

Chapter VIII

The Present Status of Colchicine and Uricosuric Agents in Management of Primary Gout

By WILLIAM D. ROBINSON, M. D.

University of Michigan Medical School

It is conventional to divide the management of gout into the treatment of the acute attacks, the interim treatment, and treatment of the tophaceous stage.¹ It is probably fair to say that, at least until 1950, virtually everything we did in the management of patients with gout was empiric. The use of colchicine developed on a purely empiric basis and has a respectable and fascinating history; the only significant clues to possible mode of action of colchicine have developed within the last few years and have been thoroughly discussed. When colchicine is given by mouth, there is quite general agreement on the dosage with 0.5 mg. or 0.6 mg. tablets, usually given one every hour, until pain is clearly relieved, or until evidence of toxicity develops, or until a total dose somewhere in the range of 7½ to 10 mg. of the drug has been given. By intravenous administration, the total amount of colchicine is usually limited to about 3 mg., given in divided doses. I was quite interested in Dr. Seegmiller's use of an intravenous dose as high as 5 mg. in 24 hours in some of the studies which he reported. He tells me that there were no serious side effects from a dose of this magnitude.

The pattern and specificity of response to colchicine has come up for discussion. As Drs. Zuckner and Wallace have pointed out, the interpretation of the therapeutic trial with colchicine depends a great deal on what is expected of it. Most of us would agree that in the classic severe podagra, when there is a fiery red, swollen joint, with overlying skin at maximum tension, there is relatively little difficulty in evaluating the response to colchicine. With the administration of colchicine there is a subjective decrease in the excruciating pain several hours before there is any convincing objective change. The first objective change occurs between six and twelve hours after the last dose of colchicine. This is a diminution in swelling, seen as the skin becomes a little bit wrinkled and loses the taut, shiny appearance. Within 24 hours there usually is some reduction in redness and swelling but a considerable redness may remain. Complete subsidence may not be seen for 48 to 72 hours.

The real difficulty in evaluating this therapeutic trial is in more chronic situations, where redness and marked swelling are not as apparent. Under these circumstances, colchicine does not produce as dramatic results and the ability to distinguish the response to colchicine in this situation from the effect which may occur in other types of joint disease may present real difficulty.

The well established attack and the polycyclic attack frequently respond incompletely to colchicine. Figures on the percentage of acute attacks which

will be controlled by colchicine used in the conventional manner will depend a great deal on the stage and relative intensity of the joint inflammation; the more acute the degree of inflammation, the more impressive is the response to colchicine.

The next point with respect to colchicine is its use in preventing relapses after acute attacks and its usefulness in reducing the frequency of acute attacks in interim management. It has become quite well accepted that maintenance colchicine in doses of 2 to 3 tablets a day should be used for a few weeks after the treatment of acute attacks of gout. It is usually recommended for at least a three week period and it is indispensable if the secondary attacks or withdrawal attacks after the use of corticosteroids or ACTH are to be prevented.

The interim management of gout has two objectives. One is the use of measures that reduce the frequency of recurrent attacks and the second objective is to induce negative urate balance.

I know that there still is some difference of opinion with respect to the value of colchicine in preventing or reducing the incidence of attacks of gout. Most patients will tolerate three colchicine tablets a day without diarrhea; there are a few that can take up to four, there are a few that cannot tolerate more than one. The customary dose is one tablet twice a day as interim management.

The evidence for the effectiveness of colchicine in reducing the frequency of recurrent attacks stems from two types of observations. In many studies using the patient as his own control, the frequency of attacks prior to the institution of maintenance therapy is estimated, and a subsequent reduction in the frequency of attacks is reported. This of course is subject to very real criticisms and I know of no way in which such a study has been done in a double blind fashion. A second and somewhat more impressive line of evidence is the ability of colchicine to reduce the frequency of acute attacks in patients who are subjected to specific precipitating factors which frequently will produce acute gout attacks. Examples are the ability of colchicine to reduce, almost to the point of elimination, postoperative attacks of gout, and its ability to reduce the frequency of acute attacks in patients fasting or on a high fat diet. I personally was very much impressed with the ability of colchicine to prevent the acute attacks of gout associated with withdrawal of ACTH administration.

Until 1951 most efforts to induce negative urate balance concentrated on attempts to decrease dietary intake of purines and the use of salicylates, usually in an intermittent fashion because they were not tolerated by continuous administration as uricosuric agents. With the advent of more effective uricosuric agents it has been possible to reduce the serum uric acid much more effectively than had been possible before.

For the purposes of this conference, there would seem to be little merit in discussing in detail the similarities and differences of each uricosuric agent. It would seem more profitable to review the experience with a group of patients who have been followed for a considerable period of time on combined management with colchicine and uricosuric agents, with the ob-

Table 32.—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 33.—Duration of Follow-up

Duration	At University Hospital	On Uricosuric Drugs
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

jectives of seeing to what extent our concepts can be modified or influenced by developments during the past year or two and in the light of the discussions at this conference. The point of departure is previously-reported observations on a group of 64 patients with primary gout, observed over a period of years in the Rackham Arthritis Research Unit at The University of Michigan Medical Center.² Our experience has been quite similar to that reported by others.

