SESSION I - BIOCHEMISTRY AND METABOLISM

DISCUSSION

DR. D. N. KERR (U.K.): Dr. Barbara Clarkson and I have studied the effect of allopurinol in four patients by the technique of Sørensen (1960) (Fig. 1) using 14C labelled uric acid, labelled in the 2-position (obtained from the Radiochemical Centre, Amersham). All patients were treated with low protein, low purine diets during the period of study, and they remained on these diets during a control period until the plasma uric acid level was steady. This technique is not applicable to patients with large tophi. The four patients involved in this study had no visible tophi. Their clinical details are summarized in Table I.

Case 2 was suffering from gout with unimpaired renal function (creatinine clearance 130 ml./min.). During the first study he continued his usual dose of probenecid, which maintained his plasma uric acid level at 5 mg./ml. During the second study he was maintained on allopurinol alone and the plasma uric acid level was virtually identical.

Cases 3 and 4 both had typical histories of gout for more than 10 years before the onset of chronic renal failure. They were receiving no uricosuric drugs during their first balance studies.

Case 1 was referred to us with a diagnosis of gout and chronic renal failure but turned out on further investigation to have probable chronic glomerulo-nephritis with osteo-arthritis. His uric acid pool size was within normal limits for his size.

In Case 2 the uric acid pool size was similar on probenecid and on allopurinol but the production rate fell with the latter as indicated in Table II. Cases 3 and 4 had raised pool sizes which were restored to normal by allopurinol. Their production rates were high normal.

TABLE I

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Diagnosis</th>
<th>Plasma Uric Acid (mg/ml.)</th>
<th>Dose of Allopurinol (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>Allopurinol</td>
</tr>
<tr>
<td>1</td>
<td>Chronic renal failure</td>
<td>7.6</td>
<td>4.6</td>
</tr>
<tr>
<td>2</td>
<td>Gout</td>
<td>5.00*</td>
<td>5.45</td>
</tr>
<tr>
<td>3</td>
<td>Gout + Chronic renal failure</td>
<td>11.2</td>
<td>3.65</td>
</tr>
<tr>
<td>4</td>
<td>Gout + Chronic renal failure</td>
<td>8.1</td>
<td>4.7</td>
</tr>
</tbody>
</table>

*Benemid.

TABLE II

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Pool Size (mg.)</th>
<th>Production Rate (mg./day)</th>
<th>Pool Size (mg.)</th>
<th>Production Rate (mg./day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1,460</td>
<td>623</td>
<td>926</td>
<td>424</td>
</tr>
<tr>
<td>2*</td>
<td>1,758</td>
<td>1,150</td>
<td>1,780</td>
<td>870</td>
</tr>
<tr>
<td>3</td>
<td>2,361</td>
<td>624</td>
<td>1,496</td>
<td>387</td>
</tr>
<tr>
<td>4</td>
<td>2,058</td>
<td>778</td>
<td>1,299</td>
<td>343</td>
</tr>
</tbody>
</table>

*Benemid.

Fig. 1.—14C uric acid specific activity in urine following administration to Case 4.
before treatment and fell to low normal during treatment with allopurinol. Case 1 had a fall in pool size and production rate comparable to that of the patients with gout.

On the basis of this small series, it is suggested that the fall in plasma uric acid that occurs during treatment with allopurinol is a reflection of a reduced production rate and is associated with a fall in pool size as might be predicted from the supposed action of the drug.

