mg. of Anturane and 200 mg. of allopurinol daily, their serum uric acid levels have fallen to normal; their urine uric acid excretions have risen slightly; and their clearance of uric acid has risen to the so-called "normal" range. It is hoped by this combination to achieve a state of "urate homeostasis."