In this group of 64 patients there were 60 males and 4 females. The average age at the onset of clinical gout was 36.7 years.

The initial attack occurred before the age of 20 years in 8 cases, between the ages of 20 and 40 years in 30, and after the age of 40 in 26 patients (Table 32). 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 33.

Eleven patients received uricosuric drugs for 5 years or more, 22 were followed for at least 3 years after uricosuric drugs were instituted, and 40 patients were observed for at least 18 months on these drugs. In view of the discussions at this conference, it is of interest to note that five of these patients had diabetes mellitus and that an additional patient was one of the seven patients with the type of glycogen storage disease previously discussed. Thirty of this group could be classified as hypertensive, with blood pressure levels in excess of 150/100. In 43 of the 64 patients, the ratio of urate clearance to creatinine clearance was determined prior to the administration of uricosuric drugs. At least five of these 38 patients could be classified as hyperexcretors, with the urate clearance ratio exceeding 10 per cent. Eight of these patients died during the period of observation, seven of them from cardiovascular renal disease, one from pneumonia.

At the time of initiation of uricosuric therapy, 50 of these 64 patients had

Table 34.—Uricosuric Agents under Investigation

Drug	No. of Patient Experiences	Usual Dose
Probenecid (Benemid)	53	1.5 Gm./day
Sulfipyrazone (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	

definite tophi; the other patients either had chronic gouty arthritis, a serum uric acid above 8 mg. per cent, or both.

The uricosuric agents used in this study are listed in Table 34. As several patients received more than one drug during a period of follow-up, a total of 94 experiences with the various drugs was obtained in the 64 patients. In general, the drug dosage was adjusted for each individual patient with the overall objective of reaching a serum uric acid of 6 mg. per cent or lower. It is evident that the most extensive experience was with probenecid.

As an overall appraisal, the results of colchicine and uricosuric therapy may be classified as good, moderate, and poor. In this series, the results are classified as good in 23 individuals, about one third of the total group. These patients experienced a marked reduction and frequency of acute attacks, maintenance of the serum uric acid at 6 mg. per cent or lower, and a decrease in size of tophi if they were originally present. In 13 of these patients, approximately 20 per cent, the results were classified as poor. In general these were uncooperative patients. Although they came under control fairly well while in the hospital, they failed to return for follow-up visits and were seen a year to several years later with severe gout and increase in size of tophi.

Of particular interest is a group of 28 of these 64 patients in whom the results could be classified as moderately satisfactory although good control was never established. While the frequency of attacks of acute gout was decreased, such attacks were not eliminated; tophi did not decrease in size, although they did not progress; serum uric levels were usually lowered but were not impressively reversed toward normal. In 22 of the 28 patients in this group the difficulty could be related to lack of cooperation on the part of the patient; the patients were frequently satisfied, but the physician was not satisfied with the degree of control of hyperuricemia which had been attained. More important, however, are the six patients in this group with significant renal disease. In these patients, the ability to reduce the serum uric acid in the face of serious impairment of renal function presented a problem, in spite of the diligent application of various drug regimens in fully cooperative patients.

The serum urate levels before and during uricosuric therapy are presented in Table 35. The average serum uric concentration before treatment exceeded 8 mg. per cent in 50 patients. During the course of therapy the average serum

Table 35.—Serum Urate Response to Uricosuric Therapy

Average Serum Urate	No. of Patients	
	Before therapy	On therapy
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 35a.—Effect of Uricosuric Drugs and Colchicine on Attacks of Acute Gout

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

uric acid was reduced to 6 mg. per cent or less in 31 patients, and below 8 mg. per cent in 49 patients.

The effect of the combination of colchicine and uricosuric drugs on the frequency of acute attacks of gout in 50 patients is presented in Table 35a. The data indicate a very distinct decrease in frequency of acute attacks, 35 patients having an average of one or less attacks per year.

In 20 patients it was possible to evaluate the effects of colchicine alone on the frequency of acute gout, prior to the administration of uricosuric agents. In 15 of these 20 there was a definite decrease in frequency of acute attacks, and in 11 there was 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 recurrence of acute gouty arthritis was well controlled on a regimen of both maintenance colchicine and uricosuric drugs, on stopping colchicine experienced a recurrence of attacks. One patient, a physician, was able to stop colchicine without difficulty after several years on successful combined therapy.

Of interest is a comparison (Table 36) of a group of patients in whom tophi decreased in size as compared to those patients in whom tophi did not appear to change.

