Regular Review

Long-term management of gout and hyperuricaemia

J T SCOTT

Gout may take the form either of acute gouty arthritis, seen as transient episodes of acute crystal-induced synovitis the most typical form of which is classical podagra, or of chronic tophaceous gouty arthritis with the accumulation of tophi on the fingers, ears, and elsewhere. All the manifestations of gout result from the deposition of monosodium urate in solid form from supersaturated blood and tissue fluids.

Hyperuricaemia is an essential prerequisite for the development of gout but is difficult to define. Serum concentrations of urate are not distributed normally in the population but are slightly skewed towards higher values, and in the range between 360 $\mu\text{mol/l}$ (6.0 mg/100 ml) and 450 $\mu\text{mol/l}$ (7.5 mg/100 ml) some overlap is found with both gouty and non-gouty populations. Urate concentrations are rather higher in men than in women. At 37°C serum becomes saturated with urate at about 420 $\mu\text{mol/l}$ (7.0 mg/100 ml), though higher concentrations can be sustained for long periods without evident deposition of urate, and for practical purposes hyperuricaemia may be regarded as being present at concentrations above 420 $\mu\text{mol/l}$ in men and 360 $\mu\text{mol/l}$ in women.

The mechanisms of hyperuricaemia and crystal deposition, the criteria for the diagnosis of gouty arthritis, and the treatment of the acute attack lie outside the context of this review and are discussed elsewhere.^{1 2} Two points nevertheless worth emphasising are that the presence of hyperuricaemia does not in itself establish a diagnosis of gout and that urate-lowering drugs have no value in the treatment of the acute attack.

Assessment of hyperuricaemia—Many factors may contribute to hyperuricaemia, and the more important are outlined in the table. Some, such as defined enzyme abnormalities, are rare and some, such as race or sex, are beyond therapeutic manipulation. Others, however, are not uncommon. For example, has the patient been taking a diuretic? Does examination show any evidence—splenomegaly, for example—of a proliferative disorder of the haemopoietic system, such as polycythaemia rubra vera?

Most patients with primary gout do not appear to possess a single genetic abnormality, deriving their hyperuricaemia from a number of contributory factors—namely, quantitative variations in genetically determined metabolic and renal function, whose precise nature have yet to be elucidated. To these are added in many instances the effects of external agents, particularly food (both the purine and energy content are important) and alcohol.

Furthermore, in all patients with gout, either primary or secondary to some defined single cause of hyperuricaemia, the cardiovascular and renal systems should be examined. Mild degrees of hypertension or of impaired renal function are not uncommon in many gouty patients; in some, and in young

Some of the factors which can contribute to hyperuricaemia

Increased formation of uric acid

- 1 Specific enzyme abnormalities, such as decreased activity of hypoxanthine-guanine phosphoribosyl transferase or decreased activity of phosphoribosyl pyrophosphate synthetase
- 2 Increased turnover of nucleoprotein, as in polycythaemia rubra vera and other myeloproliferative disorders
- 3 Diet (purines and energy)

Decreased excretion of uric acid

- 1 Alteration in renal function and contraction of extracellular fluid volume
- 2 Drugs, especially diuretics
- 3 Lactic acidemia
- 4 Starvation and ketosis
- 5 Essential hypertension
- 6 Lead poisoning
- 7 Hypercalcaemia

Other factors

- 1 Race, sex, and age
- 2 Genetic factors
- 3 Body weight
- 4 Social class and intelligence
- 5 Alcohol
- 6 Diabetes
- 7 Hyperlipidaemia

patients especially, these may be severe and require treatment. Necessary preliminary investigations therefore include a full blood count, examination of the urine for protein and estimation of the blood urea, as well of course as the serum uric acid. To these might be added an estimation of plasma lipids, though the significance of the association between hyperuricaemia and hyperlipidaemia, especially hypertriglyceridaemia, is not yet finally established.³

In younger patients a more refined screening of renal function is indicated, with an assessment of urinary urate excretion, which, except in patients with renal impairment, is an index of uric acid formation. This requires a 24-hour collection of urine after five days on a low-purine diet, total values over 3.6 mmol (600 mg) indicating overproduction of uric acid. Reliable data on uric acid production are said to be derivable from single midmorning measurements of serum and urinary creatinine and urinary uric acid,⁴ but this has not been generally confirmed. Overproducers of uric acid require further investigation in centres specially equipped for the detection of specific enzyme abnormalities.

