Long Term Uricosuric Therapy in Gout

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The effectiveness of long term uricosuric therapy was evaluated in sixty-four patients with primary gout. Serum uric acid was reduced to normal in half the patients; the majority manifested a urate diuresis. In seventeen of fifty patients with tophi, these lesions decreased in size. Acute gouty attacks were reduced to less than one per year in forty-five patients; the chronic symptoms present in fifty-one patients improved in forty. Effectiveness of therapy was categorized as good, moderate, and poor, with examples of illustrative cases.

Esseva evalutate le efficacia de therapia uricosuric a longe vista in 64 patientes con gutta primari. Le nivello seral de acido uric esseva reducite al norma in un medietate del patientes; le majoritate manifestava diurese de urato. In 17 ex 50 patientes con tophos, iste lesiones deveniva plus micre. In 45 patientes, le acute attaccos de gutta diminueva a minus que un per anno. Le symptomas chronic, presente in 51 patientes, se meliorava in 40. Le efficacia del therapia esseva classificate como bon, moderate, e non bon. Casos illustrative es citate.

THE CONTROL of gout with uricosuric drugs became practical and effective with the introduction of probenecid in 1951.[1,2] Since then additional potent uricosuric agents have been developed,[3-9] and the results with their use reported.[10-16] It is now established that gout is a disease of altered purine metabolism resulting in an increased body pool of uric acid.[17-19] Unfortunately, these drugs do not correct the basic metabolic defect, nor do they exert an anti-inflammatory action (and hence are of no value in the management of acute gout). The goal of uricosuric therapy, therefore, is to create a negative urate balance by blocking renal tubular reabsorption of uric acid.

This report deals with the effectiveness of long term uricosuric therapy in 64 cases of primary gout. Specific indications for such treatment included: (1) demonstrable tophi, (2) chronic gouty arthritis, and (3) hyperuricemia in excess of 8.0 mg. per cent. Recurrent, severe, and uncontrollable attacks of gout and the presence of renal urate calculi were considered to be relative indications.

METHODS OF STUDY

The uricosuric agents under investigation are listed in table 1. Since several patients received more than one drug during the course of the study, there were ninety-four separate experiences with individual uricosuric drugs. Most patients received maintenance doses of colchicine throughout the period of study. The diet was not specifically restricted,

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Table 1.—*Uricosuric Agents under Investigation*

Drug	No. of patient experiences*	Usual dose
Probenecid (Benemid)	53	1.5 Gm./day
Sulfinpyrazone (Anturane)	15	300 mg./day
Thiophenylpyrazolidine	7	800 mg./day
Zoxazolamine (Flexin)	11	500 mg./day
Salicylates	4	5–6 Gm./day
Combinations of above	4	

*As several patients received more than one drug during period of follow-up, a total of 94 experiences with the various drugs was obtained in these 64 patients.

although most of the patients received instructions from a dietitian how to avoid foods with high purine content; caloric restriction was prescribed when indicated.

Serum and urinary creatinine was measured by a modification of the method described by Bonsnes and Taussky,[20] the upper limit of serum creatinine in normal individuals being 1.5 mg. per cent. Serum and urinary uric acid was measured by a modification of the colorimetric method of Block and Geib.[21] Blood was obtained in the nonfasting state. In this laboratory the upper limit of serum urate values for normal men is 6.0 mg. per cent; for women it is 5.5 mg. per cent. Urinary uric acid excretion was evaluated in terms of the ratio of urate clearance to creatinine clearance (U.C./Cr.C.) The value of this ratio as an expression of urate excretion is clarified if one considers first the creatinine clearance. By the fortuitous coincidence that the minimal amount of creatinine reabsorbed is approximately balanced by the amount excreted by the renal tubules, reabsorption can be considered nil, and the creatinine clearance equal to the glomerular filtration rate. With respect to uric acid, however, normally about 95 per cent of the filtered urate is reabsorbed in the proximal renal tubules, and only 5 to 10 per cent excreted.[22,23] Thus the ratio of the urate clearance to the creatinine clearance expresses the per cent of the filtered uric acid that is ultimately excreted in the urine. Also, by this ratio, correction is possible for daily variations in urinary output.