The average serum uric acid before treatment in the 17 patients in whom the tophi decreased in size before treatment did not appear to differ significantly from the average serum uric acid before treatment in the 33 patients in whom the tophi appeared unchanged. However the average serum uric acid during treatment was distinctly lower in those in whom the tophi became smaller. During this conference we have had several lines of evidence suggesting that hyperuricemia becomes clinically significant at a level

Table 36.—Comparison of Response to 50 Patients with Tophi

	Tophi smaller	Tophi unchanged
No. of patients	17	33
Average serum urate	9.05 mg. % (range—7.1 to 11.4 mg.%)	9.76 mg. % (range—6.5 to 22.3 mg.%)
Average serum urate on treatment	5.77 mg. % (range—3.6 to 7.9 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%)	6.8% (range—2.5 to 12.0%)
Average baseline urate on therapy U.C./Cr.C.	13.3% (range—3.2 to 31.7%)	13.7% (range—6.4 to 29.3%)
Cooperation on 24-hour urine collections	88% (15 of 17 patients)	70% (23 of 33 patients)
% patients followed over 1½ years	59%	27%

of about 7 mg. per cent; and it may be significant that the average serum uric acid was not reduced below this level in the group of patients in whom the tophi were unchanged. There appears to be no significant difference between the two groups with respect to the average uric acid excretion either before or during therapy. The cooperation of the patient, at least as reflected in their collection of 24-hour urine specimens, appears to be somewhat better in the group in whom the tophi became smaller. Perhaps of greatest significance is the fact that the period of observation on the average was considerably longer in patients in whom the tophi became smaller. This suggests that the conclusions as related to time should be reserved for more prolonged observations.

In Table 37 is presented a summary of the results of combined treatment. In 70 per cent of the patients the acute gouty attacks were reduced to one attack per year or less. In one-half of the patients the serum uric was reduced to below 6 mg. per cent. In one-third of the patients with tophi there was a decrease in size of tophi. In 23 per cent of this group there appeared to be precipitation of acute gouty arthritis by the initiation of uricosuric treatment. I appreciate that our experience with respect to this phenomenon has given a somewhat greater incidence than that observed by others. This may be due to the fact that this series does include a group of patients who were started early in the use of uricosuric agents, in whom maintenance colchicine was not in effect at the time the uricosuric agents were started. However, the occurrence of acute gouty arthritis a few days to a couple of weeks after the administration of uricosuric agents has been impressive in our experience, and in some individuals has not been prevented by maintenance colchicine.

Of particular interest is the occurrence of renal calculi during uricosuric therapy in 7 of the 64 patients (11 per cent). However, in this group there

Table 37.—Summary of Results of Treatment in 64 Cases of Primary Gout

	% Patients
Improvement in chronic gout	98
Decrease in acute gouty arthritis to 1 attack per year	70
Decrease in serum urate to normal	50
Decrease in size of tophi	34
Precipitation of acute gouty arthritis by drugs	23
Died during follow-up period	12.5
Renal calculi on treatment	11
Renal function	
Unchanged	80
Deteriorated	18
Possibly improved	2

are five patients who had experienced renal calculi before they were given uricosuric agents. No conclusions with respect to the incidence of renal calculi on uricosuric therapy appeared justified on the basis of this experience.

In the light of discussion at this conference, particular interest centers on the matter of renal function in patients with gout, and the effect of uricosuric therapy on renal function. Dr. Gutman has presented to us in beautiful and logical detail the concept that the handling of urates by the kidney is designed to protect the collecting system in the kidney from being clogged up by uric acid crystals. If this concept is correct, in the use of uricosuric agents we are interfering with a protective mechanism. Therefore, I am most interested in determining whether clinical improvement in renal function has been observed in patients receiving uricosuric agents over a period of time.

In this group of patients, pre-treatment data were available in 44 patients in terms of serum creatinine levels and the 24 hour endogenous creatinine clearance. On the basis of these data renal function remained unchanged in 35 (80 per cent), deteriorated in 8 (18 per cent), and possibly improved in one (2 per cent).

There is one situation which has to be kept in mind in interpreting changes of renal function in gouty patients. We have all seen patients who have come in the hospital with acute attacks of gout, usually with considerable fever, who in addition to a sharp increase in their serum urate levels have had elevation of blood urea nitrogen and of serum creatinine. In some of these we can find evidence of infection and appreciate that there is coincident pyelonephritis along with the acute attack of gout. In others, one can conclude by inference that there must be some blockade in the collecting system, although a definite obstruction cannot be demonstrated. With appropriate management, emphasizing the use of antibiotics and hydration, rapid improvement in renal function may be obtained, with the return to a normal blood urea nitrogen and an improved level of serum creatinine, although usually some residual impairment of creatinine clearance can be demonstrated. The one patient in this series who was classified as possibly improved with respect to renal function happened to have uricosuric agents administered during the management of such an episode. It would obviously

be in error to attribute the improvement in renal function under these circumstances to the uricosuric agents.

I personally am not convinced that I have seen or heard reported clear-cut evidence of real improvement of renal function in patients on uricosuric therapy. This perhaps can be regarded as one of the real shortcomings of attempting to induce negative urate balance by increasing urinary urate excretion. This leads to the hope that the prospects for preventing the renal complications of gout may be better with the use of agents which induce negative urate balance by decreasing the production of uric acid.

