Papers and Originals

Allopurinol in Treatment of Gout

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Allopurinol (4-hydroxypyrazolo (3,4-d) pyrimidine), a structural isomer of the purine base hypoxanthine, is a powerful inhibitor of the enzyme xanthine oxidase. It was first used in the treatment of leukaemia to suppress the oxidation of 6-mercaptopurine to the therapeutically inert metabolite 6-thiouric acid. It also inhibits the oxidation of the oxypurines hypoxanthine and xanthine to uric acid, and the observation that it thereby lowered the concentration of uric acid in serum and urine led to its use in gout (Rundles, Wyngaarden, Hitchings, Elion, and Silberman, 1963).

Since our preliminary observations (Hall, Holloway, and Scott, 1964) confirming the effectiveness of the drug in lowering the level of serum uric acid, we have accumulated further experience. This may be considered in two parts—namely, (a) a therapeutic trial comparing the long-term effects of allopurinol with those of conventional uricosuric treatment in patients with uncomplicated gout, and (b) the effect of allopurinol given to patients in whom, for one reason or another, the drug was thought to be specially indicated.

Trial A. Comparative Trial of Allopurinol Against Uricosuric Treatment

For this study outpatients were taken whose gout was, so far as could be determined, primary and uncomplicated except in some cases with minor degrees of renal functional impairment. All were men. Most of them were new clinic referrals and had not been given any consistent form of uricosuric therapy: none had received such treatment within six months before entering the trial. Patients were allocated to treatment with either allopurinol or uricosuric drugs by reference to the last digit of their hospital number; those with an even digit received allopurinol and those with an odd digit uricosuric therapy. By this method of allocation 21 patients started allopurinol treatment and 19 uricosuric treatment. One patient taking allopurinol defaulted from follow-up. One patient taking uricosuric therapy defaulted from follow-up, and one left the district, so that adequate follow-up was impossible. The results therefore apply to 20 patients taking allopurinol (group I) and 17 taking uricosuric therapy (group II). Characteristics of patients studied are shown in Table I, from which it will be seen that subjects in the two treatment groups were reasonably comparable in all respects.

Drugs and Dosage

Allopurinol was given in an initial dose of 300 mg. daily, but this was increased where necessary. At the time of writing 12 of the patients were still taking 300 mg. daily, in six the

dose had been increased to 400 mg. daily, and in two it had been increased to 600 mg. daily.

The drug selected for uricosuric treatment was probenecid (Benemid), starting with a dose of 1 g. daily, rising to 2 g. daily after two weeks' treatment. (This order of dose is usually necessary to achieve an adequate uricosuric response.) Of the 17 patients in this group one has continued to take 1 g. daily and 11 have continued to take 2 g. daily. In five patients the uricosuric treatment was changed to sulphinpyrazone (Anturan) 400 mg. daily, because probenecid tablets were found to cause flatulence or pruritus, were difficult to swallow, or were distasteful.

In regulating the dose of these drugs it was aimed to produce a satisfactory fall in uric acid levels, but no attempt was made to advance the dosage beyond this. By the method of uric-acid estimation used (Technicon AutoAnalyzer) the upper limit of normal for men and post-menopausal women is 6 mg./100 ml. and that for pre-menopausal women 5 mg./100 ml. A fall of uric acid into this range was regarded as satisfactory.

Because severe acute attacks of gout tend to occur for a time after the level of serum uric acid has been lowered (see Discussion), patients were instructed to take colchicine, 0.5 mg. two or three times daily, during treatment with either drug. In those who became free of symptoms colchicine was withdrawn several months after the last attack of gout, but it is anticipated that treatment with either allopurinol or uricosuric drugs will be continued indefinitely in the absence of any toxic effects. No special diet was prescribed for these patients. In accordance with our usual practice they were told which foods contain a high purine content, and they were advised to avoid an excessive intake of these foods and of alcohol.

Methods of Assessment

At every visit patients were questioned about the number of acute attacks of gout and about any other symptoms. They were examined for the presence of tophi, and the blood-pressure was recorded and the urine tested for protein. At every visit blood was tested for serum uric acid, blood urea, haemoglobin, reticulocytes, packed cell volume, white-cell count, and serum alkaline phosphatase. The serum iron was also estimated before treatment and at intervals of about six months thereafter. These investigations were performed in the routine chemical pathology and haematology laboratories at Hammersmith Hospital, standard methods being used.

Duration of Follow-up

The mean duration of follow-up for patients taking allopurinol was 18.6 months, range 10-23 months, and for those taking probenecid 19.6 months, range 11-24 months. After the initial assessment the patients were seen at intervals of two

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weeks, one month, two months, and three months, and thereafter at three-monthly intervals.

