California Medicine

REVIEW ARTICLE

Gout and Gouty Arthritis

Current Concepts and Management

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GOUT IS AN ancient disease, probably the oldest medically recognized malady. Hippocrates wrote about it. Galen described tophi. Sydenham, Scudamore and Charcot gave classical accounts of the acute attacks. And Garrod, more than a hundred years ago, detected an excessive saturation of urates in blood of gouty victims.

Despite its antiquity and distinguished history, gout remained a neglected disease, both in clinical detection and investigative interest, until about 25 years ago. During recent years, however, significant advances have been made toward an understanding of its nature and in developing remarkably effective therapeutic measures for its control. Herein, an attempt will be made to summarize some of the advances that have influenced our current concepts of the disease and its practical management.

NATURE OF GOUT AND GOUTY ARTHRITIS

Gout is a genetically conditioned disorder of uric acid metabolism characterized by hyperuricemia, by the deposition of urate crystals in the tissue and by acute and chronic arthritis.

The exact incidence of gout is not known because the majority of persons with the inherited trait live normal spans of life without ever having clinical manifestations of the disease. A symptomatic hyperuricemia occurs in about 25 per cent of relatives of patients with gouty arthritis, but in only a few of these relatives eventually do overt signs of the disease ever develop. A clear distinction must be made between gout and gouty arthritis because only a fraction of those persons with persistent hyperuricemia ever have articular difficulties. Furthermore it should be emphasized that the finding of an elevated uric acid level may be entirely coincidental and that such elevations, transient or persistent, may be found in patients with other forms of rheumatic disorders, such as rheumatoid arthritis and osteoarthritis. The presence of hyperuricemia in a patient with arthritis does not necessarily mean that the joint disability is due to gout.

Gouty arthritis is by no means rare. Approximately 5 per cent of patients who attend arthritis clinics have the disease. Both gout and gouty arthritis have an overwhelming predilection for males. Roughly 95 per cent of cases occur in men. Certainly the burden of proof must be carried by the physician who makes the diagnosis of gouty arthritis in a female; and tophaceous gouty arthritis in a female is indeed a rarity. The condition respects neither race nor social level although the incidence of gouty arthritis is higher among men who are sufficiently affluent financially to indulge freely in provocatives of acute seizures.

The fundamental abnormal phenomenon in gout is hyperuricemia. The principal metabolic error producing this appears to be one of uric acid overproduction, but in some cases the crucial abnormality may consist of urate undersecretion. Investigations with radioactivity-tagged glycogen and with radioactive isotopes of substances incorporated into uric acid during its formation indicate

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that the rate of uric acid synthesis is accelerated in the majority of cases.

Excessive urate production appears to take place through two metabolic routes: (1) Endogenous biosynthesis from simple nitrogen and carbon precursors via shunt pathways that do not involve intermediate nucleic acid metabolism, and (2) excessive formation from preformed ingested nucleic acids or purines. The bulk of urate production results from endogenous synthesis, a fact that has practical therapeutic connotations since it explains why persistent hyperuricemia of substantial degree usually cannot be controlled by dietary restrictions alone.

The manifestations of chronic tophaceous gout are directly related to deranged uric acid metabolism. Clearly, they result from the supersaturation of urates in interstitial fluid and then their precipitation in such structures as joints, cartilage, bursae and renal parenchyma.

On the other hand, the pathogenesis of the acute bouts of gouty arthritis remains unsettled. In the past, urate metabolism was not considered to be involved, or, if so, only indirectly. The reasons were these: (1) Many persons with familial hyperuricemia, even though pronounced, remain asymptomatic throughout life, (2) the intravenous injection of uric acid with the production of blood levels as high as 20 mg per 100 ml does not precipitate a seizure, and (3) colchicine, which dramatically terminates most acute attacks, has no influence whatsoever on urate metabolism.

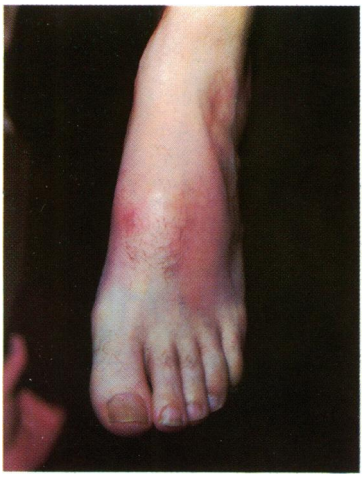
Several clues have prompted speculation that a temporary adrenocortical deficiency may be implicated in the development of acute seizures. Of the known provocatives of acute gouty arthritis, several, such as trauma, surgical operation, infection, allergic reaction, exposure to cold or heat, psychic upset and others, are stress-provoking conditions. These may produce sudden increases in adrenocortical hormone secretion and are followed by periods of decreased function, during which corticosteroids are lowered temporarily to subnormal levels. Because acute attacks are not likely to occur during stress, but rather three or four days later, they may have some relationship to depressed adrenocortical function. Such conjecture is strengthened by the fact that an episode may be relieved by the administration of adrenocortical steroids or corticotropin, and may be precipitated by the sudden withdrawal of either substance.