REFERENCES

- | | |
|---|--|
| <p>1. Robinson, W. D.: Current Status of the Treatment of Gout. <i>J. A. M. A.</i> 164: 1670, 1957.</p> <p>2. Thompson, G. R., Duff, I. F., Robinson,</p> | <p>W. D., Mikkelsen, W. M., and Galindez, H.: Long Term Uricosuric Therapy in Gout. <i>Arth. & Rheumat.</i> 5:384, 1962.</p> |
|---|--|

Discussion

DR. BARTELS: Butazolidine is so effective in the treatment of acute attacks that I think it should be discussed. I consider that Butazolidine is more effective and a better drug than colchicine. I realize that colchicine given intravenously is effective but it is inapplicable as home treatment and few patients with acute gouty arthritis require hospital care. Colchicine when given in a dose of 5/10 of a milligram hourly for six or eight doses almost uniformly produces objectionable side effects. Butazolidine, on the other hand, produces no side effects and can be good home treatment. We have a high surgical population in our hospital and the use of colchicine in our surgical patients, either preoperatively or postoperatively, is certainly objectionable whereas Butazolidine is effective.

We have now treated 134 patients with Butazolidine for acute attacks. Given in a dose of 800 mg. daily for one or two days, it is as effective as colchicine. There have been no immediate side effects and we have not seen any side effects from its use every three or four weeks or even every one or two months. Therefore this drug, it seems to me, should take the place of colchicine in clinical practice.

DR. C. SMYTH: I share your personal feelings about this drug. From the practical standpoint, phenylbutazone is just as effective as colchicine.

DR. LOCKIE: Frankly, I am a Butazolidine man after the diagnosis of gouty arthritis has been established, using colchicine in the treatment of the first attack which I see. We have not had any side effects in the dosage of 800 mg. of Butazolidine for one or two days in a large series of treatments of acute attacks.

I'd like to mention a unique experience with colchicine. The other day I saw a 37 year old lady, referred by a psychiatrist who had treated her for degenerative arthritis of the hands, who had been using colchicine, 500 micrograms twice daily or three times daily, which had been given to her in a prescription nine years previously, along with phenobarbital. Well, she didn't want to take two drugs a day, and she decided to take colchicine,

which she thought was the nerve tonic, and for nine years she had taken 500 micrograms, 3 times a day, during which time she has had three normal pregnancies.

DR. SEEGMILLER: I would like to report one experience that we have had with phenylbutazone, given in a dose of only 800 mg. for a single day, that has caused me to relegate this drug to second place in the management of gout. In this patient a thrombocytopenia developed which would have gone undetected if he had not been under study in the hospital. The drug was of course discontinued and the patient suffered no serious consequences from this as his platelet count returned to normal. I can visualize the possibility of more serious difficulties having been experienced if he had been taking the drug at home.

I agree with Dr. Robinson that daily colchicine provides a valuable agent for preventing acute attacks. I don't think any of us would recommend the continuous use of phenylbutazone or oxyphenbutazone for this purpose.

DR. ROBINSON: I would like to underscore what Dr. Seegmiller has said: there is no question as to the usefulness of phenylbutazone in the treatment of acute attacks; there is no question of its being better than colchicine in the management of the patient with a well advanced attack or the patient with a polycyclic attack in whom colchicine has an incomplete effect. In such patients, phenylbutazone permits you to get the inflammatory element under control in a way that we couldn't do when we had only colchicine.

However, when I prescribe a maintenance agent or instruct the patient in the use of an agent to abort attacks of gout, I can prescribe colchicine with full confidence that if the patient gets into trouble with toxicity he will know it, and he will stop the drug. I cannot have such confidence in prescribing phenylbutazone and trying to instruct the patient in the safe use of this drug to prevent or abort attacks of gout. For this reason I reserve phenylbutazone for patients that I have right under my thumb, either in the hospital or in town.

DR. C. SMYTH: We have seen acute massive gastrointestinal hemorrhage after the first day of treatment of acute attack of gout which I attributed to Butazolidine. The potential hematopoietic toxicities of this drug are now well known, and although we personally haven't had this experience in some 60 acute attacks, I think that most of us would agree that these hazards are real and we should stress them in this discussion.

DR. HALL: May I ask Dr. Robinson a few short questions? You had an 11 per cent incidence of renal calculi, were these all in patients who had had renal calculi prior to taking uricosuric agents? And once you've had a patient on long term uricosuric therapy and you feel that you have reduced the frequency of the acute attacks, do you still continue with maintenance colchicine?

DR. ROBINSON: In this group of 64 patients, renal calculi occurred in five patients prior to use of uricosuric drugs, and in seven patients during administration of the drugs. These figures include a single patient with symptoms of urinary tract calculi both before and after initiation of uricosuric therapy.

In answer to the second question, we have usually continued maintenance

colchicine, because frankly we do not know when to stop it. Several patients in whom acute gout was well controlled on a regimen of both maintenance colchicine and uricosuric drugs, on stopping colchicine experienced recurrence of acute gouty attacks. One patient (a physician) was able to stop colchicine without difficulty after several years on successful combined therapy.

DR. HALL: At the time of instituting uricosuric therapy, did you alkalinize the urine of the patients?

DR. ROBINSON: Not routinely, but we do make a very real effort to maintain a large urinary volume.

DR. GUTMAN: Dr. Robinson has raised a question that I think might bear discussion, the question when to begin uricosuric therapy. There is no uniformity of opinion on this point and there probably should not be because this is a decision that I think has to be made by the individual physician. I don't know of any rules that apply to every case, and a great deal depends, it seems to me, upon the attitude of the physician, the patient, the patient's family, and all the other pressures that physicians are under when they face the question of medication.

