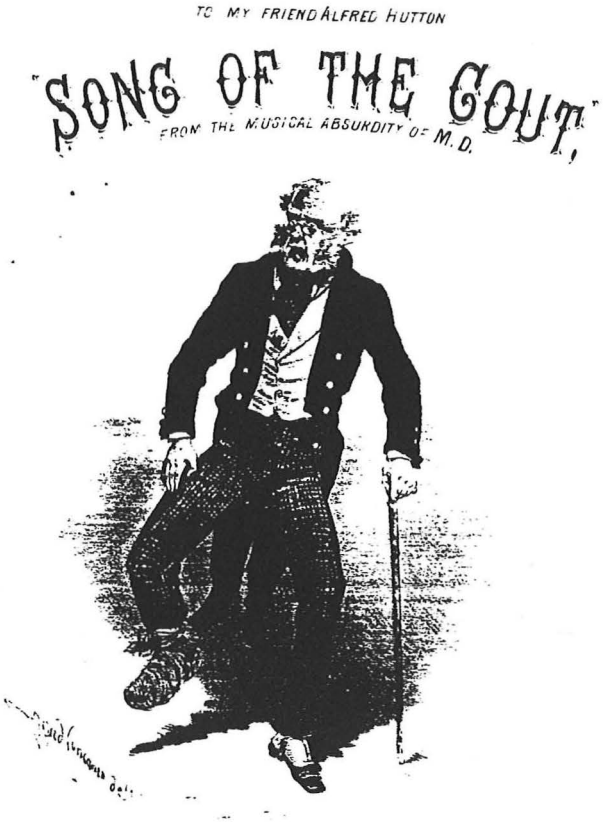
PREVENTION AND MANAGEMENT OF THE "KING OF DISEASES", GOUT



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HISTORY

The first descriptions of gout date back to 450 B.C. at the time of Hippocrates. Hippocrates labeled gout the "king of diseases and the disease of kings"(1). He made several important observations that stand true today, and these include:

1. Eunuchs do not take the gout nor become bald.
2 A woman does not take the gout unless her menses has stopped.
3 A youth does not get gout before the sexual intercourse.
4 In gouty afflictions, inflammation subsides within 40 days.
5 Swellings and pains in the joints without sores, whether from gout or from other strains, in most cases are relieved by copious effusions of cold water.
6 Gouty infections become active in spring and autumn.

Hippocrates thought gout was the accumulation of a body humor that was evil. He noted that relief for gout was dysentery and induced dysentery with a white hellebore, which is a cousin of colchicine. The remaining history of gout is presented below in outline form.

1. 160 AD The first description of tophi in patients with chronic gout were described by Galen.
2. Dark Ages The term gout was coined. Gout came from the Latin word gutta, which means drop. It was thought that the evil humors dropped into the joint.
3. 1600's Thomas Sydenham, a masterful clinician and himself a sufferer of gout provides us with a number of important clinical descriptions of untreated gout. He did not believe in evil humors, and therefore, refused to use purgative therapy. Unfortunately, his teachings led physicians to stop using colchicine-like drugs in the treatment of gout.
4. 1763 Colchicine re-introduced by Nicholas Hussam, who included a

colchicine-like drug in a shot gun patent medicine that he created (1). This medication was remarkably effective.

5. 1776 Hussam remedy was brought to the United States by Benjamin.
6. 1776 Scheele discovered uric acid in the kidney stone.
7. 1797 Wollaston demonstrated that uric acid was present in tophi.
8. 1814 Dr. James Want demonstrated that alkaloids present in the Houston remedy were responsible for its beneficial effects.
9. 1823 Scudamore distinguished gout from rheumatism and found gout in 11% of his patients.
10. 1848 Garrod identified hyperuricemia in gouty subjects and introduced a thread test for detecting hyperuricemia. He also postulated for the first time that gout was caused by uric acid deposition in the joints and that the kidneys were largely responsible for the increase in uric acid. Finally, he suggested that hyperuricemia was caused by multiple factors.
11. 1889 Fisher demonstrated that uric acid was a purine compound.
12. 1899 Freudweiler injected uric acid crystals into joints and reproduced gout. He also demonstrated that uric acid crystals were found in synovial fluid white cells. This work was, unfortunately, largely overlooked.
13. 1913 The first reliable assay for uric acid was developed by Folin and Denis. This stimulated a large number epidemiologic studies of hyperuricemia and its relationship to gout.
14. 1936 Colchicine is found to prevent gout.
15. 1950, Probenecid is found to lower the serum uric acid by increasing uric acid excretion.
16. 1961 McCarty and Hollander, rediscovered uric acid crystals in the synovial

fluid. It was at this time that it became a standard diagnostic test.

17. 1963 Allopurinol was developed. Because of the effectiveness, allopurinol was initially used by almost all physicians for all cases of gout. In recent years, the pendulum has swung back toward using uricosurics.
18. 1967. First enzyme defect (HGPRT) responsible for hereditary gout described by Seegmiller, Rosenbloom and Kelley.

CLINICAL DESCRIPTION AND NATURAL HISTORY

Acute gout is characterized by the rapid onset of inflammatory arthritis and exquisite pain. Acute gout is probably best described by Sydenham's in 1850 (31).

> `The victim goes to bed and sleeps in good health. About 2:00 in the morning he is awaken by pain in the great toe; more rarely in the heal, ankle or instep. This pain is like that of a dislocation, and yet the parts feels as if cold water were poured over them. Then follows chills and shivers and a little fever. The pain, which is at first moderate, becomes more intense. With this intensity the chills and shivers increase. After a time, this comes to its full height, accommodating itself to the bones and ligaments of the tarsus and metatarsus. Now it is a violent stretching and tearing of the ligaments--now it is an annoying pain and now a pressure and tightness. So exquisite and lively, meanwhile is the feeling of part affected that it cannot bear the weight of their clothes nor the jar of a person walking in the room. The night is passed in torture, sleeplessness, turning of the part effected, and perpetual change of posture; the tossing about of the body being as incessant as the pain of the tortured joint, and being worse as the fit comes on. Hence, the

vain effort by change of posture, both in the body and the limb affected, to obtain an abatement of the pain.'.

The accuracy of this description may in part be attributed to the fact that Sydenham himself suffered from acute gout. Over half of the initial attacks of acute gout involve the first metatarsal phalangeal joint. This joint is involved in over 95% of patients at some point in the course of their gout. With decreasing order of frequency, the in-step, heel, ankle and knee are also involved as initial manifestations of gout. Redness of the overlying skin sets gout apart from other non-infectious inflammatory arthritides. Gout need not always be articular, as it may involve bursae or tendons. Swelling of the surrounding tissues can at times be marked. The natural history of the attack is variable, lasting as little as 2 days in a mild attack and up to 10 - 20 days in a more severe attack.