Results

1. Frequency of Acute Gout

It is difficult to be precise about the frequency or severity of attacks of gout. All patients were having recurrent attacks before treatment was started (Table I), and the overall effect was to reduce the number of attacks of gout in both treatment groups. As mentioned above, all patients were given colchicine. Of the 20 receiving allopurinol, nine had no further gout since starting treatment, six had one further attack between one and nine months since, four had two further attacks between 2 and 15 months since (one mostly in the early months), and one patient continued to have severe attacks for six months after starting treatment, but has since been free of gout. Of the 17 patients taking uricosuric treatment eight had no further gout since starting treatment, six had one further attack occurring between 2 weeks and 15 months since (one of these had temporarily stopped his tablets because of pain from his duodenal ulcer), two had two attacks between 2 weeks and 17 months since, and one patient had three further attacks occurring between three and five months after starting treatment.

TABLE I.—Allopurinol-Uricosuric Trial. Characteristics of Patients Studied

	Group I Allopurinol	Group II Uricosuric Treatment
No. of patients	20	17
Mean age (range) (years)	54 (27-78)	54 (38-76)
Mean duration of symptoms (range) (years)	7.3 (0.2-31)	8.9 (1-29)
No. of acute attacks in previous year (range)	1-12	1-10
No. of patients with visible tophi	3	2
No. of hypertensive patients (diastolic B.P. over 100)	2	2
No. of patients with proteinuria	4	2
Mean serum uric acid (range) (mg./100 ml.)	9.3 (7.5-10.6)	8.5 (7.5-11.7)
" blood urea (range) (mg./100 ml.)	35 (15-56)	41 (25-61)
" haemoglobin level (range) (g./100 ml.)	14.7 (12.8-16.9)	15.0 (12.8-17.0)
" packed cell volume (range) (%)	43.9 (37-49)	44.7 (38-54)
" total white-cell count (range)	5,600	6,800
" reticulocyte count (range) (%)	(5,000-8,000)	(5,000-10,000)
" serum iron (range) (μ g./100 ml.)	2.0 (1.0-5.2)	1.9 (0.8-4.2)
" alkaline phosphatase (range) (K.A. units)	119 (74-226)	109 (32-158)
	8.8 (5-19)	7.9 (4-13)

In both treatment groups, therefore, about half the patients had no further gout after treatment was started, and in the others attacks became much less frequent. Such attacks as did occur in these early months, however, appeared to be of considerable severity.

2. Tophi

As will be evident from the description of the cases, most of the subjects in this part of the trial did not have advanced tophaceous gout. Among the three patients with very small tophi who were taking allopurinol these have disappeared in two, and the same has occurred in one of the two patients with tophi taking probenecid.

3. Serum Uric Acid

As already pointed out, drug dosage was so regulated as to produce a satisfactory fall in the uric acid level without going beyond this. Table II shows the mean level of serum uric acid in each treatment group (a) before treatment was started, (b) two weeks after treatment was started, and (c) at the last examination of each patient. From this it will be seen that a satisfactory fall in uric acid was achieved in most patients from both treatment groups. Nobody failed to show a fall in the serum level of uric acid. The falls produced with allopurinol were

rather greater than those produced by probenecid treatment, and we have the distinct impression that allopurinol can produce a more rapid and greater fall in uric acid than uricosuric drugs can. From the therapeutic point of view, however, the clinical and biochemical response in both treatment groups was satisfactory.

TABLE II.—Effect of Treatment on Serum Uric Acid

	Group I Allopurinol			Group II Uricosuric Treatment		
	Before Treatment	Two Weeks	Last Figure	Before Treatment	Two Weeks	Last Figure
Mean (mg./100 ml.)	9.3	5.8	4.7	8.5	6.3	5.2
Range	7.5-10.6	4.5-6.9	2.6-5.5	7.5-11.7	3.9-10.8	3.8-7.3

4. Blood-pressure

There was no significant change in blood-pressure in either treatment group.

5. Proteinuria

Four patients in the allopurinol group showed a trace (30 mg.) of albumin by Albustix testing before treatment, and in two of these the proteinuria increased to 300 mg./100 ml. by the same method of testing. In one further patient there was no proteinuria at the time of admission to the trial, but he developed a trace after starting treatment. Of those taking probenecid two had proteinuria at the time of admission to the trial, and there has been no change.

6. Other Results

It will be seen from Table III that no significant change took place in either treatment group with regard to blood urea, haemoglobin, packed cell volume, white-cell count (the initial count was always normal), reticulocyte count, and serum iron. (One patient did show a reticulocytosis while taking allopurinol, but he, interestingly, developed rheumatoid arthritis during this period in addition to his gout. Active rheumatoid arthritis may be accompanied by a mild reticulocytosis (Denman, Huber, Wood, and Scott, 1965). This unusual double diagnosis was of course closely checked in this patient, and there seems to be little doubt that he does have both diseases.)