I do, however, want to comment on what is I think quite widely considered to be one of the more important indications for uricosuric therapy at a relatively early stage, even before the first attack of gouty arthritis, in patients who have hyperuricemia. That is the hope, and I think it's a forlorn hope, of preventing renal damage. The reason I have doubts about this is that, first of all, I have never convinced myself that we have been able to prevent renal damage, nor have I been convinced in any of our cases that we have improved renal function by the use of uricosuric agents, although I daresay we can on occasion mobilize the tophi in the kidney as we can elsewhere. But when you consider all the connective tissue reaction to uric acid crystals, inflammatory cell invasion, and all the rest of the tissue damage that accompanies the deposition of uric acid crystals, it seems unlikely that even if we do mobilize the uric acid crystals in the kidney that we can, in so doing, restore a badly damaged kidney to normal function.

I do in particular want to add some relevant theoretical considerations. In all likelihood the site of reabsorption of uric acid by the human kidney is the proximal convolution, and probably very far up in the proximal convolution. What we are hoping to accomplish with uricosuric agents is to diminish the quantity of uric acid that is passing through the proximal convolution and thereby avoid the deposition of uric acid. But you must realize that when you give even the most potent uricosuric agents, you diminish the rate of tubular reabsorption of uric acid to the extent of perhaps 20 per cent. If you calculate the increase of urinary uric acid excretion produced and relate it to the quantity of uric acid which is filtered at the glomerulus, you realize that even though the increase in urinary uric acid excretion is considerable in terms of what is normally excreted, in terms of the huge amount of uric acid filtered at the glomerulus and reabsorbed, this is a very small proportion indeed.

Moreover, and I think this is a more serious objection, the pathologists tell us that the site of renal damage due to uric acid stone formation is not in the proximal convolution, but in the medulla, or at the junction between the medulla and the cortex; in other words, at the site of the distal tubule or in the collecting duct. We have no reason to believe that reabsorption occurs in these places to any appreciable extent, so the real damage to the kidney is by formation of uric acid microcalculi, which probably form at a site different from that which is affected by the use of uricosuric agents. I would go even further and say that by increasing renal excretion of uric acid we are further endangering, or facilitating this process of precipitation of uric acid in the collecting ducts and distal tubules. It is there that the urine is chiefly concentrated, in this way increasing the concentration of uric acid in the tubular fluid, and it is there also that the urine is chiefly acidified, so the chief conditions for facilitation of uric acid precipitation are not in the proximal tubule, but in the distal tubule and in the collecting ducts.

So, on the basis of empirical experience and on the basis also of theoretical considerations, I think it highly unlikely that the administration of uricosuric drugs diminishes the hazard of uric acid deposition in the kidney. There is every reason to believe that, if anything, it increases the hazard, and this of course is borne out by the fact that there is a small but definite percentage of iatrogenic uric acid stone formation related to the use of uricosuric agents.

DR. BARTELS: Gout is a unique disease in that you can predict whether you are going to be able to bring it under control or not by establishing the state of the patient's kidney function. In this way it can be decided whether you can effectively treat the patients. If one classifies the gouty patients according to their treatability one comes up with some different figures than have been shown here by Dr. Robinson.

If a patient has no renal disease one can be relatively sure that the uricosuric drugs will be effective. Should one find some degree of renal insufficiency, as evidenced by the presence of albuminuria or a change in PSP or elevation in the BUN, one should not at that juncture say that these patients are not treatable. In that case a determination of urinary excretion under the influence of various drugs should be undertaken. We have done this in a sizable group of patients whom we thought were untreatable and have found that sometimes they did respond by increasing the urinary excretion of uric acid. Some 17 per cent of our patients have renal damage as a result of which there is no possibility of producing any uricosuric effects.

DR. SEEGMILLER: My experience has been that even with the degree of renal impairment that gives a PSP excretion as low as 25 per cent in two hours one can obtain an increase in uric acid excretion with the uricosuric drugs, particularly sulfinpyrazone; probenecid giving some additive effect when given simultaneously. I think the resulting uricosuria still can produce a significant change in the course of the disease. With the advent of allopurinol the prospect of effective control of such a patient has been greatly enhanced.

While we're on this subject no one has mentioned the study of Reed

which is very pertinent. In 11 of 20 patients with renal dysfunction and gout, she was able to achieve a mean increase in creatinine clearance of from 55 to 75 ml./min. by treatment with a uricosuric drug (zoxazolamine), a high fluid intake and alkali. It is not clear from her study as to just which therapeutic ingredient was responsible for these results. Do you have any opinion or data on this point from your clinical studies, Dr. Bartels?

DR. BARTELS: As I mentioned, by doing these acute experiments and seeing how much uric acid is excreted, one has some idea as to whether they are controllable or not on uricosuric drugs.

DR. SMYTH: This would amount to 17 per cent of your cases?

DR. BARTELS: That's right. 17 per cent of our patients have such a degree of renal damage that there is no uricosuric response at all.

DR. SEEGMILLER: At what level of BUN do you make this decision?