Initial attacks are frequently monarticular (90%), and as the disease progresses, it becomes more polyarticular, involving upper and lower extremity joints. Systemic features such as fever and chills become more common with time. Attacks in patients with tophi frequently involve multiple joints and are associated with fever. Since the interval between attacks can become quite small, these patients often have what appears to be a chronic arthritis. At times the disease resembles rheumatoid arthritis

Tophi develope in between 25% and 50% of patients in the absence of treatment. These data were derived from the era before therapy and did not take into account those patients in whom their hyperuricemia was caused by drugs. The natural history of drug-induced gout is at present unknown. Tophi can appear any time in the first 20 years of disease, but generally occur between 10 and 20 years after the initial attack. They appear as firm swellings without local inflammatory response. The most common locations are the digits of the hand and feet and the

olecranon bursa. Tophi of the helix or anti-helix of the ear are specific for gout but much less common. Joint destruction is almost always associated with tophi. In the chronic untreated gout, destructive, disabling arthritis is a natural consequence.

DIAGNOSIS

The diagnosis of gout can be made firmly by removing joint fluid and demonstrating the presence of intracellular crystals. Extracellular crystals also strongly suggest gout, but can be found in asymptomatic individuals with hyperuricemia from renal failure and are, therefore, not completely diagnostic. In many cases, it is not possible to get joint fluid, and in those situations it is often necessary to diagnose gout on clinical grounds. figure 1 below lists the published diagnostic criteria for gout (30). The criteria illustrate that gout is an acute monarthritis or oligoarthritis that disappears completely between attacks, and recurs repetitively in the presence of hyperuricemia. When these criteria are fulfilled one can make a diagnosis of gout with a high degree of sensitivity and specificity.

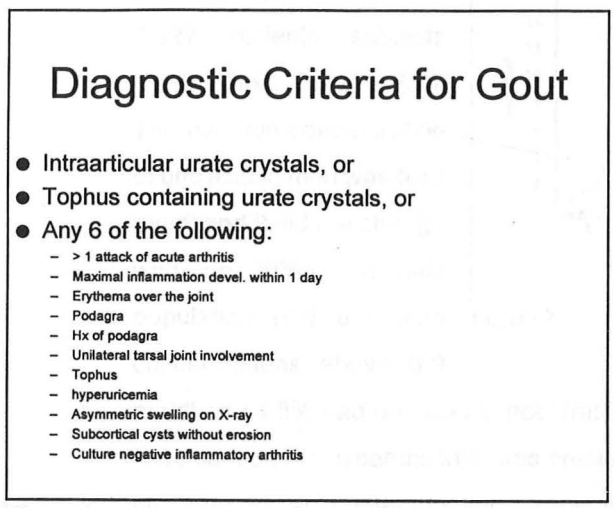

Figure 1

EPIDEMIOLOGY

Hyperuricemia. Hyperuricemia can be defined in a variety of ways. The solubility of uric acid in synovial fluid at 37 degrees is 6.8 mg/dl. Moreover, the incidence of gout increases when the uric acid rises above 7.0 (2). For these reasons many

investigators have suggested that hyperuricemia be defined as serum uric acid values above 7.0. . The mean plus two standard deviations of the serum uric acid is considerably higher than 7.0 and many laboratories list the normal limits of uric acid as two standards of deviation above the mean. Using this definition, the vast majority of patients with gout would have a "normal" uric acid. For the purposes of this discussion, hyperuricemia will be defined as a serum uric acid greater than 7.0.

Figure 2 illustrates the distribution of uric acid concentrations in men and women 32-64 years of age that was present in the 5,127 patients subjects (Framington Cohort, (3)). The average concentration of uric acid in men was 5.12 mg/dl and it did not change with age. 20% of the male population had uric acid concentrations above 6.0 mg/dl and 4.8% had uric acid concentrations above 7.0. Renal disease that might have caused the hyperuricemia was present in less than 1% of the subjects with an elevated uric acid determination. In women the average concentration of uric acid is 4.0 mg/dl and it increases 0.5 mg/dl with menopause. Uric acid determinations were 1.5 mg/dl higher in men than in premenopausal women. Similar findings were observed in the Tecumseh Community Health Study (4). These findings likely explain the lack of gouty arthritis in premenopausal women and the greater

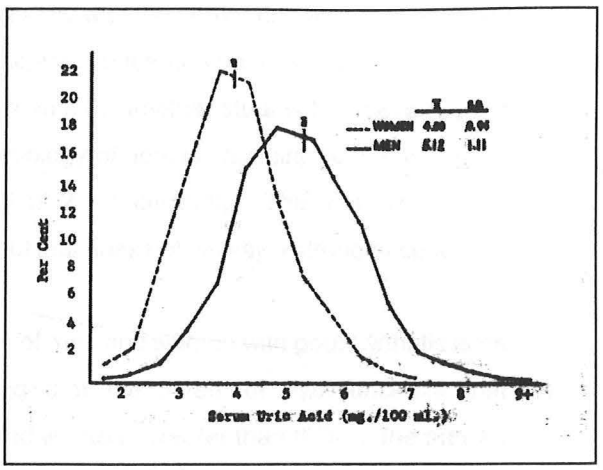

Figure 2

incidence of gout in males. Thiazide diuretics increase uric acid concentration 0.5 mg/dl on average. Cyclosporine also increases the serum uric acid level.

Gout. The prevalence of gout in the Framington Group was 2.8 and 0.4 % in men and women, respectively (3). The average age of first attack was 47.7 years in men and 54 years in women. Gout is rare in premenopausal women and children. In men there was an inverse relationship between the serum uric acid and the age of first attack. The prevalence of gout varied directly with the serum uric acid concentration being 1.1% in patients with a serum uric acid concentration less than 6.0 and 83% in those with a serum uric acid greater than 9.0. In other studies the prevalence of varies from 1-2 percent (5). The epidemiology of gout is changing (e.g. the male to female ratio was 20:1 in 1960's and is 2-7.1 currently). This may reflect the increasing incidence of drug induced gout that does not display a strong male:female predominance.

The mean uric acid concentration of men and women with gouty arthritis does not differ substantially, demonstrating that the levels of hyperuricemia that predispose to gout are similar in men and women. Greater than 87% of the attacks of gout occurred in the lower extremity and podagra occurred in 90% of patients at some time in their course.

Urinary Calculi. In the Framington study there was a direct relationship between uric acid concentration and the prevalence of renal calculi. In those patients with uric acid concentration between 7 and 8 the prevalence of stones was 13% whereas in those with a uric acid concentration greater than 9 the prevalence of stones was 40%. Calculi were also more common in those patients with gouty arthritis than those with asymptomatic hyperuricemia.

PATHOGENESIS

The factors that lead to gouty arthritis are complex. The complexities are perhaps best illustrated by the results of studies examining the incidence of hyperuricemia and gout in various populations. These studies have demonstrated that Polynesian peoples have higher serum uric acid concentrations than the rest of the world (6-8). This hyperuricemia was not evident until the introduction of the western diet and appears to be due to a defect in uric acid excretion together with the increased uric acid production triggered by the western diet (7). Most Polynesian people have a corresponding increase in the prevalence of gouty arthritis.

The tendency to develop gout in Polynesian people with hyperuricemia does not seem greater than in Caucasian Europeans. Thus, the incidence of gout is 23% in males with a serum uric acid greater than 8 mg/dl whether they live in Europe or Polynesia (6). The studies demonstrate that the genetic and environmental factors that lead to the increase prevalence of gout in Polynesian people exert their influence by increasing the serum uric acid level. The data support the concept that hyperuricemia is necessary for the development of gouty arthritis.