Clinical and Laboratory Characteristics

In this group of sixty-four patients, sixty of whom were male, the average age at the onset of gout was 36.7 years (table 2). The initial attack occurred before the age of 20 years in eight cases, between the ages of 20 and 40 years in thirty, and after the age of 40 years in twenty-six patients. The average age at the time uricosuric therapy was initiated was 49.7 years. Duration of total follow-up and duration of uricosuric therapy are shown in table 3. Twenty-two of these patients received uricosuric preparations for at least 3 years, and eleven were treated for 5 years or longer.

The average serum urate concentration before treatment exceeded 8.0 mg. per cent in fifty patients (table 4). In forty-three patients, baseline ratios of urate clearance to creatinine clearance were obtained. In thirty-eight this ratio was under 10 per cent (within the normal range), but in three it was between 10 and 15 per cent, and in two, between 16 and 20 per cent.

In fifty of the patients tophi were known to be present at the onset of uricosuric therapy. Parotid duct calculi were proved in two patients and suspected in a third.[24] Urinary tract calculi were present before treatment in five patients (7.8 per cent).

Five patients had diabetes mellitus, and one had two other metabolic de-

Table 2.—*Age at Onset of Gout*

	No. of patients
Less than 20 years	8
20–29 years	13
30–39 years	17
40–49 years	18
50–59 years	6
60 years or over	2
Total	64

Table 3.—*Duration of Follow-up*

Duration	At University Hospital	On uricosuric drugs
	No. of patients	
6 months or less	3	12
6–18 months	9	11
19–36 months	7	18
37–60 months	10	11
61–90 months	9	7
Over 90 months	26	4

fects: hyperlipemia and glycogen storage disease (Von Gierke's disease). Thirty patients showed blood pressure levels in excess of 150/100. Eight died during the period of follow-up, seven as the result of cardiovascular-renal disease, and the other of pneumonia.

Results of Uricosuric Treatment

Effect on serum and urine urate values. The response to uricosuric agents was measured by the per cent decrease or fall in the average serum uric acid from the pretreatment value. It will be noted (table 4) that during the course of therapy in thirty-one patients the average serum uric acid value was reduced to the normal range (6.0 mg. per cent or less). Furthermore, while fifty patients had average serum urate values over 8.0 mg. per cent prior to starting therapy, forty-nine showed a level below this value during uricosuric treatment.

The serum urate response to individual drug preparations is shown in table 5 and figure 1. A 30 to 45 per cent decline in serum uric acid occurred in twenty-three patients treated with probenecid, and in six of fifteen patients receiving sulfinpyrazone. Salicylates (5.0–6.0 Gm. per day) were found to be effective; however, because of eventual salicylism none of the patients was able to continue effective doses for prolonged periods of time.

The effect of uricosuric drugs on urate excretion as measured by the urate clearance:creatinine clearance ratio is seen in table 6 and figure 2. When one compares the baseline values with those on the various drugs, one sees that with each drug employed, the majority of patients experienced an increase in the U.C./Cr.C. ratio, manifesting a urate diuresis. An example of the changes in serum uric acid, urinary urate excretion, urate clearance and urate clearance:creatinine clearance ratio in an individual patient coincident with drug therapy is depicted in figure 3.

Table 4.—*Serum Urate Response to Uricosuric Therapy*

Average serum urate	Before therapy	On therapy
	No. of patients	
10.1 mg.% or greater	18	4
8.1–10.0 mg.%	32	9
7.1–8.0 mg.%	11	4
6.1–7.0 mg.%	2	14
6.0 or less	1	31
Total	64	62

Table 5.—*Serum Urate Fall with Various Drugs*

Drug	15% or less*	16–29%	30–45%	46% or more	Total no. patients
Probenecid	11	18	23	1	53
Sulfinpyrazone	3	4	6	2	15
Thiophenylpyrazolidine	1	2	4	0	7
Zoxazolamine	3	5	3	0	11
Salicylates	0	2	2	0	4
Combination of drugs	0	0	2	2	4
Total—All drugs	18	31	40	5	94

*Per cent lowering of serum uric acid from pretreatment values.