The popular hypothesis today is that the genesis of the acute attack depends on the fresh deposition of micro-urate crystals in the joint and that this is followed by the phagocytosis of the crystals during the ensuing inflammatory process. It is of interest that Garrod, more than a century ago, proposed that an acute attack was caused by formation of urates in the joint, but little consideration was given to his proposition. During the past few years, however, histologic evidence to support Garrod's concept has appeared. McCarty and Hollander[4] demonstrated some five years ago that urate crystals could be found in almost all gouty effusions, provided the aspirated material is viewed under the microscope with polarized light. Uniformly, such crystals are absent in the joint fluids of patients with non-gouty effusions, even when there is coincidental hyperuricemia of significant degree. Seegmiller, Howell and Malawista[7] then demonstrated that an inflammatory reaction, simulating acute gouty arthritis, could be produced regularly by injecting suspensions of microcrystalline sodium urate into the joints of gouty subjects. Furthermore, these reactions could be terminated rapidly by the intravenous administration of colchicine.

CLINICAL FEATURES

The natural history of classical gout may be divided into stages (Chart 1): In many patients with hereditary hyperuricemia signs of the disease never develop in the joints or elsewhere. Among those in whom symptoms do develop, the joint manifestations seldom appear before the age of 30 years, and more often they emerge during the fifth and sixth decades. The first clinical signs are usually those of recurrent acute arthritis. The pattern of the acute attack is distinctive and constitutes the most important criterion for diagnosis. It begins suddenly, progresses rapidly, is of relatively short duration and then retreats completely, without leaving joint residue. The frequency of occurrence in untreated cases varies with the severity. At the beginning, the bouts are characteristically separated by long, asymptomatic intervals of months or years. But later the tempo increases, bouts become more frequent and last longer (many days or weeks), and eventually recovery is not complete.

Finally, in progressive cases, the attacks are



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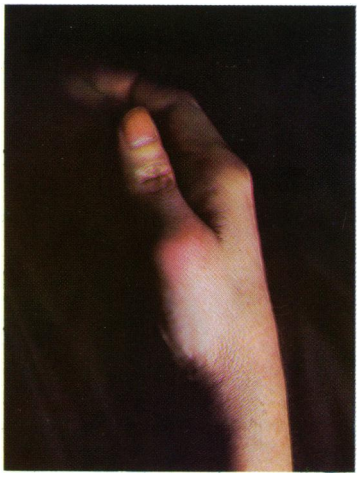

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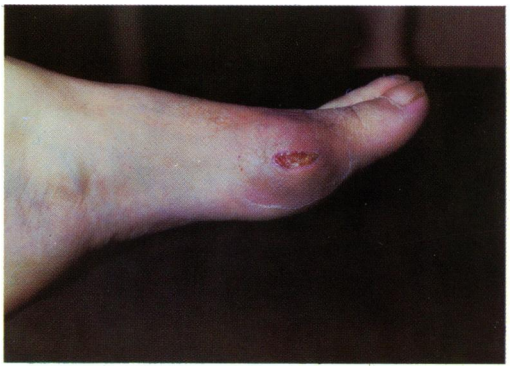

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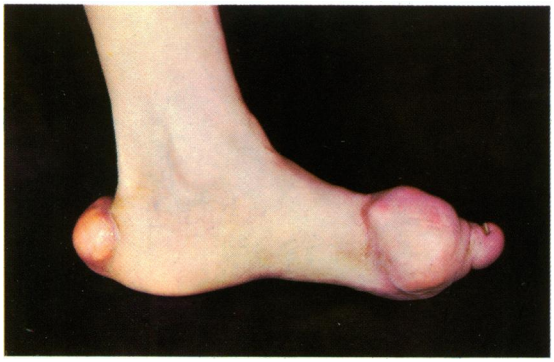