Although, hyperuricemia may be necessary for gouty arthritis, it is not sufficient. Not all males with serum uric acid concentration greater than 8.0 develop gouty arthritis (9). Moreover, in one population of Polynesian males with serum uric acid concentration greater than 8 mg/dl the prevalence of gout is only 5.5% (6). Therefore, environmental and/or genetic factors besides those that control hyperuricemia are also involved in the pathogenesis of gout. The finding that the prevalence of gouty arthritis in populations with similar serum uric acid concentrations correlates with the incidence of diabetes mellitus, and the intake of alcohol and fat, suggests that these metabolic disorders may also predispose to gout (6).

Causes of hyperuricemia The causes of hyperuricemia are listed in figure 3.

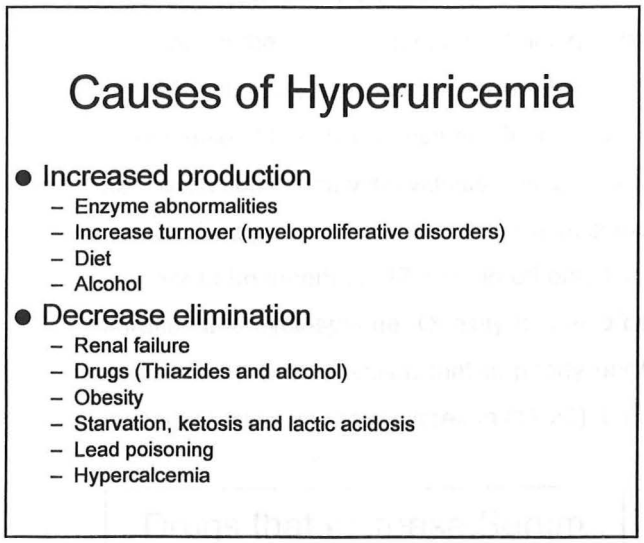

Figure 3

Hyperuricemia is the result of either increased production or decreased elimination of uric acid. Human beings are the only mammalian species lacking the urate-oxidase enzyme necessary to metabolize uric acid. "Knock-out" mice lacking this enzyme develop hyperuricemia and renal failure (10). The normal serum uric acid level is not far from the solubility product of urate (6.8) and subtle changes in diet and urinary excretion can lead to urate deposition and gout.

Increased production of uric acid occurs in genetic defects in the HGPRT enzyme which is required to reconvert xanthine into nucleic acids (11). In its absence there is a build up of xanthine which is converted to urate by xanthine oxidase. A number of mutations in the HGPRT gene have now been described. All are inherited as X-linked traits. Severe deficiency leads to hyperuricemia, mental retardation, spasticity, choreoathetosis and self-mutilation termed Lesch-Nyhan syndrome (12). Moderate deficiency leads to hyperuricemia and gout and lesser neurologic lesions (12). A mutation in the PRPP synthetase gene leading to an overactive enzyme also leads to uric acid overproduction and gout (13).

Alcohol consumption is another cause of increased urate production. Alcohol increases urate production by increasing the degradation of adenine nucleotides (14), and, in the case of beer, by providing a dietary source high in purines (15).

The majority of patients with gout have decreased excretion of uric acid as the major cause of their hyperuricemia. In a study of urate clearance by Simpkin et al., urate excretion in gouty individuals was a mean of 41% less than urate excretion of normals for a given serum uric acid (16). In some cases diminished urate clearance appears to be inherited (17,18). In others, it is caused by drugs such as thiazide diuretics and cyclosporine. Obesity has also been demonstrated to reduce urate clearance by a mechanism that is poorly understood (19,20). Weight reduction appears to improve urate excretion (19,20). Lead toxicity decreases renal function and increases the serum uric acid level frequently leading to saturnine gout. Recent studies have begun to suggest that even lead stores previously considered safe decrease urate excretion and can predispose to gout (21).

Drugs that Increase Serum Uric Acid Levels

- Diuretics (thiazides)
- Cyclosporine
- Ethanol
- Ethambutol
- Pyrazinamide
- Laxative abuse
- Levodopa
- Low dose aspirin
- Methoxyflurane
- Cytotoxic drugs
- Nicotinic acid

Figure 4

Although diminished urate clearance is present in the vast majority of patients and probably represents the most important abnormality leading to hyperuricemia, gouty patients frequently have mixed problems of overproduction and under excretion. One careful analysis of urate production demonstrated that nearly 1/2 of gouty patients have a slight increase in urate production (22).

A variety of drugs decrease uric acid excretion and thereby predispose to gout. They are listed in figure 4. The most important drugs are thiazide diuretics, because of their common usage. Thiazides increase uric acid 0.5-1.0 mg/dl on average. Thiazides role in gout is increased because of their use in patients with hypertension another major independent risk factor for gout. Cyclosporine has a profound effect on uric acid excretion. The incidence of gout in patients on cyclosporine has been estimated to be as high as 10%.

Pathogenesis of gouty inflammation

The formation of uric acid crystals is thought to be a requirement for gouty inflammation. The factors that lead to crystals formation include temperature, acidity, calcium content, protein content and uric acid concentration (23). Crystal formation is not sufficient for inflammation. Thus, urate crystals can be seen in asymptomatic knees of renal failure patients with hyperuricemia or patients with gout between attacks. The events that trigger inflammation are not known. Urate crystals can directly stimulate complement activation and activation of hageman factor (24). While these events may play a role in gout they are neither necessary nor sufficient. It is thought that polymorphonuclear cell activation is critical for gouty inflammation and that this event as activated by phagocytosis of urate crystals.

The tendency for polymorphonuclear cells to phagocytize urate depends in part upon the proteins that adhere to them. In general, protein adherence inhibits phagocytosis. This inhibitory effect is thought to be mediated by apolipoproteins B and E. Apolipoprotein E may be particularly important in this regard as it is produced locally by synovial lining cells (25). In contrast to the inhibitory effects of these proteins, IgG is known to increase crystal phagocytosis and neutrophil activation (26).

Binding of crystals to polymorphonuclear cells stimulates them to release a number of proinflammatory cytokines including reactive oxygen species, collagenase, PGE_2, IL1 and IL6 (27-29). These stimulate the influx of other inflammatory cells, and result in fever, pain, and the synthesis of acute phase proteins.

Despite all that is known about gout several interesting questions remain. Why don't all patients with uric acid concentration greater than 8.0 develop gout? Why does gouty inflammation subside spontaneously? What triggers episodes of gouty inflammation? What stimulates the first polymorphonuclear cells to enter the joint?

TREATMENT OF ACUTE GOUT

The first priority when approaching a patient with acute gout is to relieve their pain and inflammation. The agents which accomplish this are not necessarily those used in preventing future attacks which are considered separately below.