Effect on tophi. There was evident diminution in size of tophi in seventeen of fifty patients (table 7). The mean serum urate value was 5.77 ± 1.12 mg. per cent during treatment in the group in whom tophi decreased in size, as compared with a value of 7.07 ± 1.82 mg. per cent in the group in whom this change did not occur; this difference, despite the rather large standard deviations, is thought to reflect a somewhat better response to therapy in the group with decreased tophi. Moreover, those whose tophi decreased in size were treated longer. If one considers cooperation in collection of 24 hour urine specimens as an index to the patient's conscientiousness in adhering to the therapeutic program, there again appeared to be a slight difference in favor of the group whose tophi decreased in size. However, when the individual patient is considered, several persons noted for their conscientious adherence to details and who were followed for years did not demonstrate decrease in tophi in spite of an adequate lowering of serum uric acid levels. These results are in keeping with the concept that some tophi are sequestrated and not readily accessible to the body fluids.

Effect on acute gout. In fifteen patients acute gout appeared to have been precipitated by initiation of uricosuric therapy in spite of concomitant maintenance doses of colchicine. With perseverance, the acute attacks could usually be controlled and treatment continued. In two patients, however, this complication eventually prevented effective uricosuric therapy.

Before treatment, twenty-four patients averaged six or more attacks of acute gout per year (table 8). After institution of therapy with daily maintenance doses of colchicine and uricosuric drugs, thirty-five patients experienced less than one attack per year (although in one patient the acute attacks were not controlled).

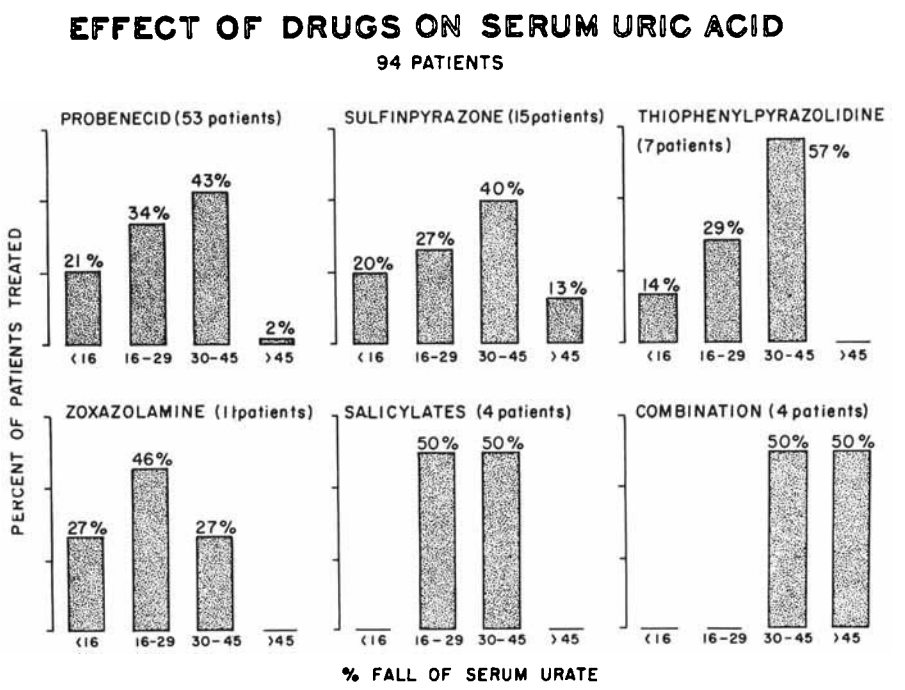

Fig. 1.—Bar height represents percentage of patients experiencing indicated fall in serum urate represented by that bar during uricosuric therapy.