TABLE III.—Other Results

	Group I Allopurinol		Group II Uricosuric Treatment	
	Before Therapy	Latest Figure	Before Therapy	Latest Figure
Mean blood urea (mg./100 ml.)	35	34	41	41
" haemoglobin (g./100 ml.)	14.7	13.8	15.0	14.1
" packed cell volume (%)	43.9	46.6	44.7	45.6
" white blood cell count (cells/c.mm.)	5,600	5,800	6,800	6,300
Mean reticulocyte count (%)	2.0	1.8	1.9	1.9
" serum iron (μ g./100 ml.)	119	117	109	110

7. Alkaline Phosphatase and Other Tests of Liver Function

Serum alkaline phosphatase was measured at most times of assessment in King-Armstrong units (normal less than 14 units). In group II the mean level before treatment was 7.9 units (range 4-13) and there was almost no change during therapy, the mean level at the last assessment being 8.4 units (range 5-12). Five patients in this group showed a slight increase, five had a slight decrease, and in seven the figure was unchanged. In group I the mean initial figure was 8.8 units (range 5-19) and there was a mean increase of 2.1 units

during the treatment period, the mean level at the last assessment being 10.9 units (range 6–27). Of the 20 patients in this group 15 showed a slight rise in alkaline phosphatase levels, four were unchanged, and only one showed a decrease. Only one patient with a normal initial alkaline phosphatase showed an abnormal figure (16 units) at the last assessment, and the small mean rise appeared to be of little significance; but it was thought desirable to carry out further tests of hepatic function. These additional tests had not been performed before treatment was begun, but the probenecid-treated patients were available for comparison with the patients who had been given allopurinol. Patients were recalled for the additional investigations after the latest assessment: sera from all 20 patients in group I and from 14 of the 17 in group II were examined at the Wellcome Research Laboratories (except for bromsulphalein retention, which was estimated at Hammersmith).

Serum albumin and globulin were normal in all patients; so was the colloidal gold test. Thymol turbidity was normal (less than 4 units) in all patients except one in group II, in whom it was 6 units. Serum bilirubin was normal (less than 1 mg./100 ml.) in most patients, but lay between 1 and 2 mg./100 ml. in three patients in group I and one patient in group II.

Serum glutamic oxaloacetic transaminase was normal (less than 40 units) in all patients except one from each group, in both of whom it was 43 units. Serum glutamic pyruvic transaminase was normal (less than 30 units) in most patients, but was raised in four patients in group I (33, 47, 54, and 68 units) and in one patient in group II (41 units).

Sulphobromophthalein (Bromsulphalein) retention (normal 5% or less at the end of 45 minutes) lay above 5% in 14 of the 20 patients in group I (mean 8.0% retention, range 2–15%) and in 12 of 13 patients in group II (mean 9.7%, range 4–20%).

No reason for this high incidence of abnormal results in both treatment groups was discovered. None of the patients showed any clinical evidence of liver disease. Most of them gave a history of considerable alcohol consumption, though none could be regarded as chronic alcoholics in the usual sense of the term. Abnormalities were not confined consistently to the same patients—that is, there was no tendency for a patient with one abnormal result to show abnormalities in other tests. Inquiry at both the Hammersmith and the Wellcome Research laboratories, where all these investigations are in satisfactory routine use, gave no indication of technical error.

8. Radiology

Patients had joint radiographs taken before and during treatment; but over the comparatively short period during which they have so far been followed the only radiological change has occurred in two men receiving allopurinol, whose radiographs showed healing of bony lesions. One of these radiographs is shown in Fig. 1.

Side-effects

The questions of acute gout and liver function have already been considered. No serious side-effects have been encountered in either treatment group. In group I two patients developed skin rashes which were slight and transient, and which disappeared while treatment was continued. One patient noticed mild spontaneous bruising (though no haematological abnormality was found), and one complained of persistent dyspepsia. One had a mild leucoplakia-like lesion of the gums, which also cleared while treatment was continued. The direct relation of all these minor symptoms to allopurinol itself is questionable, and, in general, tablets of allopurinol seemed readily acceptable.

In group II one patient complained of difficulty in swallowing probenecid tablets, two of flatulence, one of finding the tablets

distasteful, and one of pruritus. Treatment in these five patients was changed to sulphapyrazone, which they took without difficulty. One further patient complained of dyspepsia while taking probenecid but continued treatment, and one stopped treatment temporarily because of epigastric pain, which was shown to be due to a duodenal ulcer. He subsequently resumed probenecid without any trouble.

FIG. 1.—Radiograph of first metatarsophalangeal joint (left) before and (right) one year after treatment with allopurinol, showing healing of gouty lesion.