Colchicine

As discussed in the history above, colchicine has been used since the time before Christ in the treatment of gout (1). It was initially used because of its ability to induce diarrhea with the thought that purging would relieve the patient of evil humors. It is now known that colchicine binds to microtubules and inhibits their polymerization. Microtubule function is required for polymorphonuclear cells to phagocytose uric acid crystals and become activated. Colchicine also inhibits cellular proliferation which may accounts for its toxicity on gastrointestinal mucosa and bone marrow. Its effectiveness in gout was best demonstrated by Ahaern, et al in 1987 in a manuscript entitled "Does Colchicine Work" (32). In this study, the

investigators studied 43 patients with an acute episode of gout. Half were treated with colchicine and half with placebo. Clinical improvement with colchicine occurs in 64% of patients, whereas placebo induced improvement in only 23%. Improvement took 36-48 hours to occur in most patients, however, and was associated with diarrhea in 100% of patients. It is interesting to note that 36% of the patients did not respond to colchicine. Most of these unresponsive patients had gout for several days prior to beginning therapy. It is generally thought that colchicine is a very ineffective drug when used late in the course of an acute episode. The lack of a response in 30% of patients and the high toxicity have lead most investigators in this field to suggest that colchicine only rarely be used as the initial therapy in gout.

Colchicine can be used either intravenously or orally. Oral colchicine is given at a dose of .5 or .6 mgs every hour until one of three results occurs: 1; Gastrointestinal side-effects, 2; improvement in joint inflammation, 3; maximum dose of 8 to 10 mgs in 24 hours has been achieved. After treatment of an acute episode of gout, no further colchicine should be given for at least seven days. It is rapidly absorbed orally, and is excreted very slowly through hepatic, renal and intestinal routes.

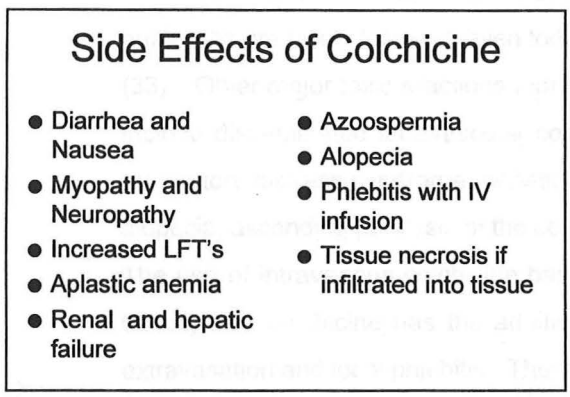

Figure 5

The side effects of colchicine therapy are listed in figure 5. Oral colchicine causes diarrhea in nearly 100% of patients. The dose of oral colchicine is titrated as described above to minimize gastrointestinal toxicity, but

eventually causes diarrhea as noted above. When used intravenously, it does not cause diarrhea, but intravenous colchicine can cause aplastic anemia. Aplastic anemia has also rarely been reported following the use of oral colchicine. In generally, however, oral colchicine induces diarrhea before patients can take sufficient colchicine to induce aplastic anemia. Review of the cases in which intravenous colchicine therapy led to aplastic anemia revealed inappropriate use of the drug in almost every case. This has lead to specific guidelines for the use of intravenous colchicine (33-36). These include:

1. The dose of colchicine should not exceed 2-3 mgs and cumulative doses for a single attack should not be more than 4-5 mgs.
2. The patient should receive no more colchicine by any route for 7 days.
3. Colchicine doses must be reduced in the presence of renal or hepatic disease, patients receiving oral colchicine prior to the attack and in older patients with apparently normal renal function.
5. Colchicine is contraindicated in combined hepatic and renal disease, creatinine clearance <10 ccs/min, and extrahepatic biliary obstruction.

A recent trial examining intravenous colchicine use suggested that these guidelines are rarely followed, even today, and suggest a need for further education (33). Other major toxic reactions that have described from intravenous colchicine include disseminated intravascular coagulation, respiratory depression and adult respiratory distress syndrome, hepatic and muscle necrosis, renal damage, fever, alopecia, ascending paralysis of the central nervous system and seizure disorders. The use of intravenous colchicine has been out-lawed in Great Britain due to its toxicity. IV colchicine has the additional danger of severe tissue necrosis with extravasation and local phlebitis. Therefore, it needs to be diluted in normal saline

without glucose and given slowly, using a dependable intravenous access.

Non-steroidal Anti-inflammatory Agents

Non-steroidal anti-inflammatory agents (NSAIDS) are the standard of care for the management of acute gout. NSAIDS have been shown to induce moderate to marked improvement in gouty symptoms in 85-90% of patients within 2 days (37-39). Although all NSAIDS are beneficial, those agents with a short half-life reach peak levels and are more rapidly effective (39). Since gout is self-limited illness, the speed at which an agent is effective is extremely important. NSAIDs inhibit prostaglandin synthesis, which plays an important role in the pathogenesis of the inflammation. Unfortunately, prostaglandins are necessary for maintenance of a gastric mucosa and are important in maintaining renal blood flow particularly under settings of abnormal renal function or compromised renal perfusion. Therefore, anti-inflammatory agents induce gastric and duodenal ulcers and can cause renal insufficiency. Patients on NSAIDs may also experience headaches, drowsiness, psychiatric reactions, as well as abnormal liver function tests and abnormalities of platelet function. The latter is critical in patients on anti-coagulants. A list of contraindications to NSAIDs are listed in figure 6. Patients with contraindications to NSAIDs should be given

Contraindications to NSAID use
• Moderate to severe renal failure • Conditions characterized by poor renal perfusion (eg. CHF or hepatorenal syn.). • Active gastric or duodenal ulcer. • Anticoagulation or Coagulopathy • NSAID or ASA hypersensitivity

Figure 6

steroids or colchicine.

Corticosteroid Therapy

Wolfson, et al introduced the use of ACTH in acute gouty-arthritis in 1949 (40). Since that time ACTH has been used by a number of investigators with success. The most dramatic report was a controlled trial comparing indomethacin with ACTH in the management of gouty episode (41). The study was limited to those individuals with an attack that had begun in the twelve hours prior to presentation. The 36 patients receiving intramuscular ACTH received forty international units. Indomethacin was given at a dose of 50 mgs four times daily. The mean interval to relief of pain was 3 hours to the ACTH group and 24 hours to the indomethacin group. There were no side-effects in the ACTH-treated group. However, of the 40 patients receiving indomethacin, 22 had abdominal discomfort or dyspepsia, 15 had headaches and 12 had difficulty with mentation. The authors concluded that ACTH was more effective and better tolerated than indomethacin. Systemic steroids have also been used to treat acute gout with significant success (42). Ten or 15 years ago, textbooks used to say that there was a high degree of relapse following steroid therapy. More recent reports, however, suggested that this is not the case. Moreover, one could undoubtedly prevent these relapses with low-dose colchicine therapy if necessary. The dose of prednisone used, varies between 20 and 40 mgs. Prednisone is generally effective in the vast majority of people. Most studies report effectiveness similar to indomethacin in that complete relief of pain and swelling in all patients is achieved about seven days after therapy begins. The pain relief and decreased swelling occurs within 24 hours. Steroids can also be injected intra-articularly. Whereas there are no control trials comparing intra-articular injection of

steroids with any other therapy, there are a number of case reports of rapid response of gout to intra-articular injection of steroids. In my experience, this is an extremely effective way of managing monarticular gout. The major advantage of steroid therapy is that there is minimal toxicity.