In twenty patients it was possible to evaluate the effects of colchicine alone on the frequency of acute gout. In fifteen of these there was a definite decrease in frequency of acute attacks, and in eleven there was a reduction to less than one attack per year. However, in five there was no marked improvement. In three patients there had been a decrease in frequency of attacks on colchicine alone, but with adequate uricosuric therapy there was an additional decrease to one attack or less per year. Other patients, in whom acute gout was well controlled on a regimen of both maintenance colchicine and uricosuric drugs, on stopping colchicine experienced a recurrence of acute gout. One patient, a physician, was able to stop colchicine without difficulty after several years on successful combined therapy. It is quite clear, however, that uricosuric drugs are of no value in the treatment of the acute attack of gout. Possibly a prophylactic effect may be associated with the establishment of increased urate excretion and return of the serum urate toward normal.

Effect on gouty arthritis. Symptoms of chronic gouty arthritis, e.g., stiffness, joint soreness and aching, were present in fifty-one individuals. Upon institution of therapy these symptoms improved in forty patients but were essentially unchanged in eleven. It is believed that these symptoms have their origin in tophaceous articular deposits, frequently with associated secondary osteoarthritic changes. Subacute gout may also contribute to the symptoms and is often improved on initiation of maintenance colchicine therapy. The tophaceous component improves only slowly, being dependent on mobilization of deposited urates.

Table 6.—*Effect of Uricosuric Drugs on Urate Excretion*

Drug	No. of patients with urate clearance/creatinine clearance ratios of				
	5% or less	6–10%	11–15%	16–20%	21% or more
Probenecid	0	13	19	10	1
Sulfinpyrazone	1	2	8	4	1
Thiophenylpyrazolidine	1	3	1	2	0
Zoxazolamine	1	2	2	2	2
Combination	0	0	1	1	2
Baseline	11	27	3	2	0

*Arrayed into groups of 5 per cent.

Effect on the kidney. Seven patients experienced symptoms related to urinary tract calculi during uricosuric therapy, whereas five had had this complication before treatment. One patient experienced calculi before and after initiation of uricosuric drugs. Thus, in this series the incidence of renal calculi was essentially the same before and during uricosuric therapy.

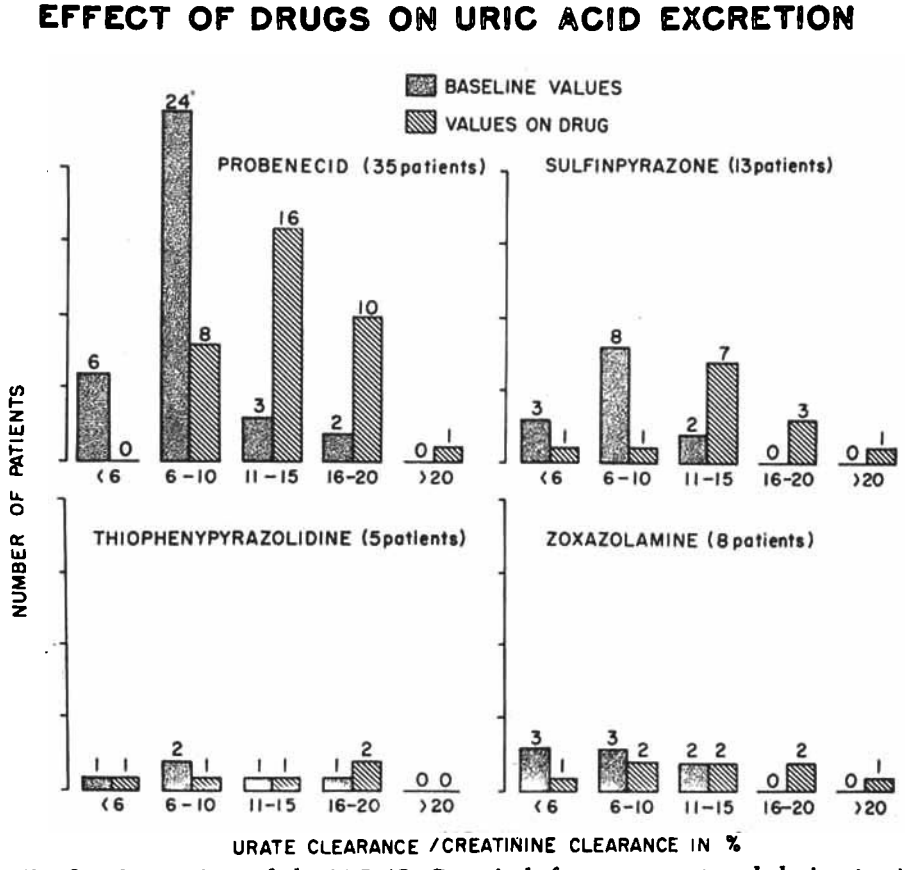

Fig. 2.—Comparison of the U.C./Cr.C. ratio before treatment and during treatment with various uricosuric drugs. The height of bars represents number of patients having U.C./Cr.C. ratios represented by that bar.