Trial B. Effect of Allopurinol in Other Patients

Sixteen further patients were treated with allopurinol for gout because there appeared to be special features which precluded their entry into the comparative trial described above. Details of these patients are outlined in Table IV. Cases 1–4 are the four patients previously described in our preliminary trial; of these Cases 1 and 4 had additional reasons for receiving allopurinol, as shown in the Table.

The special indications for the use of allopurinol in these patients can be summarized thus:

	No. of Patients	Case Nos.
Preliminary trial	2	2, 3
Nephrotic syndrome with probenecid	1	1
Other adverse reactions to uricosuric agents	5	4, 5, 8, 11, 14
Gout not adequately controlled by uricosuric treatment	3	7, 13, 16
Renal failure	4	6, 9, 10, 15
Uric acid stone formation with severe chronic gouty arthritis	1	12

The nephrotic syndrome in Case 1 occurred about a year after treatment with probenecid was begun (severe oedema, proteinuria 24 g. in 24 hours, serum albumin 1.6 g./100 ml., serum cholesterol 490 mg./100 ml.) and remitted after the drug

FIG. 2.—Case 6. Serum uric acid and blood urea between 1953 and 1965, showing initial fall in serum uric acid with probenecid but progressive failure of therapy, with increasing renal impairment; satisfactory response to allopurinol.

TABLE IV

Case No.	Sex and Age	Main Clinical Features	Tophi	Blood Urea (mg./100 ml.)	Reason for Allopurinol	Daily Dosage (mg.)	Months of Therapy	Initial Serum Uric Acid (mg./100 ml.)	Lowest Follow-up Serum Uric Acid (mg./100 ml.)	Effect of Allopurinol Therapy	Side-effects	Comment
1	M 62	Onset gout aged 17. Later large tophi. Probenecid started in 1962	+	76	Probenecid only partially effective and caused nephrotic syndrome (also in preliminary trial of drug)	300 increasing to 600	25	12.0	4.9	No further acute attacks gout. Chronic joint pain disappeared and tophi smaller	Allopurinol stopped because of erythematous rash after 2 months. Rash did not reappear when drug restarted	
2	F 72	Onset gout aged 54. Large discharging tophi. No previous uricosuric therapy	+	59	Preliminary trial of drug	300	8	12.2	5.7	No acute gout during 4 months' allopurinol therapy	Mild petechial rash 4 months after starting treatment	Allopurinol stopped and replaced by probenecid. Subsequent course remains satisfactory
3	M 50	Onset gout aged 38	+	24	Preliminary trial of drug	300	24	8.8	4.9	Acute attacks of gout have persisted	2 severe attacks during second week of therapy	Patient often omits tablets and uric acid level fluctuates
4	F 56	Ureteric calculi removed aged 38 (composition unknown). Stag horn calculus removed aged 45. Onset gout aged 51	-	56	Probenecid, sulphapyrazone, and phenylbutazone all caused a severe rash (also in preliminary trial of drug)	300	23	9.3	5.0	2 attacks gout on therapy but less severe	None	
5	M 53	Onset gout aged 43. At age 50, passage of 2 oxalate calculi: hypercalciuria	-	43	Mild erythematous rash due to probenecid	300 increasing to 400	23	10.0	4.8	Satisfactory fall in serum uric acid level	Erythematous rash one month after allopurinol started; did not reappear when drug restarted	Further renal colic with passage of an oxalate stone
6	M 81	Onset gout aged 38. Later renal failure with slow rise in blood urea since 1953	+	118	With rising blood urea serum uric acid no longer controlled by probenecid (Fig. 2)	300	23	10.0	4.8	No further gout; satisfactory biochemical control	None	Further rise in blood urea probably due to underlying renal disease. Symptomatically very well
7	M 42	Onset gout aged 24. Hypertension first noticed at age of 34. Treatment with methyl dopa started at age of 40	+	26	Serum uric acid not well controlled with probenecid and twice-yearly attacks of gout continued	300 increasing to 400	21	10.5	3.8	2 attacks of gout since treatment started: satisfactory reduction in serum uric acid	None	
8	M 57	Onset gout aged 47	+	23	Diarrhoea and malaise after sulphapyrazone and probenecid	300	17	11.5	5.7	Fluctuating serum uric acid level	2 attacks of gout, one very severe in early months of treatment	Often misses tablets
9	M 57	?Nephritis in childhood. Onset gout (familial) aged 27. Progressive renal failure since age of 50	+	210	With rising blood urea serum uric acid no longer controlled by probenecid	300	15	8.7	4.6	Serum uric acid level controlled but a few further attacks of acute gout occurred	3 months after starting treatment transient erythematous rash. This did not recur when drug restarted	Death from uraemia
10	F 57	Pre-eclamptic toxæmia aged 31. Onset hypertension with proteinuria aged 51. Received thiazide diuretics: subsequent progressive renal failure. Onset gout aged 59	+	160	With rising blood urea serum uric acid no longer controlled by probenecid	300	1	11.8	7.8	Moderate fall in serum uric acid level	None	Allopurinol stopped because of uracemic vomiting. Death from peritonitis and renal failure
11	M 56	Patent ductus arteriosus and Eisenmenger syndrome. Secondary polycythaemia and gout	+	46	Previous uricosuric therapy said to have caused a rash	300 increasing to 600	15	12.0	3.6	Cessation of incapacitating gouty attacks	None	
12	M 62	Onset gout aged 28, frequent severe attacks. Uric acid calculus passed aged 35. Hypertension first noted aged 36	+	47	Uric acid stone formation and severe chronic gouty arthritis	300	12	10.8	3.5	Satisfactory fall in serum uric acid level and no gout since starting allopurinol	None	
13	M 52	Onset gout aged 36 with development of massive tophi. In 1965 haematemesis and melaena probably related to multiple drug therapy	+	40	Gout uncontrolled by uricosuric drugs, indomethacin, colchicine, corticosteroids	300 (+ probenecid 2 g. daily)	10	8.2	5.3	Cessation of acute attacks with satisfactory biochemical control	None	Allopurinol combined with probenecid because of massive tophi
14	F 60	Onset of gout aged 57	-	71	Nausea with probenecid and sulphapyrazone	300 increasing to 400	5	9.5	5.4	Good biochemical response but still has acute attacks	Five attacks of gout since starting drug	
15	M 50	Onset of gout aged 46. Malignant hypertension aged 49 responding to guanethidine	-	75	Mild renal failure (uricosuric drugs were not tried)	300	5	10.3	3.6	No further attacks		
16	M 69	Onset of gout aged 35. Past history of renal calculus, composition unknown	+	51	Widespread painful tophi despite probenecid	300 increasing to 400	4	10.5	6.3	Reduction in size of tophi, now painless	Two attacks of acute gout in early weeks of treatment	