Treatment of the Resistant Attack

Colchicine and NSAIDs have been reported to fail in individuals with a large urate crystal load in the synovium and in those who present several days after the attack began. In these individuals, steroids, colchicine and NSAIDs may have additive anti-inflammatory effects (43). Before adding the second agent, however, coincidence joint sepsis must be ruled out. Multiple cases of septic arthritis have been reported in which urate crystals were identified in the synovial fluid. In other words, the finding of urate crystals on synovial fluid examination does not rule out septic arthritis. In those cases where septic arthritis has been ruled out and gout is thought to be intractable, combination therapy has proven successful. An algorithm is provided in figure 7 for managing acute gout.

Asymptomatic Hyperuricemia

Over the past twenty years there has been a major change in our thoughts concerning asymptomatic hyperuricemia. It is known that marked hyperuricemia associated with chemotherapy can induce renal failure. Moreover, renal function correlates quite closely with hyperuricemia and uric acid can be found deposited in the interstitium of patients with renal failure and hyperuricemia. Because of these observations, it was thought that uric acid, even at low levels could be directly toxic

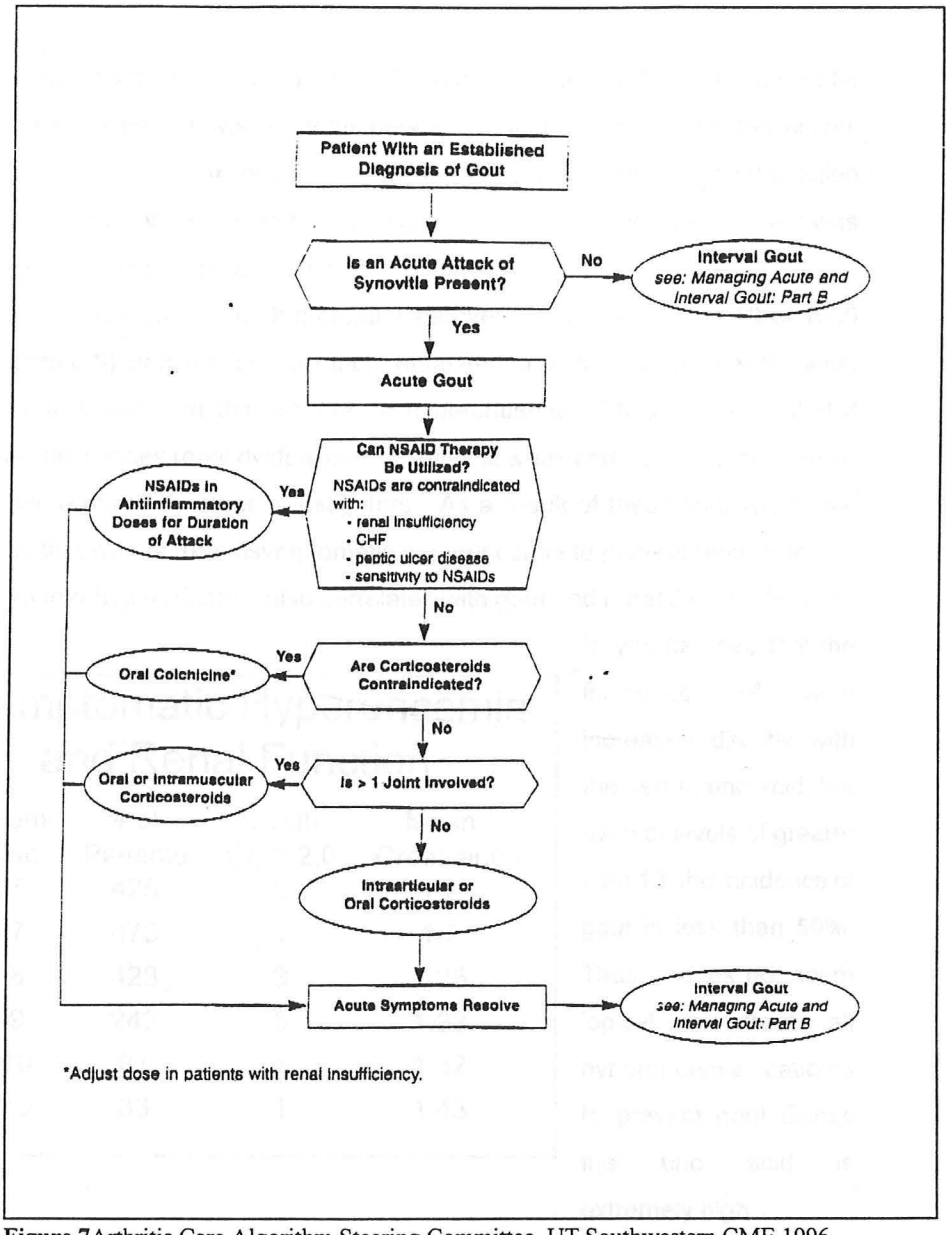

Figure 7 Arthritis Care Algorithm Steering Committee, UT Southwestern CME 1996

to the kidney. It was initially recommended that all patients with hyperuricemia be treated. More recently, however, large perspective trials have dispelled this notion. For example, in the Normative aging study (44), patients with normal renal function and hyperuricemia were followed for ten years. At the end of ten years, there was a very weak correlation between the level of initial serum urate and the final mean serum creatinine, but creatinines over 2 only occurred in 10 of 1600 patients (figure 8), and in each case there appeared to be a reasonable explanation for the renal failure that did not include hyperuricemia. Thus, it seems that if hyperuricemia causes renal dysfunction, its effect is weak and inconsistent. Similar findings were made by other investigators. As a result of these findings, it was suggested that we not treat asymptomatic hyperuricemia to prevent renal disease. It is known that hyperuricemia also correlates with gout and renal calculi. In figure 9, you can see that the incidence of gout increases directly with the serum uric acid, but even at levels of greater than 10, the incidence of gout is less than 50%. Thus, it does not seem logical to treat all hyperuricemia patients to prevent gout unless the uric acid is extremely high.

Asymptomatic Hyperuricemia and Renal Function

Serum Urate	# of Patients	# with Cr. > 2.0	Mean Creatinine
< 6	425	0	1.2
6-7	473	1	1.2
7-8	423	3	1.25
8-9	243	5	1.33
9-10	61	1	1.32
> 10	33	1	1.43