Indications for lowering the serum uric acid—Nowadays the amount of uric acid in the blood can be controlled relatively easily. When an acute attack of gout has been relieved the next question is long-term management. Whether or not to lower the serum uric acid is an important decision, because once started such treatment must be continued regularly and indefinitely. Urate-lowering drugs should not be prescribed

indiscriminately: both doctor and patient must be convinced of their necessity.

Indications for lowering the serum uric acid vary slightly with individual patients, but in general treatment should be started in the following circumstances.

- (1) Gout with chronic joint changes or tophi.
- (2) Frequent acute attacks.
- (3) Gout with evidence of renal damage.
- (4) Gout accompanied by a consistently raised serum urate concentration—say, 480 $\mu\text{mol/l}$ (8.0 mg/100 ml) or over, because the disease is then usually progressive, in terms of both frequency of attacks and the development of chronic joint damage.

In the absence of these criteria, however—for example, after only one or two attacks with moderately raised serum uric acid—nothing is lost by awaiting the course of events for a while. In particular, long-term treatment should not be started when there is any doubt about the diagnosis (with the possible rare exception of the patient who attends with atypical joint symptoms in the presence of hyperuricaemia, when it may be justifiable to lower the serum uric acid for some months as a form of therapeutic trial). Such an approach is unsatisfactory, however, and ideally treatment should be deferred until things have been clarified—for example, by the detection of urate crystals in an inflamed joint. Gout is today overdiagnosed and overtreated. “Non-gout” is common, in which a patient with some sort of musculoskeletal symptom is found to have hyperuricaemia. This is then corrected by urate-lowering drugs, which in these circumstances are both unnecessary and symptomatically ineffective. “When in doubt, think of gout” remains a sound enough adage, but the less typical the presentation the less likely—by far—the diagnosis of gout and the need for urate reduction.

Urate reduction—The drug used most commonly in Britain to lower serum concentrations of uric acid is allopurinol. Allopurinol competitively inhibits the enzyme xanthine oxidase, which oxidises xanthine and hypoxanthine to uric acid, and it also suppresses overall purine biosynthesis: serum and urinary concentrations of uric acid fall rapidly and remain depressed for as long as the drug is continued.

The maintenance dose of allopurinol is that required to reduce the individual's uric acid concentration to normal: it usually lies in the region of 300 to 400 mg daily. Smaller doses may be indicated where there is renal impairment. Allopurinol produces a very rapid fall in serum uric acid, and attacks of gout in the early weeks of treatment are occasionally frequent and severe. Concurrent administration of colchicine 0.5 mg three times daily, or phenylbutazone 100 mg three times daily, or indomethacin 25 mg three times daily or some other non-steroidal anti-inflammatory agent is therefore indicated for a few months, and the patient should be warned about the possibility of acute gout. There is something to be said for starting with a daily dose of 100 mg, increasing it gradually: single daily dosage produces a sustained fall in serum urate.⁵ Eventually attacks of gout become less frequent and cease altogether, while tophi become smaller and disappear.

Apart from occasional rashes (particularly common, unfortunately, in patients with renal failure, in whom allopurinol is especially indicated) and very rare acute hypersensitivity reactions, allopurinol is a safe drug with infrequent side effects. Because of its inhibitory effect on purine biosynthesis (in addition to its action as an inhibitor of xanthine oxidase) the theoretical complication of formation of xanthine stones occurs with extreme rarity. The drug appears to increase the risk of bone marrow suppression in patients with neoplastic diseases

who are receiving chemotherapy, particularly cyclophosphamide.⁶ Crystals of xanthine and hypoxanthine have been found in biopsy specimens of skeletal muscle from patients with gout who were being treated with allopurinol,⁷ but this finding does not appear to have any clinical importance.

Because of the efficiency and acceptability of allopurinol, uricosuric agents are now used much less often than previously. These drugs lower the serum uric acid by inhibiting renal tubular reabsorption, thus increasing the urinary output. Those used therapeutically in Britain are probenecid and ethebenecid (0.5 to 1.0 g twice daily), and sulphinpyrazone (100 mg three or four times daily). The individual maintenance dose, as with allopurinol, is determined by serial estimations of serum concentrations of uric acid, which should be kept at normal levels. Uricosuric agents are usually well tolerated; dyspepsia and rashes are uncommon complications. Nephrotic syndrome has been reported with probenecid⁸ but this is extremely rare.

Salicylates are uricosuric, but the high dosage necessary for this purpose makes them generally unacceptable. At low serum concentrations they raise the plasma urate and antagonise the action of probenecid and sulphinpyrazone.