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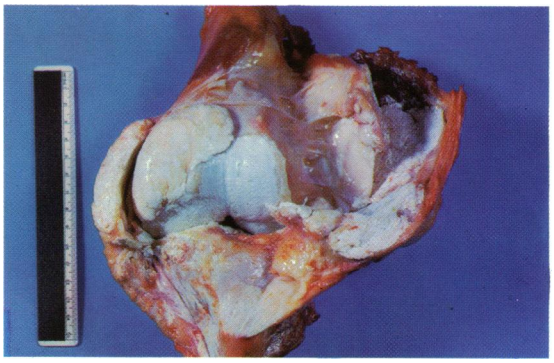

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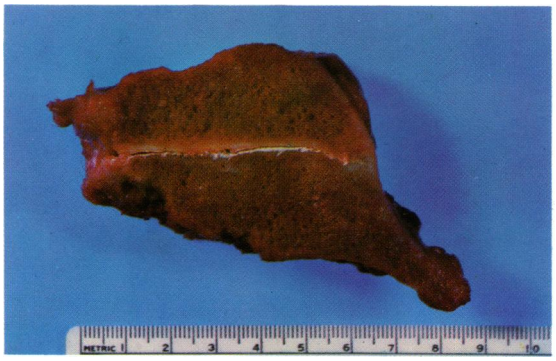

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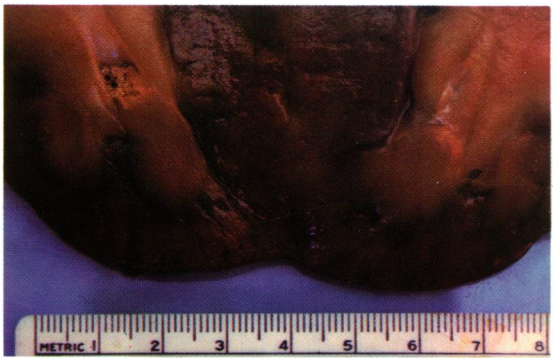

Figure 7.

Figure 1.—Acute gouty arthritis of tarsal joints.

Figure 2.—Episode of acute gouty arthritis involving metacarpophalangeal joint of thumb.

Figure 3.—Subsiding acute episode superimposed on chronic tophaceous gouty arthritis (see text).

Figure 4.—Advanced chronic tophaceous gouty arthritis.

Figure 5.—Knee joint filled with amorphous urates in severe chronic tophaceous gouty arthritis.

Figure 6.—Urates exuding from sacroiliac joint (see text).

Figure 7.—Chronic gouty nephropathy with urate deposits in pyramids.

followed by residual chronic symptoms and pathologic changes. Amorphous urates are deposited in the joints and other tissues and the stage of chronic gouty tophaceous arthritis is reached. Acute episodes are now superimposed on chronically involved joints. Uratic deposits may now have accumulated in subcutaneous, cartilaginous and renal tissues as well as in osseous and articular structures.

In the early phases, a single joint is involved, or at most two joints. Polyarthritis is rare. A bunion joint is affected at some time during the early attacks in about 65 per cent of cases, but any joint may be involved. Other favored sites include the tarsal joints (Figure 1), an ankle, knee, elbow or wrist.

The features of an acute attack are distinctive. The joint becomes sore, and within a few hours it is excruciatingly painful. The involved area is hot, swollen, dusky red and extremely tender. Early attacks, if untreated, generally last three to 14 days and then subside, but tenderness may persist for two to three weeks longer. Characteristically, complete resolution occurs, and the joint becomes normal in both function and appearance. The pattern: An acute, short-lived arthritis followed by complete restitution of function and then an asymptomatic interval. The repetition of these events—not the serum uric acid value—should be considered as the most important single criterion for diagnosis.

Acute gouty arthritis involving the metacarpophalangeal joint of the thumb is depicted in Figure 2. The joint was exquisitely painful, tender and hot. Two days after an intramuscular injection of phenylbutazone (1 gm) it appeared entirely normal. More than likely it would have responded similarly, though not as dramatically, to phenylbutazone or colchicine given orally in full dosage. This episode, like so many, began in the early morning hours. The patient was awakened with pain at three o'clock, and within a few hours the inflammatory signs were in full bloom.

A subsiding acute episode superimposed on chronic tophaceous arthritis of a bunion joint is shown in Figure 3. The referring physician misdiagnosed the condition as an infected bunion and incised the bursa. Urates were exuding from the lesion and there was desquamation of skin. The disease had progressed to a chronic stage with bursal and osseous tophi, but acute bouts still recurred.