Figure 8

Renal calculi are also more prevalent in patients with hyperuricemia. The

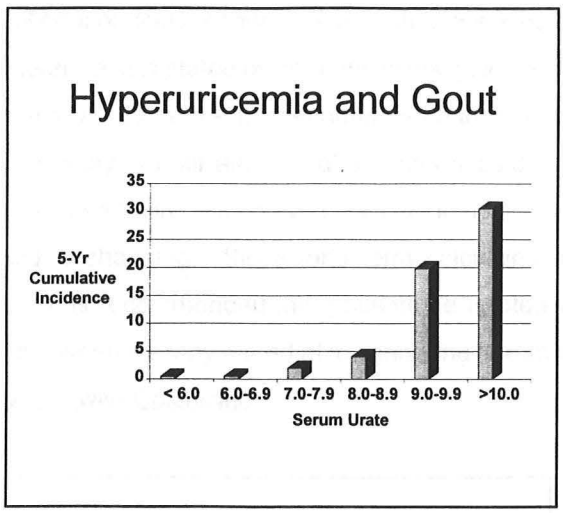

Figure 9

prevalence of renal calculi approaches 50% when the serum uric acid is greater than 12. This is particularly common in those patients with acidic urine, or when the urinary uric acid is excretion is greater than one gram for 24 hours. However, unless the uric acid is extremely high, it seems unreasonable to prevent renal calculi in patients with asymptomatic hyperuricemia. Therefore, the general recommendation is to just follow asymptomatic hyperuricemia. Unfortunately, our data is limited when the uric acid goes over 13. There simply are not enough patients who have been followed prospectively to know whether this level of hyperuricemia is damaging to kidneys. Most textbooks recommend treating hyperuricemia when it gets over 13. I would agree with this recommendation for several reasons. First, it is likely that uric acids greater than 13 are damaging to the kidney. Second, the incidence of renal calculi and gout are extremely common in this group, and it is likely that most of the patients you are treating will be spared the ravages of gout or renal calculi in the future. However, it is not unreasonable to follow patients for evidence of renal dysfunction, renal calculi or gout, even within this group of patients.

Prevention of gouty arthritis

It is said that any change in uric acid, be it up or down, can precipitate an

attack of gout or delay recovery. Although, there is no documentation of this dogma in the literature, it is stated by so many investigators in the field that is likely to have some validity. Therefore, it is recommended that treatment with uric acid lowering drugs be delayed until after an attack has subsided, and that anti-inflammatory agents be used to prevent gouty attacks at the beginning of therapy when the serum uric acid is changing. Since long term colchicine use is better tolerated than NSAIDs, it is recommended that patients be treated with "prophylactic" doses of colchicine when therapy aimed at lowering the serum uric acid level is initiated.

Prophylaxis with Colchicine

Effectiveness of Colchcine Prophylaxis

Treatment Group	Serum Urate	Attacks of Gout/Mos	% with Side effects*
Placebo + Probenecid	6.2	0.48	40
Colchicine + Probenecid	6.3	0.19	75

* None of the side effect necessitated stopping the drug

Figure 10

The use of colchicine to prevent gout was first suggested by Cohen in 1936 (45), but later evaluated in a large series of patients by Gutman and Yu in an uncontrolled retrospective study (46). In their experience, colchicine markedly diminished the frequency of gouty attacks, even in individuals not on hyperuricemia therapy when compared with pretreatment baselines. The large number of patients and the dramatic nature of the

results make the data quite convincing despite the lack of appropriate controls. The only controlled trial of colchicine as a prophylactic agent was done on a series of patients on probenecid. In a placebo controlled trial, colchicine markedly reduced the rate of recurrent gouty attacks in 20 patients compared with a placebo treated group of 18 patients (figure 10), all patients received probenecid. Despite the ability of colchicine to prevent acute gouty attacks, it is not recommended that colchicine be used as a sole agent to prevent gouty arthritis. As mentioned earlier, the national history of gout is to progress to a destructive arthritis in many patients. It is not thought that colchicine therapy effectively prevents joint destruction. Moreover, colchicine becomes less effective with increasing total body uric acid load. Therefore, while it might be effective early in the course of gout when uric acid is accumulating in the tissues, it will becomes less effective later leaving a more difficult management problem. Therefore, colchicine should be used to prevent gouty arthritis when agents that lower the serum uric acid are begun or in patients who have persistent attacks of gouty arthritis despite control of hyperuricemia. The effective dose varies between 0.5 and 1.5 mgs per day. The vast majority of patients are controlled on 1 mg of colchicine per day. At these doses, colchicine gastrointestinal toxicity is reasonably uncommon and generally responds to further dose reduction. However, an occasional patients on chronic colchicine will develop nausea, bone marrow suppression, renal failure and/or hepatic failure. Even more common, is the occurrence of a myopathy and neuropathy. This latter syndrome is characterized by proximal muscle weakness and axonal neuropathy and an elevated CPK. These findings, together with evidence of insertional activity on EMG, frequently leads to the false diagnosis of polymyositis. The syndrome responds to withdrawal of the drug. Recent evidence suggest that the syndrome is nearly always seen in patients with creatinine clearances of less than 15 mls per minute. The dose

of colchicine should, therefore, be reduced in renal failure to 0.5 or 0.6 mg/d.

Which patients require therapy to lower the serum uric acid level

One of the major questions facing the clinician is which patients should receive agents to lower the serum uric acid or to prevent gouty attacks? As mentioned earlier, the natural history of gout is that a significant percentage of patients develop destructive arthritis, and one of the goals of therapy is to prevent destructive arthritis. Therefore, any patient with evidence of destructive arthritis on x-ray or the presence of tophi requires therapy to lower the serum uric acid. Another goal of therapy, however, would be to decrease the frequency of inflammatory arthritis. Therefore, in those individuals that are having frequent attacks of gout, it seems reasonable to lower the serum uric acid.

The problem occurs in those patients with very infrequent attacks of gout or a single episode of gout. Most investigators would agree that a single episode of gout does not justify life-long therapy with urate lowering drugs. Most people would probably not be very compliant with a life-long drug for a single episode of gout. With the first episode of gout it seems wise to suggest dietary modifications, weight-loss and changing from diuretics to other forms of hypertension control. If these changes are unsuccessful and the patient has another attack within one year, it is then time to begin considering preventative therapy, which is outlined below.

Diet and Weight Reduction

It is long been known that gout is associated with obesity. Obesity alters the metabolism of uric acid by decreasing renal excretion of uric acid (20,47). Weight reduction by a low calorie diet restores uric acid secretion to normal levels (20,47). Thus, if weight loss can be accomplished, it may obviate the need for further drug

therapy.

In some cases it may be helpful to recommend low purine diets (See figure 11). Diets low in purines can reduce serum uric acid on an average of 0.5 mg per deciliter when strict adherence to the diet is observed. In general most patients will not be able to follow a strict diet and can therefore expect an even more modest change. However, in patients who are willing to change their dietary intake and who have relatively modest hyperuricemia, a low purine may be useful (22).

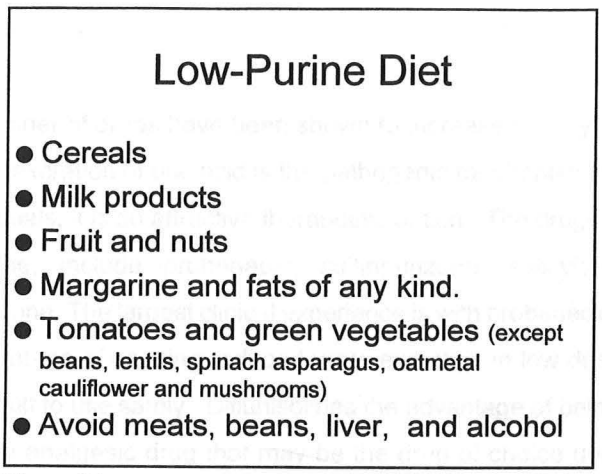

Figure 11

The final dietary modification that can ameliorate hyperuricemia is a decrease in alcohol intake. Alcohol can have a profound effect on uric acid production when used regularly and in heavy excess (14,15). If it is possible for the individual to discontinue alcohol consumption, it may eliminate the need for agents to lower uric acid levels.