DR. BARTELS: I do not think anyone had a BUN over 40 mg. per cent. I believe there should be studies in this area. No patient should be eliminated from this therapy unless this test is done.

DR. DECKER: I'd like to direct a question to Dr. Gutman. It is evident that the use of uricosuric drugs puts more uric acid into the tubule and delivers it to the site where it may do damage. Under these circumstances, we should reconsider the whole problem of prophylactic uricosuria in the essentially healthy individual who has had no gouty attacks, has had no tophi, but has an elevated serum uric acid. I wonder if this is ever justified. Is there then an indication for giving uricosuric agents solely on the basis of the level of the serum uric acid? Dr. Hall has given us good reason to believe that a substantial proportion of these people are going to their graves without ever knowing about their serum uric acid. Would you care to comment on this question?

DR. GUTMAN: I've always been very conservative in the use of uricosuric agents. We have usually refrained from administration of uricosuric agents until we see the first indication of tophaceous deposit. Now, maybe that's too conservative.

But the thinking behind this is this: you must remember that hyperuricemia begins in males at the age of puberty, so that by the time you see your patients at the age of 35, 40 or 45, they've already had hyperuricemia of essentially the same degree for 20 or 30 years when they first consult you. The administration of uricosuric drugs is therefore no acute emergency.

We know also from the results of epidemiological studies that there are many more patients who have hyperuricemia than ever develop even a single attack of acute gouty arthritis. It is likely that most patients who have the gouty trait never develop any clinically overt manifestations of the disease. Somewhat less than half of all patients who do develop overt gout, and these again are the minority of patients with the gouty trait, ever develop any tophi at all, and of this proportion only a small fraction ever form tophi of such extent as to represent any appreciable cosmetic or physical disability. So, the indications for uricosuric therapy in the way of prevention of tophi apply to only a diminishingly small proportion of the gouty population.

The average interval between the first attack and the first tophus is

about ten years or so (11.2 Dr. Wyngaarden says). You are therefore faced with the prospect of giving a drug for prophylactic reasons over a very long period indeed to a patient who has less than a 50-50 chance of ever developing appreciable tophaceous deposits. Fortunately, probenecid and sulfinpyrazone are not very toxic, but they are not wholly innocuous and are rather expensive. It seems to me that the odds, under these circumstances, rather favor the point of view of withholding uricosuric agents. The really important question is: can you prevent renal damage? As I said before, I think the answer to that question is probably "No." Therefore, everything considered, I've maintained a rather ultraconservative point of view in regard to the administration of uricosuric agents. That's one side of the picture. Now, the other side is, when patients come in to see me and I discover, even in the asymptomatic patient, a serum uric acid level of 10 or 12 or more milligrams per cent, I get a little nervous about this, and for the benefit of the physician as much as of the patient, we give uricosuric agents.

DR. KRAKOFF: I just want to comment that Dr. Gutman's nervousness in the face of a serum uric acid of 10 or 12 mg. per cent was probably minor compared to the frenzy of the house officer who sees a leukemic patient with a serum uric acid of about 25 mg. per cent. The temptation of the house staff in these situations to give probenecid immediately is enormous. Whatever useful role I might have been able to play is largely in restraining these patients from receiving probenecid. I am quite sure that I have seen patients who were tolerating a serum uric acid level of 20 to 25 mg. per cent with a good urine output, who have been pushed into uric acid nephropathy and renal failure by the injudicious administration of uricosuric drugs in this situation.

DR. BAUM: Dr. Gutman, in your view of this, then, the deposition of uric acid in the kidney in the patient with a high serum uric acid is not due to the high blood level but to the large amount of uric acid that's leaving the kidney. I thought it was the feeling among pathologists that the deposition in the interstitium of the kidney in patients with gout was more related to the elevated blood level than to the amount being excreted. In this event, wouldn't you think that uricosuric therapy would be the treatment of choice because as you clear tophi from the periphery you are clearing, in a sense, microtophi from the interstitium of the kidney?

DR. SMYTH: Dr. Gutman, do you want to reverse your decision previously stated?

DR. GUTMAN: No. It may sound strange, but I think that the development of tophi peripherally, in the joints, etc., is certainly related to the serum uric acid level whereas in the development of tophi in the kidney, I suspect, this is not the case. In other words, in the kidney we have a rather special situation in which the damage, I believe, is due more to the excretory process. The concentration of uric acid in the urine, the pH of the urine, and the volume of the urine, these are the factors I think are paramount in importance in determining the extent of renal damage. I think that what Dr. Robinson said in reference to maintenance of high urine volumes is the simplest and most effective way we have of preventing renal damage.

DR. H. SMYTHE: Dr. Decker's and Dr. Gutman's argument can be attacked

on two points. The first one is this question about the excessive delivery of uric acid to the tubules on uricosuric therapy. This does occur in the first few weeks of treatment, but after treatment is established the mean uric acid output is the same as before treatment. Therefore, you have to protect the patient during a relatively short period of initiation of therapy by initiating therapy slowly, by maintaining high fluid volumes, and by alkalization of the urine fairly carefully, with testing of the urine with nitrazine papers. I think this should be done and is logical treatment.