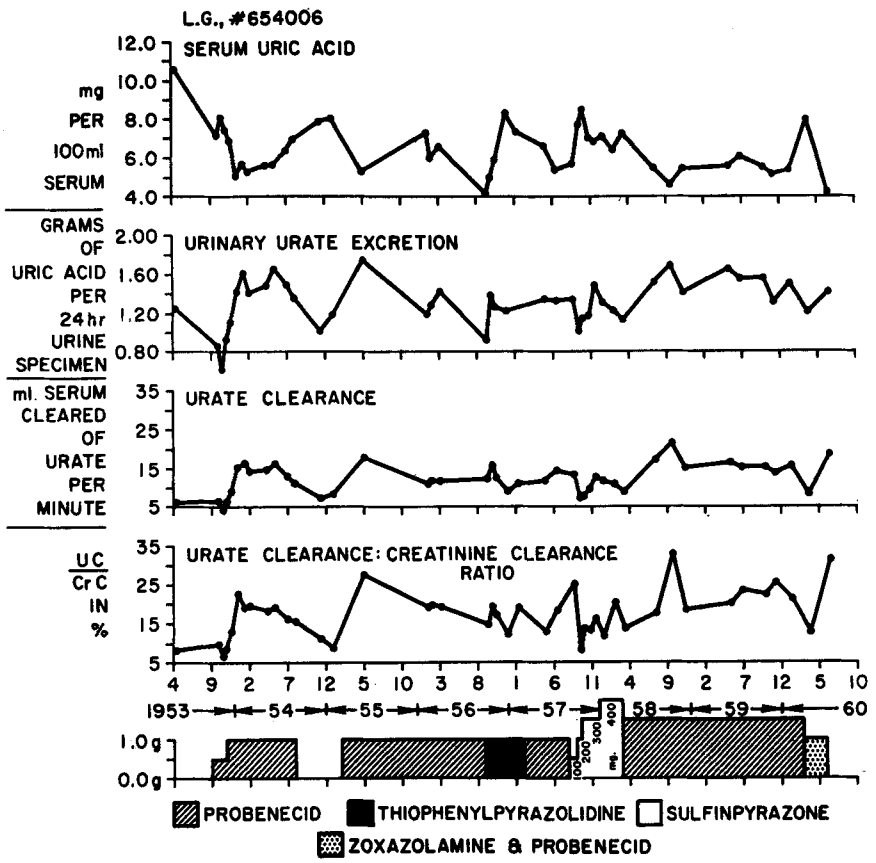

Fig. 3.—Response of serum and urinary urate, urate clearance, and U.C./Cr.C. ratio to uricosuric therapy in a selected case (L. G., No. 654006).

In forty-four patients for whom pretreatment data were available, the renal status, in terms of serum creatinine and 24 hour endogenous creatinine clearance values, remained unchanged in thirty-five, grew worse in eight, and possibly improved in one during the course of therapy. The patient with questionable improvement was a 26 year old white man (J. P., No. 858074) who had had severe tophaceous gout for 6 years; hematuria had been intermittent for several years. On initiation of uricosuric treatment, coincident with a severe attack of gout, the serum uric acid was 28.3 mg. per cent, the NPN was 97 mg. per cent, and the creatinine clearance was 28 L. in 24 hours. There was one-plus albuminuria, and many red and white blood cells were present in the urinary sediment. The blood pressure was normal. There was no anemia. Pyelograms and renograms indicated multiple calculi, hydronephrosis, and markedly impaired function. With intensive treatment which included hospitalization for 33 days, antibiotics, hydration, and protein restriction, in addition to uricosuric drugs, over a period of 2 months there was a decrease in the serum uric acid to about 11 mg. per cent, a gradual fall of the NPN to 32 mg. per cent, and a rise in the creatinine clearance to 113 L./24 hours; the urine,