was withdrawn, the degree of azotaemia (blood urea 76 mg./100 ml.) remaining more or less unchanged throughout. This must be a very rare complication of probenecid, but it has been convincingly reported (Ferris, Morgan, and Levitin, 1961). Allopurinol was an effective alternative treatment in those patients who had experienced other adverse reactions to uricosuric therapy or whose gout had not been adequately controlled previously. In three of the four patients with progressive renal failure (Cases 6, 9, and 10) uricosuric agents had become ineffective. In all three cases there was a satisfactory fall in the serum level of uric acid, and this was accompanied in Case 6 by a gratifying disappearance of the symptoms of gout (Fig. 2). The other two patients died from their progressive renal disease.

In general the biochemical and clinical response of these patients to allopurinol was very satisfactory. The clinical improvement in Cases 1, 6, 11, 12, 13, 15, and 16 was striking. On the other hand, serum levels of uric acid in Cases 3 and 8 fluctuated, but these two patients are known to take their tablets irregularly.

Discussion

The results from the present study confirm earlier reports of the effectiveness of allopurinol in the treatment of gout (Rundles *et al.*, 1963; Hall *et al.*, 1964; Yü and Gutman, 1964; Klinenberg, Goldfinger, and Seegmiller, 1965; Delbarre, Auscher, Labrousse, and de Gery, 1965; Houpt, 1965; Smyth, 1965; Rundles, Metz, and Silberman, 1966), and indicate that the drug maintains its action over a prolonged period. Case 1 above has been taking allopurinol for more than two years, with sustained clinical improvement. Episodes of acute gout cease or become less frequent, tophi become smaller, and the discomfort of chronic gouty arthritis is alleviated as control of the serum uric acid is maintained by regular medication. The tablets are easily taken.

All investigators have, however, commented on the precipitation of acute gouty attacks early in treatment, though some have claimed that these can be averted by starting with small doses—for example, 100 mg. daily—combined with colchicine prophylaxis. Acute attacks also occur with uricosuric agents, and in Trial A there was little difference between allopurinol and probenecid in this respect. But the acute episodes following allopurinol in some of the patients in Trial B, where there was a more advanced degree of hyperuricaemia and of clinical gout, were sometimes very severe. The development of gout in these circumstances is probably related to the effect of a falling level of serum uric acid rather than to a specific effect of a particular drug. In such a situation a tophus, or microtophus, previously more or less in equilibrium with the surrounding tissue fluid, starts to go into solution. Owing to fluctuations in tissue-fluid concentration of urate small foci of recrystallization will occur in the vicinity. Such deposition will then produce the inflammatory reaction of gout, perhaps by the mechanism of phagocytosis suggested by Seegmiller and Howell (1962). Whether or not this hypothesis is correct, it is clearly important to warn patients, on starting treatment, that they may yet experience a few severe attacks of gout, otherwise such an event could result in a disconcerting lack of rapport. Other clinical side-effects mentioned above seem to be of little importance, and serial estimation of red cells, haemoglobin, reticulocytes, and white cells showed no departure from normal values.