In the advanced phases with osseous tophi, the joints become stiff, enlarged and deformed.

CLINICAL COURSE OF CLASSICAL GOUT

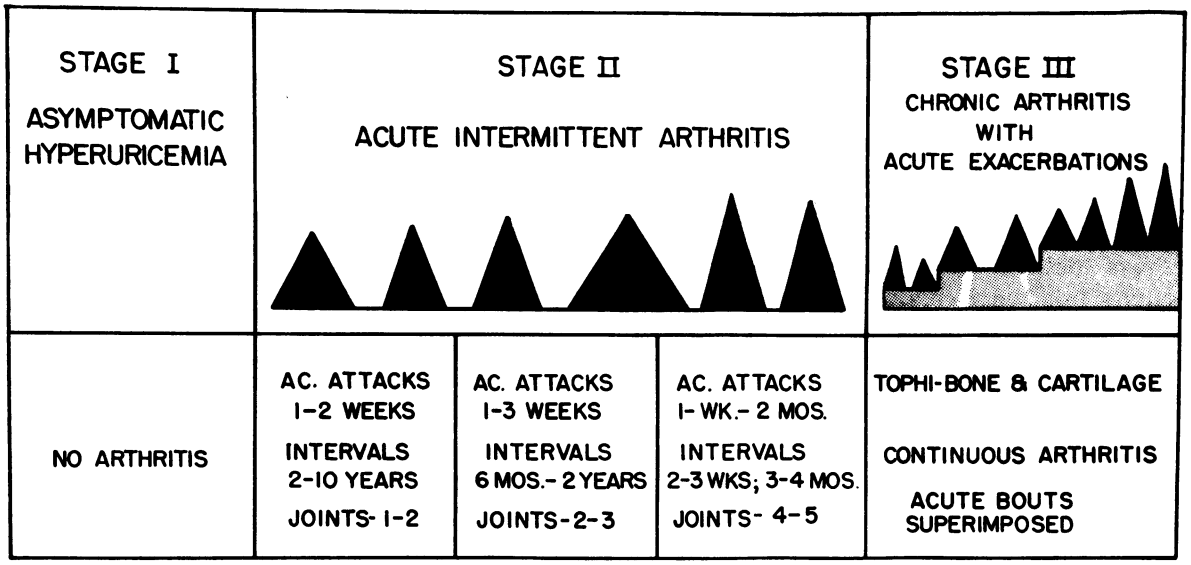

Chart 1.—Natural history of classical gout. In many patients with hereditary hyperuricemia signs of the disease never develop in the joints or elsewhere and the disease does not extend beyond Stage I. When overt signs do develop (Stage II) the first clinical signs are usually those of recurrent acute arthritis. At first acute attacks last one or two weeks, affect one or two joints and are spaced two to ten years apart. In later phases of Stage II, bouts increase in frequency, last longer, involve more joints and are spaced at shorter intervals. In progressive cases there is a step-up of the attacks, and residual chronic symptoms and pathologic changes develop (Stage III). The joints are then chronically involved but acute episodes are superimposed.

Involved joints are sore, painful on weight bearing, and no longer is there freedom from discomfort between attacks. Huge osseous and articular tophi in chronic gouty arthritis are demonstrated in Figure 4. In some cases, tophi, even of this size, will disappear entirely after prolonged uricosuric therapy, or even more surely if the uricosuric agent is employed in conjunction with an xanthine-oxidase inhibitor, such as allopurinol.

The knee joint and the bursae of a patient with severe tophaceous gout who died of renal failure and came to autopsy is shown in Figure 5. These structures were literally filled with amorphous urates.

Erroneously, it was held for years that gouty arthritis never affects the spine, but an example of sacroiliac involvement with urates exuding from the joint is shown in Figure 6. In the same patient several small posterior intervertebral or apophyseal joints in the lumbar region also contained urates in abundance, findings that should abolish the notion that gout never affects spinal articulations.

Chronic gouty nephropathy is, of course, the most serious complication of gout. Uric acid stones or gravel occur in 10 to 15 per cent of patients at some time during the course of the disease. Nephropathy, with progressive impairment of renal function, was in the past responsible for about 15 per cent of deaths in patients with chronic tophaceous disease. Uratic deposits tend to obstruct the collecting tubules and produce an interstitial reaction resembling pyelonephritis, and the tubular obstruction may actually predispose to infection. Gouty nephropathy with uratic material deposited in the pyramids is depicted in Figure 7. It is assumed that the nephropathy of gout is caused by the deposition of urates resulting from an increased filtered load of uric acid by the kidneys. Therapeutically, this is an important consideration, especially now that agents capable of inhibiting the overproduction of urates are available. In patients with nephropathy, overproduction can be curtailed and it is not necessary to rely solely on chemicals that increase uric acid excretion.