But perhaps the more important objection to their line of argument is the assumption that the renal failure is due to tophaceous deposits in the kidney. These are very spectacular lesions but they are spotty and inconstant. Dr. Sokoloff and other pathologists describe a more important lesion leading to renal failure, namely nephrosclerosis. The degenerative vascular complications associated with gout may be related to the same basic problem that leads to the risk of coronary heart disease in gouty subjects. For this reason much of our concern about the development of future therapy should be directed toward a study of the degenerative vascular complications of gout.

DR. SEECMILLER: I've been interested in Dr. Gutman's thoughts on the evolutionary value of conservation of uric acid by the renal tubule. It seems to me that it may have had a survival value only when a paucity of watering holes presented a greater chance of dehydration than we generally experience today. Nature has performed an experiment observed so far in only one person that is pertinent in this regard. Kirk and Praetorius reported studies of a man who seemed to lack a tubular reabsorptive mechanism for uric acid. In this regard he was the human counterpart of the Dalmatian coach hound. He should therefore be experiencing all of the hazards that Dr. Gutman has been describing. As I recall there was no history of kidney stones or renal damage in this patient. There are clinical experiences that suggest the importance of a high fluid intake in augmenting uric acid excretion. I have a family in which there are three gouty overproducers of comparable renal function who, without uricosuric drugs, and while consuming a purine-free diet, excreted around 1,100 milligrams of uric acid per day—two to three times the normal. Presumably they all share the same basic metabolic defect of overproduction. Two of the brothers had experienced kidney stones. The third one who had not had kidney stones had, on his own volition, followed the advice to drink fluids that had been given to his other brothers and was found to be excreting over 6 liters of urine per day. He had the lowest serum urate concentration of the three. Augmentation of uric acid clearance at high urine flow rates has been documented in the studies of Rieselbach and associates. There are reports in the literature of uric acid renal calculi undergoing reabsorption with a high fluid and alkali treatment. We have seen one gout patient in whom this occurred.

All of these considerations point to the importance of a high fluid intake in gout patients to aid in the excretion of uric acid. If the hazards described by Dr. Decker and Dr. Gutman are extremely grave we should expect to see some evidence of kidney damage as the result of uricosuric therapy. I

haven't seen any cases in which I felt that uricosuric therapy had a deleterious effect on kidney function.

DR. WYNGAARDEN: There was a case report in the Rhode Island Medical Journal some years ago describing a patient whose renal function was made markedly worse by uricosuric therapy; from the data there it did not seem that it was due to stone and crystal formation induced by advancing renal failure.

Dr. Seegmiller's comments remind me of a point which perhaps should have been made earlier in the conference when we were discussing genetic patterns, that is the consistency of type within a given family. He mentioned three overproducers in one family. We have a family with two overproducers, brothers, in one family, and another family with two brothers and a son with gout, all of whom have very high uric acid levels and normal glycine incorporation. One of them has a normal PRPP turnover and they all have very low clearance of urate.

DR. GUTMAN: Would you agree that the incidence of uric acid stone generally is higher in people getting uricosuric agents?

DR. SEEGMILLER: It is my impression that much depends on the precautions that one can induce patients to take. We do insist on 3 liters of fluid intake a day and really emphasize it at each visit. If the patient is an overproducer of uric acid or has a history of stones, we add alkali. When we first started using sulfinpyrazone without strong emphasis on these precautions one of our patients did develop renal colic and passed a stone. Since that time we've had really very little difficulty with uric acid stones. A few of our patients have passed calcium stones at various times.

I should like to mention another group of three patients that has been instructive. These are patients who have come to us because of uric acid stones before they had ever developed any joint symptoms. They had frequent hematuria and had had recurrent passage of stones and at times had daily sludge in the urine. They were all overproducers of uric acid. We managed them with a high fluid intake and a large amount of alkali (15 grams of sodium bicarbonate or trisodium citrate per day) and ever since starting this therapy they have had no difficulties at all with stones.

DR. GUTMAN: I wish all treatment were conducted as well as yours but unfortunately it is not. So many patients are referred to us by other physicians for just this problem, the precipitation of uric acid stones, and we contribute to the percentage to some extent ourselves.

If you increase the concentration of uric acid in the urine and maintain a low pH, you facilitate the precipitation of uric acid stone. Now, if you counteract this conscientiously by giving large fluid volumes, if the urine pH is very low and you give alkali, you can overcome the hazard. In carefully conducted practices this is usually successful, but not all patients are as carefully followed and not all patients carefully follow instructions. In Israel, for example, where the temperature is very high, there is an incidence of 70 per cent of stone among gouty patients as compared to something between 10 and 20 per cent in this area. I suppose that the danger even in this country would be greater in hot weather after exercise.

DR. BARTELS: In reference to the comments made by Dr. Gutman, the question is, is the danger of stone formation based on the amount of uric acid which is delivered to the kidney, or the amount which goes through the kidney? Based on the assumption that it is related to the amount delivered to the kidney, we have intentionally, in some 39 patients who are stone formers with high serum uric acid, treated these patients with uricosuric drugs, and in this group we have not seen an increase in the incidence of stones; actually the reverse. A fair number of these patients have been individuals who have had previous surgery for stone removal and even nephrectomy.