As Yü and Gutman (1964) remark, however, xanthine oxidase is a versatile enzyme acting on a diversity of substrates, and prolonged suppression of its activity could conceivably produce other metabolic effects besides impairment of uric acid formation. It is therefore of interest that a congenital absence of the enzyme can occur in the rare condition xanthinuria, of which three cases have so far been reported. The first of these patients (Dent and Philpot, 1954; Dickinson and Smellie, 1959) remained well apart from the direct effects of xanthine calculi;

and another patient, though possessing congenital skeletal defects and presenting with a pheochromocytoma, felt no ill-effects from the lack of xanthine oxidase itself beyond the failure to convert xanthine and hypoxanthine to uric acid (Engelman, Watts, Klinenberg, Sjoerdsma, and Seegmiller, 1964). The patient of Ayvazian (1964) had haemochromatosis in addition to xanthinuria. This may have been an unrelated coincidence, but there is evidence to suggest that the reduction of ferric to ferrous ferritin, which is the first stage of iron mobilization in the liver, is mediated by xanthine oxidase (Green and Mazur, 1957).

Powell and Emmerson (1966) report that rats consuming a diet of laboratory meal, allopurinol, and iron develop significantly more hepatic storage iron than appropriate control animals with haemosiderosis of the liver but no increase of iron in extrahepatic organs. In six patients treated with allopurinol they found one who showed a rise in serum iron from 154 to 270 $\mu\text{g.}/100\text{ ml.}$ after seven months' treatment, levels in the other five remaining unchanged. Rundles, Metz, and Silberman (1966) estimated serum iron levels in 10 patients after several months' treatment, and found minimal elevation in only one of them. The patients in Trial A of the present study showed a rather wide initial range of serum iron values in both treatment groups (Table I), but there was no alteration in mean values at the latest estimation (Table III), nor did any individual patient show a significant consistent change. The mean serum iron level of the allopurinol-treated patients in Trial B showed a slight and insignificant rise from 98 to 107 $\mu\text{g.}/100\text{ ml.}$

Liver-function Tests

Tests of liver function in this study are difficult to interpret. Because 15 of the 20 patients in group I showed a rise in alkaline phosphatase levels (though a very slight one, the mean rise for the 20 patients being only 2.1 units), it was thought worth while carrying out the further tests of liver function reported above. The high incidence of abnormal results in both treatment groups, particularly with respect to sulphobromophthalein retention, was an unexpected outcome of this extended investigation and is being pursued further. There have been few reports of hepatic abnormalities in patients receiving allopurinol. Forty-six patients studied by Rundles, Metz, and Silberman (1966) showed no evidence of an adverse effect when screened by an extensive series of biochemical investigations, including serum bilirubin, serum transaminases, lactic acid dehydrogenase, alkaline phosphatase, and serum protein electrophoresis, but not, however, sulphobromophthalein retention, a sensitive index of liver function. In two of the patients of Yü and Gutman (1964) with gout secondary to haemopoietic disorders, probably involving the liver, the cephalin flocculation test became strongly positive coincident with the administration of allopurinol; this also occurred in a patient of Rapado Errazti (1965), though apparently coinciding with a viral infection; while two further cases have developed liver impairment with jaundice when taking allopurinol, recovering on withdrawal of the drug (T. Hanley, personal communication, 1966).

In the present study the abnormalities occurred both in patients receiving allopurinol and in those receiving probenecid, indicating either that both drugs cause liver damage (and probenecid, with the single exception of the patient described by Reynolds, Schlant, Gonick, and Dammin (1957), has never been reported to do this) or that the drugs themselves have nothing to do with the abnormal results. The latter would imply that minor degrees of liver dysfunction are common in gouty subjects, though liver-function tests have previously been found to be abnormal in only a minority of patients with gout (Wolfson, Cohn, Levine, Rosenberg, and Hunt, 1949). On the present evidence allopurinol cannot be incriminated as a

hepatotoxic drug, though no doubt further information about this will be forthcoming.

Because allopurinol causes a fall in the levels of uric acid in the plasma and urine and a rise in the urinary oxypurines, xanthine, and hypoxanthine, there is a theoretical risk of xanthine stone formation following prolonged administration. However, although Klinenberg *et al.* (1965) did not find any consistent change in overall purine excretion during allopurinol therapy, the experience of most others (Rundles *et al.*, 1963; Yü and Gutman, 1964; Krakoff and Meyer, 1965) and of ourselves (Hall *et al.*, 1964) indicates that the combined increase of xanthine and hypoxanthine in the urine is usually much smaller than the accompanying decline of urinary uric acid. This may be due either to additional inhibition of an earlier stage of purine metabolism or to re-utilization of xanthine and hypoxanthine. Plasma clearance of oxypurines is more rapid than that of uric acid, and plasma concentration rarely exceeds 1 mg./100 ml. (Goldfinger, Klinenberg, and Seegmiller, 1965). The urinary level of oxypurines during allopurinol therapy is usually well under 200 mg. daily, though higher levels are occasionally found (Yü and Gutman, 1964). Xanthine stone formation has not yet been reported in patients taking the drug.