TREATMENT

For, physicians thoroughly familiar with the drugs now available, the management of gout and gouty arthritis is indeed a most gratifying medical experience. With the proper selection and use of drugs, and with close patient-physician cooperation, almost all cases of gout can be satisfactorily controlled. Like diabetes mellitus, gout varies in severity. The restrictions imposed and the medicines prescribed must be individualized, therefore, depending on the stage of the disease, its severity and extent, and the rapidity of its progress. Patients with infrequent acute attacks, interspersed with free periods lasting for many months or years, need little or no interval treatment. At the other extreme, dietary restrictions and uricosuric agents or xanthine-oxidase inhibitors are routinely indicated for patients with tophaceous gout. Treatment is not required for persons with asymptomatic hereditary hyperuricemia, but they should avoid obesity, purine-rich foods and the known provocatives of acute seizures. Today, the most common therapeutic sin —in contrast with that of 25 years ago—is one of commission, not omission. This consists in the indiscriminate treatment of a coincidental elevation of serum uric acid value. Today, the rheumatologist is too frequently faced with the necessity of undiagnosing gouty arthritis and of abandoning drugs and measures that have been prescribed without warrant on the basis of an elevated urate level alone.

Acute Gouty Arthritis

The treatment of acute gouty arthritis may be divided into two parts: Management of the seizure and the application of preventive measures during symptom-free intervals. Irrespective of the drug used, treatment should be started within a few hours of the onset of acute symptoms. The longer treatment is delayed, the more resistant and more prolonged is the episode.

Colchicine is a specific for acute gouty arthritis and remains the drug of choice of many physicians. When taken early and in full dosage, it will successfully terminate 85 to 90 per cent of attacks. The usual dosage is 0.06 mg every one or two hours until pain is relieved or until nausea or loose bowel movements, or both, ensue. The total dosage during any one course should not exceed 12 to 16 0.06 mg tablets. Frequently the tolerated and effective dose is quite constant and the patient often learns to stop the drug one or two tablets short of the amount that produces undesirable gastrointestinal symptoms. The response is usually dramatic, and within four to 12 hours the joint pain, redness and swelling and tenderness begin

to subside. Pain may be completely relieved in one to three days. Maintenance doses—one or two 0.06 mg tablets a day—should be continued for at least two to three weeks in order to prevent recurrence. For patients who for one reason or another cannot take the drug orally, colchicine may be given intravenously. If the dosage by this route does not exceed 3 mg, gastrointestinal symptoms are usually obviated. It is customary to give a second intravenous dose of two or three mg after 12 or 24 hours.

During the past few years a number of colchicine analogues have been prepared and evaluated. Of these, desacetylmethylcolchicine and trimethylcolchicinic acid are effective for acute gouty episodes and have considerably less gastrointestinal toxicity. These drugs should not be considered as satisfactory alternative agents, however, because they may bring about other side effects such as tendency to produce agranulocytosis and loss of hair.

The mode of action of colchicine is not known. It does not counteract inflammation of any other type, and it has no effect whatsoever on uric acid formation or excretion. A newly postulated theory is that colchicine relieves gouty inflammation by diminishing or interrupting the phagocytosis of urate crystals, thereby breaking the cycle of inflammatory response to freshly deposited crystals.

Phenylbutazone (Butazolidin®) is, in my experience, the most effective drug for acute gouty arthritis. It is more reliable and certainly more agreeable than colchicine. Given early in an attack and in adequate dosage, it causes the pain of acute gouty arthritis to subside dramatically within a few hours (within 24 hours in 95 per cent of attacks), and the signs of inflammation usually resolve within 48 to 72 hours. In well established attacks, when the synovitis has existed for several days, the response is slower and may not be complete for a number of days.

The usual program for administering phenylbutazone orally for an acute episode is to prescribe a large initial dose of 400 to 600 mg, followed by 200 mg every two hours for two or three doses, so that a total of 1,000 mg is given during the first 24-hour period. Beginning on the second day and continuing until the inflammation has subsided, 100 mg three to four times a day is prescribed, the frequency depending on the severity of the attack and the response. Noxious side effects, which occur so commonly with full therapeutic doses of colchicine, are not a problem with phenylbutazone. An occasional patient experiences gastric irritation from large initial doses, and in such circumstances the drug may be administered intramuscularly. Given infrequently and for short periods, such as for an acute gouty attack, phenylbutazone rarely produces toxic reactions.