**Dr. B. T. Emerson (Australia):** A standard method of assessing urate production is by estimating the incorporation of glycine into uric acid. We have undertaken this in one patient with severe primary gout after stabilization for 5 days on a purine-free diet during a control period. We then repeated the study under identical conditions after he had been on a dose of 400 mg. of allopurinol for 3 months. Fig. 2 shows the specific activity of the uric acid isolated from 24-hr aliquots of urine from this patient after 5 μc ¹⁴C glycine was given at zero time. The top line shows the great variation in the urinary uric acid, reaching a peak on the fourth day and declining thereafter; the lower line, after the second dose of ¹⁴C glycine was given, shows the great reduction in incorporation into uric acid during allopurinol therapy. As the serum and urinary uric acid remained stable during both periods of study, this directly confirms that allopurinol reduces the amount of uric acid which is formed in the body. However, it does not provide any information about the relative amounts of glycine alternatively incorporated into xanthine and hypoxanthine.

![](image)

**Dr. M. A. Ogrzylo (Canada):** I should like to ask Dr. Hitchings or Dr. Elion, why, if allopurinol is bound as strongly to xanthine oxidase as they say, one cannot completely suppress uric acid formation? Or do you believe that if you were allowed an unlimited dose level you could do this? In the various reports there is always a certain minimum below which the urinary uric acid is not reduced.

**Dr. Hitchings:** Both Dr. Rundles and I showed the dose-response curve of this one patient, and it was a linear log dose response. It extrapolated to zero uric acid at a dose of 5 g. per day. Dr. Rundles has gone up to 1 g., or even a little higher, but nobody has approached 5 g., and we should not wish to do so, but we feel that it probably could be done if one poured in enough drug.

**Dr. Ogrzylo:** Can it be done in animals?

**Dr. Hitchings:** No. I think I showed the dose-response curve in the rat in a slide of Miss Elion's. At 50 mg/kg the allantoin formation was down to 20 per cent. of normal. We probably could have gone higher; we just did not do so.

**Dr. Elion:** I think that there is probably another limit that of the absorption of the drug, particularly when given orally. If one gave 5 g. daily, I am not sure that even 80 per cent. of it would be absorbed.

**Dr. Rundles:** I know of no reason why one should not explore the upper limits of drug dosage. We have gone up to 1-2 g./day for as long as 10 days, and have seen no deleterious effects. You might expect some tendency for stone formation from pyrazolopyrimidines, but we have not pushed the uric acid down to 1-5 mg./per cent. for many days at a time with no adverse effects. It makes our house officers a little nervous, but I know of no reason why it should not be done.

**Dr. J. E. Seegmiller (U.S.A.):** We have given 1,200 mg. allopurinol per day to a woman with gout who weighed only 45 kg., and she developed symptoms of renal colic which disappeared when we lowered the dose. Although we strained the urine we were never able to recover any solid material to determine whether this was indeed xanthine, or whether it was allopurinol or its metabolites. I wondered whether Dr. Elion or Dr. Hitchings could give us some idea as to the possibility that, at the very high doses of drug, there might be some allo-xanthine precipitating out in the urinary tract.

**Dr. Elion:** I should not like to see 5 g. allo-xanthine excreted per day, but I think that for the higher levels of the drug that are used—roughly 800 to 1,000 mg./day—the total amount of allo-xanthine could be as high as 700 mg. The solubility of allo-xanthine in water is about 350 mg./l. at body temperature, so that if the urine volume were reasonably large—and I think that in gouty patients one would always want to keep it around 21°C.—there would be no difficulty with allo-xanthine precipitation.

**Dr. Hitchings:** We feel that we are closest to the critical level with xanthine excretion. This is another reason for not pushing the doses too high because, while there is ordinarily some margin of safety with regard to the solubility of xanthine in man, we have seen xanthine precipitation in the kidney apparatus in all of the smaller animals. When one makes a calculation based on solubility and the amount of xanthine excreted, the margin of safety is not all that wide. One should not be too sanguine about the possibility of producing xanthine stones in patients, and one should maintain a high water flux in patients who are taking allopurinol. I might point out, too, that total water flux is more important than alkalinization so far as xanthine is concerned, because the pKa of xanthine is 7.5 where that of uric acid is 5-5, so that you do not get the large increase in solubility as a result of alkalinization with xanthine that you get with uric acid.