Choice of Treatment

Allopurinol has not therefore been shown to possess any serious toxic properties, and is taking its place as a therapeutic agent. For most patients a daily dosage of 300 mg. appears to be adequate, and in the present series it was never necessary to give a dose of more than 600 mg. Occasionally, however, doses of 800 or 1,000 mg. may be required (Rundles, Metz, and Silberman, 1966). In early or uncomplicated gout there appears to be little to choose between allopurinol and conventional uricosuric therapy: patients from both groups in Trial A have had a very similar and satisfactory response to treatment. It may be that its potent effect in lowering the level of serum uric acid combined with its ready acceptability as a tablet will eventually make allopurinol the drug of choice in the treatment of hyperuricaemia, but many will still wish to use uricosuric treatment, which is established as effective and safe, in preference to the newcomer. There are, however, several situations where allopurinol already seems to be indicated, either alone or in combination with uricosuric therapy:

1. *Severe Tophaceous Gout.*—Such patients—for example, Cases 1, 12, and 13—probably respond better on the whole to allopurinol than to uricosuric drugs: not only do acute attacks cease but there is less discomfort from chronic gouty arthritis.

2. *Gout which is not Controlled by Uricosuric Treatment.*—This is not a common situation, being nearly always due to irregular tablet-taking. Cases 7 and 13, however, had apparently been taking probenecid regularly, but their acute attacks did not cease altogether until they had been established on allopurinol treatment.

3. *Intolerance to Uricosuric Drugs.*—This also is uncommon, most patients being able to take either probenecid or sulphinpyrazone. However, in such patients—for example, Cases 1, 4, 5, 8, and 11—allopurinol is a useful alternative.

4. *Gout in which there is Known to be Gross Overproduction of Uric Acid, with a Very High Level of Urinary Uric Acid.*—It is true that the heaviest additional load of urinary uric acid induced by uricosuric therapy is not sustained, falling to some extent as the plasma level falls, and that possible renal damage during this early period can be averted by gradual increase in dosage, a high fluid intake, and alkalinization of the urine. Nevertheless, uricosuric treatment in these patients does result in a continued passage of large quantities of uric acid through the kidneys, which is avoided by the use of allopurinol. Patients with gout secondary to haemopoietic disorders fall into this category, of which our own experience with allopurinol is limited to Case 6. Yü and Gutman (1964) successfully treated nine refractory cases of secondary gout with allopurinol.

5. *Uric Acid Stone Formation.*—Most or all of these patients maintain a strongly acid urine throughout the 24 hours (Metcalfe-

Gibson, McCallum, Morrison, and Wrong, 1965), which predisposes to the formation of uric acid stones. Inhibition of uric acid stone formation by allopurinol seems clearly indicated in this situation.

6. *Gout with Advanced Renal Failure.*—In this situation uricosuric agents become useless because their action in blocking tubular reabsorption of uric acid is ineffective when uric acid is no longer being filtered at the glomerulus (Cases 6, 9, and 10). This is a particularly clear-cut indication for allopurinol.

7. *Acute Uric Acid Nephropathy*, in which treatment of leukaemia or reticuloses by cytotoxic drugs leads to nucleoprotein breakdown and the excretion of massive amounts of uric acid. The prevention and treatment of this condition is fully discussed by Krakoff and Meyer (1965), DeConti and Calabresi (1966), and Watts, Watkins, Matthias, and Gibbs (1966), who stress the importance of starting allopurinol treatment before cytotoxic therapy is begun, in order to cover the period of maximum tissue breakdown.

In some of these situations it seems reasonable to combine the use of allopurinol with uricosuric drugs. The action of the latter upon the excretion of allopurinol itself has not yet been reported, though the excretion of its metabolite alloxanthine is said to be increased by probenecid (Rundles, Elion, and Hitchings, 1966). During a period of in-patient study carried out with Case 12 before long-term allopurinol was begun the fall in serum uric acid produced by a combination of allopurinol and sulphinpyrazone was found to be greater than that produced by the same dose of each drug given independently (Fig. 3). The subsequent clinical course of this patient has been satisfactory with allopurinol alone. The enormous tophi and unhappy condition of Case 13, however, seemed to demand recourse to long-term combined therapy, on which he has done very well.

Fig. 1.—Case 12. Effect of sulphinpyrazone and allopurinol, alone and in combination, upon levels of serum and urinary uric acid.