The response of acute gouty arthritis to phenylbutazone given intramuscularly in a single dose of 0.5 or 1.0 gm is dramatic, almost like a parlor trick. If given early, an attack frequently may be aborted within a few hours. The intramuscular material is very handy for an episode that follows surgical operation or occurs under circumstances which preclude the oral administration of drugs.

Indomethacin (Indocin®) has analgesic and anti-inflammatory effects in acute gouty arthritis. But, to obtain results, large amounts are needed, such as an initial dose of 200 to 300 mg, followed by three or four additional doses of 100 mg each on the first day. Then 200 to 400 mg a day is required for another three to four days. In general, the response is similar to that obtained with phenylbutazone, but it has not proved to be nearly as reliable. Furthermore, many patients are simply unable to tolerate the large doses that are required for relief. Effective dosage is all to often interrupted by the occurrence of such side effects as epigastric distress, nausea, headache or dizziness.

Adrenocorticotropic hormone (ACTH) given intravenously (20 units) or intramuscularly (30 to 40 units) is capable of rapidly suppressing an acute gouty seizure but may be followed by a so-called "withdrawal attack." A large intramuscular dose of a long-acting *corticosteroid analogue,* such as 40 to 60 mg of triamcinolone acetonide (Kenalog®) or methylprednisolone acetate (Depo-Medrol®), is often effective. In stubborn cases steroids may be used advantageously in conjunction with phenylbutazone. For a refractory attack, relief may be obtained by injecting the joint locally with a long-acting corticosteroid analogue. But, in general, corticosteroids and ACTH should be considered only as adjunctive measures, to be held in reserve for the occasional case in which response to phenylbutazone or colchicine is unsatisfactory.

Interval Management

During stage II there may be periods of months or years when the patient is free of all symptoms. The length of the periods varies with the severity

of the disease, and the therapeutic measures recommended must vary accordingly. Management between attacks has two objectives: To prevent recurrences of acute episodes and to prevent chronic tophaceous changes. If the disease is mild and attacks occur no more often than every one or two years, and if they respond promptly to colchicine or phenylbutazone, then no therapy during the symptom-free periods is needed. Some experienced rheumatologists prescribe colchicine, 0.06 or 0.05 mg daily, as prophylaxis even against infrequent attacks, while others give the drug under special circumstances such as following trauma, infections, surgical operations or other stress. If attacks recur every few months, then daily maintenance doses of colchicine should be prescribed routinely.

Rigid dietary restriction is no longer necessary. The heavy ingestion of rich foods may increase urate levels and may serve as provocatives of an acute attack, but, except in mild cases, urate levels cannot be kept within normal range by dietary restrictions alone. The gouty subject synthesizes uric acid endogenously from simple chemical units of his own fat, carbohydrate and protein. Nowadays patients are asked to avoid high purine foods such as liver, kidneys, sweetbreads, sardines, anchovies, tongue and the like. Meat is usually allowed once or twice a day, depending on the severity of disease, and alcohol is usually permitted in moderate amounts.

Urate diuretic drugs are initiated under the following circumstances: (1) In all subjects with gouty arthritis who are under the age of 30 years, (2) when tophi, whether subcutaneous, osseous, cartilaginous or visceral, are present, (3) when acute attacks continue to recur frequently in spite of prophylactic doses of colchicine.

Chronic Tophaceous Gout

With the drugs now available the vast majority of patients with chronic tophaceous gout can be treated successfully. The goals of therapy are: (1) To control chronic arthritic symptoms by reducing the size of existing osseous and articular tophi, (2) to prevent or reduce the frequency of superimposed acute attacks, and (3) to prevent or decrease the tendency toward urate deposition.

Maintenance doses of colchicine (0.06 mg once or twice daily) should be given routinely in an effort to diminish the occurrence rate of acute seizures. Such doses, which are well tolerated over periods of years, should be a part of basic management and should be used in conjunction with urate diuretics when these are indicated.

Uricosuric drugs act by increasing the urinary excretion of urates, producing a state of negative urate balance and reducing the total body pool of urates, including tophaceous deposits. To be effective these drugs must be given uninterruptedly for protracted periods, perhaps for the remainder of the patient's life.