Agents used to lower serum uric acid levels

From the preceeding discussion, it is clear that optimal therapy frequently involves lowering the serum uric acid. This can be accomplished by either

increasing uric acid excretion or decreasing uric acid production. I will discuss the advantages and disadvantages of each therapy first and then conclude with an algorithm designed by the Arthritis Care Algorithm Steering Committee to help physicians determine the appropriate therapy for individual patients.

Uricosuric drugs

A number of drugs have been shown to increase urinary uric acid excretion. Since underexcretion of uric acid is the pathogenic mechanism of hyperuricemia in most individuals, it is an attractive therapeutic option. The drugs currently in use for this purpose, include probenecid, sulfinpurizone, salicylate, diflunisol, and benzbromarone. The largest clinical experience is with probenecid. Salicylates have the disadvantage of causing reduced urate excretion in low doses and, therefore, can be difficult to use safely. Diflunisol has the advantage of being both a uricosuric drug and an analgesic drug that may be the drug of choice under circumstances where analgesia would be desirable. Sulfinpurizone is much more potent than probenecid on a weight per weight basis, and is more effective in patients with renal dysfunction. It also inhibits platelet aggregation.

Side effects of Probenecid

- Gastrointestinal (8%)
  - Nausea and vomiting
  - Diarrhea
- Hematologic (case reports)
  - hemolytic anemia
  - blood dyscrasias
  - Proteinuria
- Alters the metabolism of many drugs.

Figure 12

The side effects of uricosuric agents are listed in figure 12. The greatest potential risk of therapy with all of these agents is nephrolithiasis induced by enhancing uric acid excretion. For this reason, it should never be used in people whose 24 urinary uric acid excretion is greater than

800 mgs for 24 hours. The risk of nephrolithiasis is greatest in the first month. Once a steady state has been reached, urinary uric acid excretion really shouldn't be greater on these drugs than it is at baseline. During the initial month, it is recommended to both alkalinize the urine by giving sodium bicarbonate 1 gram 3 to 4 times daily, and encourage fluid intake. To further reduce the risk of nephrolithiases, the drug should be used at a low dosage, such as 250 mgs b.i.d. of probenecid and then increased monthly by 250 mgs b.i.d. until the desired serum uric acid is obtained. The drugs have few, if any, other side-effects except for non-specific gastrointestinal symptoms, and rare case reports of bone marrow and hepatic dysfunction. Although the drugs themselves have few side-effects, they do alter the metabolism of a number of other drugs, and this needs to be kept in mind when prescribing them. Because of its increased potency, sulfinpurizone carries a greater risk for nephrolithiases, I would suggest reserving it use for those people with renal dysfunction in whom probenecid has not been effective.

Allopurinol

In the early 1960's a group of investigators working for Wellcome Research Laboratories were attempting to develop new and better chemotherapeutic agents related to 6-mercaptopurine (6-MP). Several of these compounds were found to have little or no anti-tumor activity, but were found to inhibit xanthine oxidase. One of these drugs appeared biologically inert. Initial interest in the drug was in its ability to potentiate the effect of 6-MP because it blocked the degradative oxidation of the active compound (48). During studies of its effect of 6-MP metabolism and efficacy in cancer, it was found to lower serum uric acid levels. It was then tried in patients with gout and found to effectively lower serum uric acid values at doses that were

well tolerated. Allopurinol is well absorbed orally, and rapidly metabolized to oxipurinol which has the half-life of about 16 hours. Both compounds are potent inhibitors of Xanthine oxidase. Because of its longer half-life, oxipurinol accounts for the majority of the allopurinol effect. Oxipurinol is cleared from the body through the kidney, and therefore, the dose of allopurinol should be reduced in patients with renal failure. The dose of allopurinol should be based on individual needs. The general recommendation is to start at a very low dose (100 mg/day) and then titrate up until the uric acid is in the desired range. It is particularly important to start at low doses in patients with renal dysfunction. There are no controlled trials demonstrating the clinical efficacy of allopurinol compared to a placebo or to uricosuric therapy. However, there is one controlled trial comparing intermittent allopurinol with continuous allopurinol (49). The intermittent allopurinol group got two months of allopurinol per year, and after the first year of therapy the people on continuous allopurinol had significantly fewer attacks than those receiving intermittent therapy. In fact, after two years of therapy, there were no further attacks in the continuous group, while 10 of the 140 patients in the remittent group had continuous attacks. The ability of allopurinol to prevent renal stones is better documented. In one study of calcium oxalate stones in patients with hyperuricosuria and normocalcuria, allopurinol diminished the rate of renal stones by 50%. In an uncontrolled trial of 92 patients with hyperuricemia and chronic renal calculus disease, allopurinol was effective in reducing the serum uric acid to 5 mg per deciliter in all patients and eliminated a new stone formation in 63% of the cases (50). Finally, in a study done here at UT Southwestern of 21 patients with hyperuricosuria and recurrent calcium oxalate nephrolithiasis, 85% of the patients had a remission and 100% had reduced stone formation (51).

Allopurinol is generally well tolerated (see side effects listed in figure 13.

About 2% of the patients develop mild pruritic erythematous rash, which prevents further administration. This is particularly common in patients with renal dysfunction.

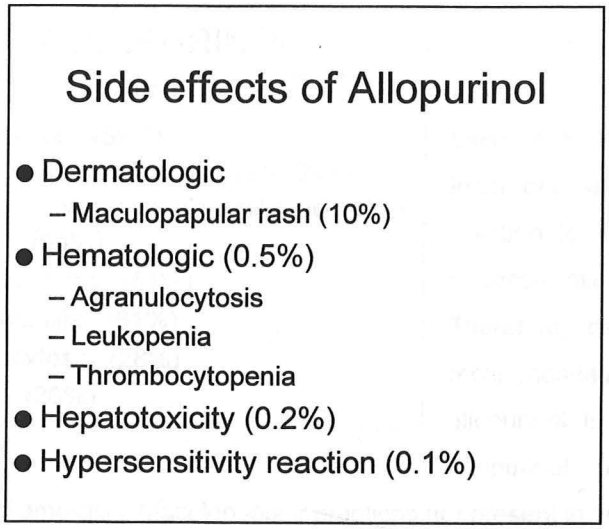

Figure 13

Some patients with a skin rash to allopurinol exhibit lymphocyte reactivity to oxipurinol (52), suggesting that the immune response may be directed at the metabolite of allopurinol, rather than in allopurinol itself. A much smaller subs et of patients, perhaps, 1 in 1400 developed a very severe hypersensitivity reaction (see figure 14) characterized by skin rash, fever, leukocytosis, eosinophilia, worsening renal function, hepatitis, and a skin rash which has resulted in death in 21% of cases (53,54). The skin rash can be characterized as either maculopapular eruption or a toxic epidermal necrolysis. The latter rash frequently places patients in the burn unit with significant morbidity and mortality. The toxicity is more likely in patients with renal dysfunction and/or hypertension on diuretics. It is unfortunate that the vast majority of the deaths attributed to allopurinol occurred in patients with asymptomatic hyperuricemia in whom therapy was not indicated.