Summary

Further experience is described with the xanthine oxidase inhibitor allopurinol in the treatment of gout. In a comparative trial patients with uncomplicated gout were randomly allocated to treatment either with allopurinol or with uricosuric drugs: 20 patients on allopurinol and 17 on uricosuric drugs have been observed for a mean period of about 19 months. Dosage was adjusted to produce an adequate fall in the serum level of uric acid. Of the 20 patients receiving allopurinol 12 continued to take 300 mg. daily and none required more than 600 mg. Most patients on uricosuric treatment were taking probenecid 2 g. daily.

The clinical and biochemical response in both treatment groups was generally satisfactory, with little to choose between the two forms of treatment, though the fall in serum level of uric acid tends to be faster and greater with allopurinol than with uricosuric drugs. The allopurinol tablet is small and readily acceptable.

Sixteen further patients have been treated with allopurinol, because it was thought to be specially indicated in preference to uricosuric treatment. The main reasons for this were adverse reactions to uricosuric agents, renal failure, and inadequate control of gout by uricosuric drugs. The response to allopurinol was again very satisfactory.

No serious toxic effects were encountered. Severe attacks of acute gout can follow the rapid lowering of serum uric acid either by allopurinol or by uricosuric drugs. This makes it worth while starting with low doses and giving an additional drug—for example, colchicine—to suppress acute attacks during early months of treatment.

An unexpectedly high incidence of abnormalities in the sulphobromophthalein (Bromsulphalein) excretion test, and to a smaller extent in other tests of liver function, was found in patients taking allopurinol and in those on uricosuric treatment. The reason for this is not apparent, but there is no evidence that either type of drug treatment was responsible.

It is as yet uncertain whether allopurinol will replace uricosuric treatment as the standard method of lowering the serum uric acid. Certain situations are discussed where allopurinol seems to be clearly the treatment of choice.

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Exercise Electrocardiogram in Myxoedema

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It is accepted that symptoms of cardiac ischaemia may be precipitated by treatment of myxoedema. It has therefore been the usual practice to treat patients in the older age groups with very slowly increasing doses of thyroid hormone. The exercise electrocardiogram (E.C.G.) has been extensively used as a more sensitive detector of cardiac ischaemia than the resting record (Master, Field, and Donoso, 1957; Lloyd-Thomas, 1961a, 1961b). We have studied the exercise E.C.G. in myxoedema, with the initial object of detecting ischaemia which might be exacerbated on treatment. The clinical and patho-physiological implications of the findings are discussed in the light of present knowledge of myocardial function in myxoedema.

Patients and Methods

The studies were performed on 12 patients with classical primary myxoedema and one with hypothyroidism following thyroid surgery. Hypothyroidism was confirmed by measurement of basal metabolic rate, thyroidal uptake of radioiodine, or plasma protein-bound iodine. Their average age was 42.4 years (range 15–62). Details of these patients are shown in Table I. No patient had a history suggestive of cardiac pain, nor were there any physical features of heart failure. After patients had rested for 30 minutes a resting E.C.G. was recorded (leads I, II, III, IIIR or AVF, CR₁, CR₄, and CR₆ or CR₇).

The E.C.G. was then repeated after exercise in the manner described by Lloyd-Thomas (1961a). Usually 50 to 100 ascents and descents of the staircase were accomplished in five to eight minutes.

The post-exercise E.C.G. recordings were commenced two minutes after exercise ended and continued for 10 to 20 minutes. E.C.G.s were recorded by means of a direct-writing electrocardiograph. The sensitivity was always 1 mV/cm.

TABLE I

Case No.	Age and Sex	Duration of Disease	B.M.R.*	¹³¹ I Uptake†	P.B.I. (μg/100 ml.)	Plasma Cholesterol (mg/100 ml.)	Initial HB (g/100 ml.)	Duration of Treatment before Re-testing
1	40 F	Since childhood	-20	3		216	8.4	17 days
2	49 F	2 years	-30	7		410	12.6	6 months
3	46 F	2 "	-25	13		465	13.3	2½ "
4	62 F	Many months.						"
		? years	-23	9		150	11.3	3 weeks
5	15 F	3 months	-63		1.2		12.9	3 months
6	36 M	3 years	-36	3	2.0		12.1	7 "
7	22 F	Since childhood						"
		hood		2		288	11.1	3 "
8	37 M	3–4 years	-35	13	1.8	260	13.4	7 "
9	47 F	Many months					9.9	1 year
10	57 F	4 years		6		510		
11	37 M	? years	-39			503	10.2	3 years
12	58 F	2 "		6		480	12.5	3 "
13	48 F	? years		11		460	7.8	"

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* Referred to standards of Robertson and Reil (1952).
 † % neck uptake of dose at 24 hours.