DR. OGYZLO: I think the comments about the urine volume in regard to keeping the urates in solution are very pertinent. I was interested in Dr. Seegmiller's description of his patient with changes resulting from alterations in urine volume alone. We took 20 normals and 20 gouty patients and put them on a study where they had one day of intake of 1,000 cc's; compared that with one day of intake of 4,000 cc's; no other change, one day of a complete fast, and one day of a uricosuric agent.

The only things that altered the urinary excretion or changed the serum uric acid value were the fasting and uricosuric agent. There was no significant change in excretion at all on simply changing urine volume from 1,000 to 4,000 cc's a day.

The other question in regard to stones is, their occurrence in patients who do not have gout. These are patients referred by the genitourinary service who don't have gout or hyperuricemia and whose urinary output is only of the order of 400 to 500 mg. per day. Now how do you explain this?

DR. GUTMAN: Such patients, according to Dr. Henneman, have a very acid urine pH.

DR. DECKER: I would like to mention an observation we made which was of interest to us. The tranquilizing drug, chlorprothixene or Daractan, in daily dose of 50 mg. was as uricosuric as sulfipyrazone, 200 mg., or probenecid, 500 mg. This drug is similar to a phenothiazine but is not a phenothiazine and it is also basic, not an acid. It has been used as a tranquilizer for four years and has a good safety record. In a representative clearance study, using it at bedtime for three days, the serum urate changed in this subject from 7.5 mg. per cent to 5 mg. per cent and the uric acid clearance was doubled from 7 to 15 cc. per minute.

DR. C. SMYTH: Dr. Howell, would you like to comment on your experiences with Griseofulvin?

DR. D. HOWELL: I really have very few statements to make about this agent. We became interested in it as a result of the finding that this drug had two properties of some interest. One, it interrupts cell division in various tissue cultures, and in other systems interrupts cell division at the metaphase, but probably more important it interferes with granuloma formation in cotton pledgets planted in various animals.

We initially reported a study with a dramatic effect in acute gouty arthritis in 20 patients, with a prompt and complete response in all but two. There

were practically no side effects. We have tried 12 more patients since our formal report of 1962. We have limited its use to a certain group, those who have active peptic ulcers with danger of bleeding, perforation or uncontrollable pain who also have acute gout and in whom it is unwise therefore to use colchicine orally.

All but one of these patients have done well on a schedule of management, which included 10 to 12 capsules of the new 0.25 gram Griseofulvin given by mouth over a period of three days. Rapid defervescence of objective signs of acute inflammation occurred with these patients. This was the same good response that had been observed in our first series. However, the problem of the expense of the drug and the large number of capsules required makes me hesitate to recommend this drug as the best way to manage such patients. In our experience, given intravenously, we have found it to be rapidly effective, it is inexpensive, and without side effects. I would say that one could choose between these two methods of approach to the patient who does not tolerate or in whom it is unwise to use oral colchicine.

DR. ZVAIFLER: Has porphyria been seen in human patients? I know it has been recently produced in animals with this agent.

DR. D. HOWELL: I believe that at human dosage levels porphyria does not occur.

DR. ELDER: It might be worth mentioning one other drug that we've been looking at. We haven't enough experience yet to report this with a great deal of confidence but we've been using indomethacin in our rheumatoid patients. The British have already published several reports on the use of indomethacin in acute gouty arthritis, and in the last month I've had the opportunity to treat four patients with attacks of acute gout with indomethacin. We start with an empiric dose of 150 mg., which has been our average total daily dose, but in acute gout we have given 150 mg. as a stat oral dose.

Two of the patients we saw within 24 hours of the time of their acute attack and one had typical podagra, the other one had an attack involving the wrists; both hobbled into the clinic, one unable to walk, the other unwilling to allow anyone to examine his arm, and within about half an hour to 45 minutes after taking 150 mg. of indomethacin by mouth both of them were essentially pain free. They still had some swelling and erythema, which disappeared over the next 48 hours or so, requiring no further use of the drug.

The other two patients had been having their attack for approximately three days in one case, in the other case about five days and had been resistant to Butazolidine, colchicine and also steroid. In neither of these two cases was indomethacin quite as effective although both of them obtained quite a dramatic response over a 24 hour period.

DR. PLOTZ: We have been using indomethacin now for about three years and our experience and the collected experience of others comprises some 500 cases of acute gouty arthritis. There is very little doubt, as was previously pointed out, that indomethacin is an effective anti-inflammatory drug in the management of acute gout as in other acute inflammations.

The first effect is observable within about two hours and we have found

that we will occasionally get a rebound unless indomethacin is continued for a period of five to seven days, unlike colchicine. Unlike phenylbutazone, there is no uricosuria with indomethacin; there is no effect on the serum urate level. Also unlike phenylbutazone and colchicine, there is very little risk of any serious side reaction. About 15 per cent of patients develop either headache or dizziness but this is transitory and other than this there are, except in the presence of overt peptic ulcer, virtually no side reactions, at least in the management of acute gouty arthritis. We have also in a most preliminary way, found that indomethacin has no apparent effect on the action of probenecid.