In the treatment of early uncomplicated gout there is little between allopurinol and uricosuric agents, both of which are effective in lowering the serum uric acid. One recent suggestion is that overproducers of uric acid are more “appropriately” treated with allopurinol and underexcretors with uricosuric drugs.⁹ Such an argument is superficially attractive but may be specious: most patients with gout show evidence of impaired clearance of uric acid¹⁰ but may nevertheless be managed perfectly well with allopurinol. Allopurinol is clearly indicated, however, in extensive tophaceous gout; in gout where there is known to be gross overproduction of uric acid with high urinary excretion; when uricosuric agents have failed to control serum concentrations of uric acid effectively (given, however, that the most common cause of this is failure to take tablets regularly); when uricosuric agents are poorly tolerated; in gout associated with severe renal failure, where uricosuric drugs become ineffective; when uric acid stones are present; and in acute uric acid nephropathy, in which treatment of leukaemia or reticuloses by cytotoxic drugs leads to nucleoprotein breakdown and excretion of massive amounts of uric acid.

If urate-lowering drugs are discontinued, serum concentrations of uric acid rise rapidly to pretreatment levels.¹¹ Gouty arthritis may not recur even over a prolonged period, but once a decision has been made to start treatment it should probably be continued indefinitely.

Additional measures—Severe dietary restriction is nowadays unnecessary in gout, though moderation should be recommended with regard to alcohol and high-purine foods such as sweetbreads, liver, kidney, fish roe, and tinned fish. Gouty individuals tend to be overweight and this may require attention, since reduction in weight itself lowers the serum uric acid¹² and thus corrects mild degrees of hyperuricaemia. Indeed, the patient with gout should receive advice about his whole life style insofar as he will accept it: for example, a moderate amount of exercise is almost certainly beneficial. Hypertension, if present, should be treated as necessary. The question sometimes arises of prescribing thiazide or other diuretics for patients with gout who may have incidental hypertension. These diuretics raise the serum uric acid by their action on the renal tubule, an effect which may, however, be overcome by uricosuric drugs or by allopurinol.

Asymptomatic hyperuricaemia—In these days of health screen-

ing and multichannel biochemical investigation raised serum concentrations of uric acid may be found in persons with no history of gout. The risks, such as they are, of asymptomatic hyperuricaemia have probably been exaggerated.

Prolonged hyperuricaemia certainly carries a proportionate risk of gouty arthritis, but the widely quoted data from the Framingham study,¹³ giving an incidence of 90% of persons with a serum uric acid above 540 $\mu\text{mol/l}$ (9.0 mg/100 ml) developing gout, are based on very small numbers with this degree of hyperuricaemia. Other studies have not confirmed such a high risk: for example, Fessel¹⁴ found that only three out of 66 men with such high concentrations (in whom pre-existent gout, cardiovascular and renal disease, and diabetes had been excluded) developed gout after four years. In any case, gouty arthritis can be dealt with if and when it occurs.

Rather more concern may be felt about the possible development of kidney disease, with the argument that raised serum concentrations of uric acid should be reduced because of the possibility of progressive renal failure and renal calculi. Evidence is hard to come by. The findings of a recent American survey,¹⁵ in which a large number of hyperuricaemic individuals and normouricaemic controls were followed over a period of years, indicated that azotaemia attributable to hyperuricaemia is generally mild and develops no more frequently than azotaemia in normouricaemic people. The theoretical risk is probably of no clinical importance, at least unless serum concentrations of uric acid are very high. Similarly, the risks of urolithiasis seem small and no higher in those with hyperuricaemia than in those without: in the American study¹⁵ the risk was so low, indeed, that it was considered justifiable to await the occurrence of the first stone before starting drug treatment. Nephrologists commonly treat the raised serum uric acid accompanying renal failure with allopurinol; such treatment is justifiable on the grounds that it is harmless and possibly beneficial, but in our present state of knowledge no more can be said than that.

The third problem of asymptomatic hyperuricaemia lies in its possible relation to cardiovascular disease. A link between hyperuricaemia and atheroma has been suggested in the past¹⁶⁻¹⁸ but has not been borne out by clinical experience¹⁹ or epidemiological studies.^{20 21} In the Framingham survey¹³ a relation was found between the occurrence of gouty arthritis

and signs of coronary artery disease, but on removal of patients with gout from the analysis no association between coronary disease and hyperuricaemia was apparent. Uric acid was not one of the variables found to be associated with the development of angina pectoris in the five-year study of Medalie *et al.*²² A trend towards an increased prevalence of coronary artery disease in hyperuricaemic persons was found to lack statistical significance when the factors of body weight, hypertension, and medication were taken into account.²³ In the absence of such associations hyperuricaemia does not appear to be a coronary risk factor, and there are no grounds whatever for believing that, by itself, lowering the serum concentrations of uric acid will have any effect in reducing the risk of cardiovascular disease.