Table 7.—*Comparison of Response to Therapy in Fifty Patients with Tophi*

	Tophi smaller	Tophi unchanged
No. of patients	17	33
Average serum urate before treatment	9.05 mg.% (range—7.06 to 11.35 mg.%)	9.76 mg.% (range—6.47 to 22.32 mg.%)
Average serum urate on treatment	5.77 mg.% (range—3.62 to 7.93 mg.%) s = 1.12	7.07 mg.% (range—4.6 to 11.2 mg.%) s = 1.82
Average baseline urate excretion—measured by U.C./Cr.C.	5.8% (range—3.1 to 8.7%)	6.77% (range—2.5 to 12.0%)
Average urate excretion on therapy U.C./Cr.C.	13.3% (range 3.17 to 31.7%)	13.73% (range 6.4 to 29.3%)
Cooperation on 24 hour urine collections	88% (15 to 17 patients)	70% (23 of 33 patients)
% patients followed over 1½ years	59%	27%

Table 8.—*Effect of Uricosuric Drugs and Colchicine on Attacks of Acute Gout*

Attacks per year	Before therapy	After therapy
	No. of patients	
1 or less per year	3	35
2–5	23	14
6–10	16	1
11 or more	8	0
Total	50	50

aside from a trace of albumin, became normal. This favorable course was coincident with subsidence of the acute gouty attacks. However, it should be emphasized that while improvement was concomitant with uricosuric treatment, it could not be directly attributed to it. "Reversal" of renal insufficiency in association with prolonged uricosuric therapy in a patient with tophaceous gout has been previously reported.[25]

Untoward effects. With these uricosuric agents, nine patients developed gastrointestinal symptoms (pyrosis, nausea, and vomiting) usually alleviated by taking the medication postprandially. Dermatitis medicamentosa was related to probenecid in one patient and zoxazolamine in another. Although hepatic damage from these drugs has been reported,[26,27] this complication was not encountered in our study.

Discussion

The results of long term uricosuric therapy in gout may be classed as good, moderate, and poor. In our series good results were achieved in twenty-three individuals, about one-third of the total group; results were moderately successful in twenty-eight or somewhat more than one-third; results were poor in thirteen or about one-fifth.

Good results with uricosuric agents. Inclusion of a patient in this category implies successful control of acute attacks of gout, i.e., "clinical control," and achievement of normal or near normal serum uric acid levels, i.e., "chemical control." It is clear that the prerequisites for good results with uricosuric

agents include: (1) the careful indoctrination and strong motivation of a cooperative patient; (2) strict attention to all facets of treatment, with frequent adjustments of the program; and (3) the availability of reliable serum uric acid values. Details of two cases representative of this group follow:

The first patient (L. G., No. 654006), a white man, developed gout at the age of 22 years; before this, one kidney had been removed subsequent to a football injury. At the age of 40, when uricosuric therapy was initiated, he was subject to frequent, polycyclic attacks of gout, precipitated by fatigue, emotional tension, physical exertion, and change of seasons. Tophi were numerous and were rapidly enlarging. The serum uric acid varied from 10.6 to 9.3 mg. per cent; renal function was normal. Over the ensuing 7 years, with constant administration of various uricosuric agents plus maintenance colchicine, the attacks of acute gout ceased, tophi decreased in size, and the serum urate value declined to 4.5 mg. per cent. In figure 3 the response of the serum uric acid, urinary urate excretion, urate clearance, and urate clearance:creatinine clearance ratio is graphically depicted. Concomitant with this improvement, the patient has been able to return to normal physical activity enabling him to meet the demands of a busy and creative academic life.