Probenecid (Benemid®) is a highly efficient uricosuric agent and is now used extensively. The dosage required to maintain the serum urate level at normal or near normal varies from 0.5 to 3.0 gm per day. In the majority of patients a daily dose of 1.5 gm is needed, but the optimum amount should be determined by serial blood level studies made at intervals of two to four weeks. Gutman and Yü[2] determined that about 10 per cent of patients need only 0.5 gm daily, 25 per cent require 1.5 to 2.0 gm daily, 50 per cent need 1.0 gm and only 15 per cent require more than 2.0 gm a day to maintain satisfactory blood urate levels. Such amounts are capable of increasing urate excretion by as much as 50 to 200 per cent, and prolonged administration usually leads to a softening, reduction in size and even disappearance of existing tophi.

The patient should drink sufficient water to insure a daily urinary output of 2,000 ml or more, since probenecid increases the chance of uric acid stones. Alkalinization of the urine is not recommended unless there is a history of urinary calculi. Salicylates counteract the action of probenecid and should not be used in conjunction with it.

Sulfinpyrazone (Anturane®), an analogue of phenylbutazone, is another highly efficient uric acid diuretic. The uricosuric action of sulfinpyrazone is well sustained over long periods of administration, and recommended dosage is from 200 to 400 mg a day, the uricosuric action of 400 mg a day being comparable to that of 1.5 to 2.0 gm or more of probenecid a day. Doses of 400 mg a day have been found to increase urate excretion by 30 to 60 per cent.[1,3] Side effects are few, and the drug may be used successfully as a substitute for probenecid in the long-term treatment of chronic gout. At times sulfinpyrazone may be the urate diuretic of choice, especially in patients who have gastrointestinal intolerance to probenecid or who experience increased frequency of acute attacks with its administration.

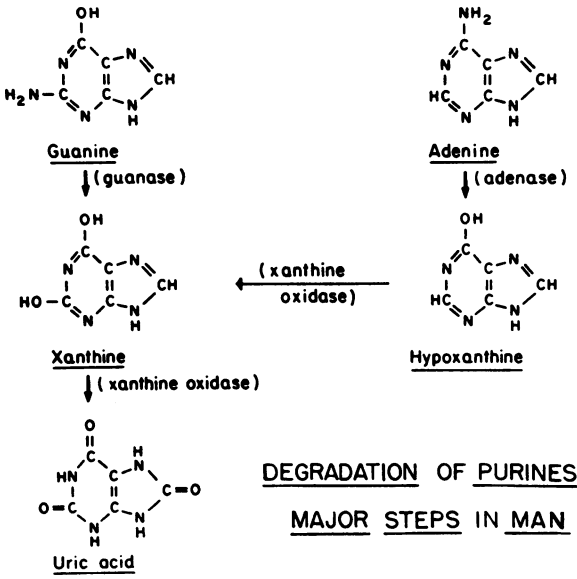

Chart 2.—Degradation of purines: major steps in man.

Allopurinol. An exciting and promising new approach to the treatment of gout has followed the discovery of allopurinol (Zyloprin®, HPP). A few years ago, during the course of investigations on the effect of thiopurines in patients with leukemia and lymphomas, it was found that allopurinol and several of its analogues reduced urate production and thereby lowered blood and urinary levels of uric acid. It followed logically to test the influence of the drug in patients with hereditary gout.

Allopurinol is actually an analogue of hypoxanthine. Its action is entirely different from that of probenecid; it lowers uric acid by interfering with the production of uric acid and does not act as a uric acid diuretic. Allopurinol is a xanthine-oxidase inhibitor. The major steps in the degradation of purines to uric acid are shown in Chart 2. The enzyme responsible for the conversion of the purines, hypoxanthine and xanthine to uric acid is xanthine-oxidase. Allopurinol inhibits the action of xanthine-oxidase, thereby reducing the conversion of purines to uric acid.