Allopurinol toxicity is particularly troublesome in that adverse reactions to allopurinol are more common in patients with renal insufficiency in whom uricosuric agents are frequently not effective. This results in a significant percentage of

patients who are unable to take allopurinol or uricosuric agents. Recently, a number of manuscripts have suggested desensitizing patients with extremely low doses of allopurinol and working up to a therapeutic dose very slowly (55-57). While this had been effective in a number of patients, at least one patient had a severe reaction to allopurinol during the desensitization protocol (56). Therefore, desensitization is not recommended when the reaction to allopurinol is considered severe. Allopurinol also enhances the toxicity of ampicillin. Maculopapular eruptions are present in 10% of patients taking amoxicillin and allopurinol at the same time. Allopurinol can also cause mild elevations of the liver function tests and rare bone marrow toxicities. Finally, allopurinol enhances the toxicity of azathioprine and 6-MP (48,54).

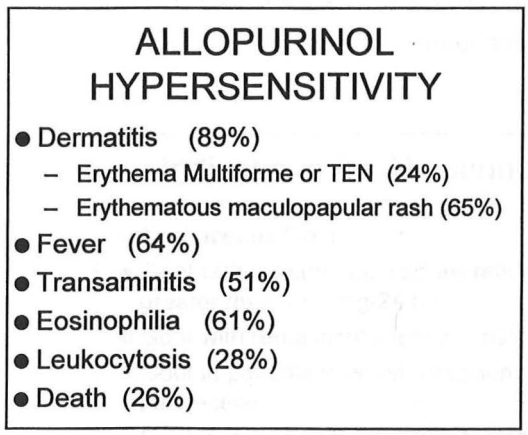

Figure 14

The toxicity of allopurinol have led most investigators to recommend that it be used only in those patients in whom uricosuric drugs could not be used or were ineffective or in those patients with tophaceous gout. The indications for allopurinol are listed in Figure 15. The algorithm in figure 16 depicts the current recommendations for preventing gouty arthritis based on the available data. **Effect of withdrawing anti-hyperuricemia drug therapy.**

When anti-hyperuricemia therapy is initiated and the attacks of gout controlled, one question that arises is how long to continue therapy. The answer to this question appears to be, for the rest of the patients' life. In one study of 21 patients with tophaceous gout who stopped therapy, 43% had recurrent tophi after a mean of 39 months and 81% had recurrent attacks of arthritis (58). Another trial compared continuous and intermittent allopurinol therapy in patients with tophaceous gout (49). The investigators noted more frequent attacks in those people on intermittent allopurinol. The data support the concept that life-long therapy is indicated.

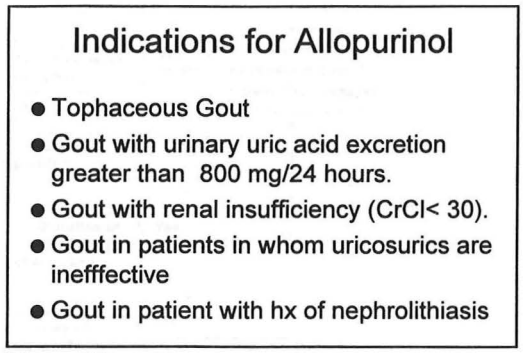

Figure 15

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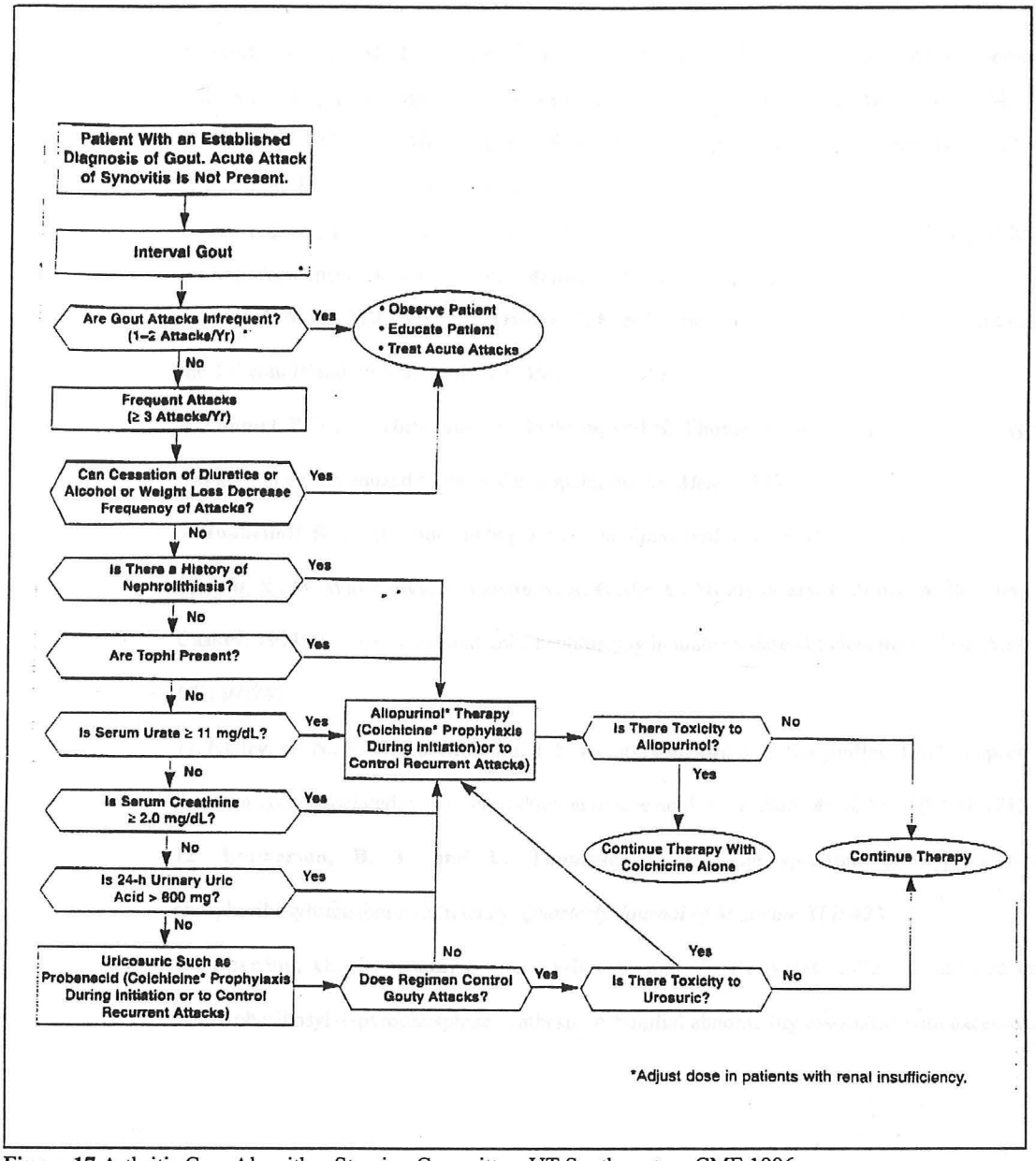

Figure 17 Arthritis Care Algorithm Steering Committee, UT Southwestern CME 1996

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