The second patient (L. H., No. 645218), a white man, developed gout at the age of 19. When first seen, at the age of 30, he was crippled by severe heel-cord and hamstring contractures and by prominent gouty and osteoarthritic changes in the feet. For months, crutches had been required. He was experiencing multiple attacks of gout. Draining tophi were present. The average serum uric acid value was 10.9 mg. per cent. Treatment with probenecid was initiated, and although this was associated with the precipitation of acute gout, concomitant use of maintenance colchicine, supplemented occasionally with phenylbutazone, eventually overcame the problem. Early in the course of therapy two episodes of ureteral colic occurred. After many months of treatment, and with the aid of selected physical therapeutic measures, he was able to walk without crutches. The tophi ceased to drain and decreased in size. The acute attacks of gout diminished in frequency. One and one-half years after initiation of this program of rehabilitation, the patient was able to assume a responsible job and became self-supporting. Now, 9 years later, the serum uric acid concentration is 4.2 mg. per cent. The patient has recently developed diabetes mellitus. Interestingly enough, two brothers are subject to recurrent acute attacks of gout. His son, now 16 years of age, has also recently sustained an initial attack of gout and has hyperuricemia.

Moderately successful results with uricosuric agents. The twenty-eight patients in this category may be divided into two groups. In the first were patients with severe gout complicated by renal impairment. Six of the twenty-eight cases fell into this group. Despite their full cooperation in the diligent application of various drug regimens, only partial control of the disease was possible. While the frequency of attacks of acute gout were decreased, they were not eliminated; tophi did not decrease in size, although they were kept from enlarging. Serum urate levels were usually lowered but were not impressively reversed toward normal. The following case represents this group:

The patient (L. V., No. 800173), a white woman, probably developed podagra before the age of 20. In 1951, at the age of 51 years, when reliable records were first available, hyperuricemia was present. By 1954, when she was first seen by us, many large and rapidly expanding tophi were present. The serum uric acid was 11.2 mg. per cent. There was slight azotemia, the NPN being 53 mg. per cent, the serum creatinine 1.76 mg. per cent, and the creatinine clearance 43.1 ml. per minute. After surgical removal of a large tophus, the patient was placed on a regimen including probenecid, dietary restriction,

and colchicine. Initially, acute gout was controlled by the simultaneous administration of colchicine, phenylbutazone, and low doses of adrenocortical steroids; and eventually stabilization of the clinical course was achieved. With probenecid, however, the serum urate level was reduced by only about 5 per cent; with thiophenylpyrozolidine the average reduction was 20 per cent; with sulfinpyrazone, 17 per cent; and zoxazolamine, 21 per cent. In the last 2 years of her life, a combination of agents was used, but the results were not notably superior to those with the individual preparations. Over a period of 7 years, although the tophi may have ceased to enlarge, they did not decrease in size. The acute attacks of gout, however, decreased in frequency. On the other hand, hypertension remained unchanged and the patient developed progressive renal failure and azotemia [with a rise in blood urea nitrogen (BUN) to 130 mg. per cent] which led eventually to her death.

In the second group in this category are included patients whose medical records are replete with missed appointments, omission of medication, and drug dosage obviously altered to the patient's whims. In most of these patients the disease was mild. Nothwithstanding incomplete laboratory and clinical control, these patients were satisfied with the fact that the acute attacks had been rendered less frequent and tophus formation slowed or even halted. One such case follows:

The patient (E. K., No. 663041), a white male contractor, had experienced podagra at the age of 36. When he was 48 years old, uricosuric therapy was initiated because of obvious tophi and the occurrence of five or more acute, disabling attacks of gout per year. The serum urate level at that time averaged 8.18 mg. per cent. On a program of probenecid and colchicine, the serum uric acid promptly fell to a mean of 7.3 mg. per cent, with some values as low as 5.6 mg. per cent. This was associated with subsidence of the acute gouty attacks and possibly some decrease in tophus size. However, as return visits became more infrequent, and medication dosage became irregular, the serum uric acid rose to values in the neighborhood of 8 mg. per cent. At the time of his last visit, tophi were again obviously larger although the symptoms of acute and chronic gouty arthritis had not reappeared.