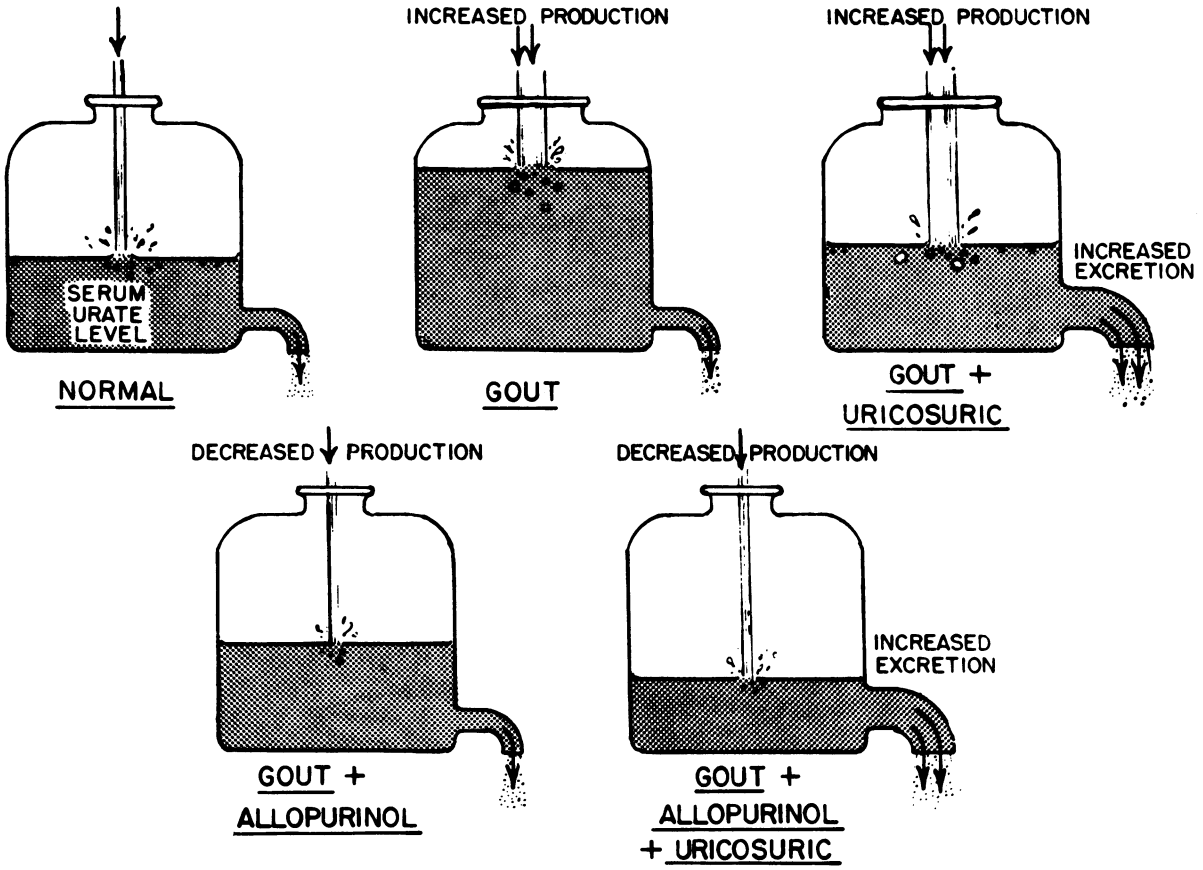

Chart 3.—Illustrating effect of allopurinol and uricosuric agents in control of both abnormalities of urate metabolism in gout—overproduction and underexcretion.

It decreases endogenous production whereas probenecid increases excretion. With its administration, uric acid levels in the blood and urine can be lowered to normal or below within a few days. They can be held there almost indefinitely, unless the disease is extraordinarily severe or kidney function is extremely impaired.

The results of large treatment series have now been reported, especially by Rundles and associates[5,6,8] at Duke University. In general, the response of patients with gout to allopurinol has been striking and the drug is tolerated very well. So far, no serious toxic effects have been encountered from allopurinol. An increased tempo of acute attacks may follow the rapid lowering of uric acid either by allopurinol or uricosuric drugs. This makes it worthwhile to start with low doses and to give colchicine concomitantly to suppress acute attacks during the early months of administration. Doses of 200 to 400 mg a day, given by mouth in divided doses, are usually sufficient to control cases of moderate disease. Rarely are doses greater than 600 mg a day required, even in the presence of urate nephropathy, which today serves as the most important indication for its use.

Allopurinol and uricosuric agents, such as probenecid or sulfinpyrazone, are effective when given together, actually complementing each other. So it now appears that at last we have arrived at a point where both abnormalities of urate metabolism in gout—namely, overproduction and underexcretion—can be therapeutically controlled (Chart 3).

GENERIC AND TRADE NAMES OF DRUGS

Phenylbutazone—*Butazolidin*
Indomethacin—*Indocin*
Adrenocorticotropic hormone—ACTH
Triamcinolone acetate—*Kenalog*
Methylprednisolone acetate—*Depo-Medrol*
Probenecid—*Benemid*
Sulfinpyrazone—*Anturane*
Allopurinol—*Zyloprin,* HPP

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