Unsuccessful results. Those in whom control was unsuccessful were for the most part uncooperative individuals, some of whom were alcoholic. Characteristically the patients had acute gout when first seen. Although the initial treatment, usually in the hospital, was successful, soon after discharge on a program of uricosuric therapy the patients were lost to follow-up, only to return some years later with huge tophi, often severely crippled by their disease. In addition, however, in a few patients we found it impossible to achieve a satisfactory uricosuric effect because of the precipitation of acute gout concomitant with initiation of uricosuric therapy, or because of idiosyncrasy to the drug employed. Fortunately there are now available several potent uricosuric agents which can be used should idiosyncrasy to one occur. The two cases that follow represent these two reasons for lack of success:

The first patient (B. K., No. 880156), a white man, was first seen at the age of 38 years. He had had gout since the age of 16 and was a confirmed alcoholic. Severe polycyclic attacks of gout of many week's duration led to the initial hospitalization in 1957. The serum uric acid was 13.0 mg. per cent, and there were many tophi. Laennec's cirrhosis and hemolytic anemia were present. With colchicine, phenylbutazone, and steroids the acute gout

Table 9.—*Summary of Results of Treatment in Sixty-four Cases of Primary Gout*

	% patients
Improvement in chronic gout	98
Decrease in acute gout to 1 attack per year	70
Decrease in serum urate to normal	50
Decrease in size of tophi	34
Precipitation of acute gout by drugs	23
Died during follow-up period	12½
Renal calculi on treatment	11
Renal function	
Unchanged	80
Deteriorated	18
Possibly improved	2

cleared. Probenecid was then started. Over the 4 months' period of hospitalization the serum urate fell to 8.3 mg. per cent (40 per cent decrease). The patient was discharged, much improved and able to return to work. Soon thereafter he was lost from the clinic. When heard from 3 years later, he had discontinued his medications and was again a chronic invalid with many tophi, repeated acute attacks of gout, and disabling chronic gouty arthritis.

The second patient (R. U., No. 764315), a 33 year old white man, had had gout for 8 years. When first seen in 1953 he had no tophi; the serum uric acid was 11.4 mg. per cent. With colchicine and oral steroids it was possible to control the acute attacks. During the 18 months that he was carefully followed in our clinic, probenecid therapy was attempted on three separate occasions only to have acute gout develop within 3 days, leading to withdrawal of the drug. During this period repeated attacks of acute gout, uncontrolled by maintenance doses of colchicine, were accompanied by the appearance of tophi. As a further complication of therapy, there was dermatitis medicamentosa associated with phenylbutazone.

Summary

The effectiveness of long term uricosuric therapy was investigated in sixty-four patients (table 9). The drugs used included probenecid, sulfinpyrazone, thiophenylpyrazolidine, zoxazolamine, salicylates, and various combinations of these agents.

The average age of the patients at the onset of gout was 36.7 years; the average age at the time of institution of uricosuric therapy was 49.7 years. The duration of treatment in twenty-two patients was over 36 months. Fifty had demonstrable tophi.

In half the cases the serum urate level was reduced to normal (below 6.0 mg. per cent). In thirty-five of fifty patients the number of acute attacks decreased to one or less per year; and in forty of fifty-one patients, chronic gouty symptoms improved. In 17, the tophi decreased in size.

To obtain complete control of the disease, close cooperation must exist between the patient and the physician and reliable laboratory facilities must be available. Strict attention to details and individualization of patient care are required to achieve both clinical and laboratory control of this metabolic disease. Unfortunately, in forty-one of the patients in this series, the effect of prolonged uricosuric therapy proved to be only moderately successful or

poor, either because of the nature of the disease and its complications or certain factors inherent in the personality of the patient.

Conclusions

We are of the opinion that with the currently available therapeutic agents complete control of gout should be possible, provided the patient is completely cooperative and renal function is adequate. This implies control of the acute attacks, chronic symptoms, and tophus formation. To achieve these goals, however, requires a dedicated, well informed, and enthusiastic physician who will insist upon both "clinical control" (abolition of acute attacks) and "chemical control" (lowering of serum uric acid values to normal).

ADDENDUM

Since the completion of this study the drug zoxazolamine has been withdrawn from the market because of several reports of liver damage associated with use of this drug. In our series, there was no evidence of hepatic damage in the eleven patients who received the drug.

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