How, then, should the person with asymptomatic hyperuricaemia be managed? He should certainly receive a full clinical assessment outlined in the early part of this article, as for a patient with overt gout. Very rarely indeed, however, will it be found necessary to prescribe urate-lowering drugs. I think I have only one such patient—a boy of 12 at the time whose elder brother, presenting with gouty arthritis, was found to have a partial deficiency of hypoxanthine-guanine phosphoribosyl transferase.²⁴ The younger boy was found on investigation to show a similar deficiency with gross rises of serum and urinary concentrations of uric acid: though free of symptoms and with normal renal function, he was thought to have a considerable risk of developing gout and renal calculi so that prophylactic treatment with allopurinol was thought to be justified. Uric acid concentrations have remained normal in the subsequent 10 years, and he has remained well, which might not otherwise have been the case.

Mild degrees of hyperuricaemia, at any rate, may, therefore, be observed judiciously but left untreated. Opinions differ with regard to higher concentrations of uric acid—say, about 540 $\mu\text{mol/l}$ (9.0 mg/100 ml)—but on balance such people, particularly if hyperuricosuric, should probably be given the benefit of the doubt and treated with allopurinol.

J T SCOTT

Consultant physician,
Charing Cross and West London hospitals;
Honorary physician,
Mathilda and Terence Kennedy Institute of Rheumatology

¹ Kelley WN, Weiner IM, eds. *Uric acid*. Berlin: Springer-Verlag, 1978.

² Scott JT, ed. Gout. In: *Copeman's textbook of the rheumatic diseases*. 5th ed. Edinburgh: Churchill Livingstone, 1978:647-91.

³ Scott JT. Obesity and hyperuricaemia. In: Kelly WN, ed. *Crystal-induced arthropathies. Clinics in rheumatic diseases*. Vol 3. London: W B Saunders, 1977:25-35.

⁴ Simpkin PA. Management of gout. *Ann Intern Med* 1979;90:812-6.

⁵ Brewis I, Ellis RM, Scott JT. Single daily dose of allopurinol. *Ann Rheum Dis* 1975;34:256-9.

⁶ Boston Collaborative Drug Surveillance Program. Allopurinol and cytotoxic drugs. Interaction in relation to bone marrow depression. *JAMA* 1974;227:1036-40.

⁷ Watts RWE, Scott JT, Chalmers RA, Bitensky L, Chayen J. Microscopic studies on skeletal muscle in gout patients treated with allopurinol. *Q J Med* 1971;40:1-14.

⁸ Scott JT, O'Brien PK. Probenecid, nephrotic syndrome and renal failure. *Ann Rheum Dis* 1968;27:249-52.

⁹ Boss GR, Seegmiller JE. Hyperuricaemia and gout: classification, complications and management. *N Engl J Med* 1979;300:1459-68.

¹⁰ Snaith ML, Scott JT. Uric acid clearance in patients with gout and normal subjects. *Ann Rheum Dis* 1971;30:285-9.

¹¹ Loebl WY, Scott JT. Withdrawal of allopurinol in patients with gout. *Ann Rheum Dis* 1974;33:304-7.

¹² Nicholls A, Scott JT. Effect of weight-loss on plasma and urinary levels of uric acid. *Lancet* 1972;ii:1223-4.

¹³ Hall AP, Barry PE, Dawber TR, McNamara PM. Epidemiology of gout and hyperuricaemia. A long-term population study. *Am J Med* 1967;42:27-37.

¹⁴ Fessel WJ. Hyperuricemia in health and disease. *Semin Arthritis Rheum* 1972;1:275-99.

¹⁵ Fessel WJ. Renal outcomes of gout and hyperuricemia. *Am J Med* 1979;67:74-82.

¹⁶ Dreyfuss F. The role of hyperuricemia in coronary heart disease. *Diseases of the Chest* 1960;38:332-4.

¹⁷ Eidlitz M. Uric acid and arteriosclerosis. *Lancet* 1961;ii:1046-7.

¹⁸ Hansen OE. Hyperuricemia, gout and atherosclerosis. *Am Heart J* 1966;72:570-3.

¹⁹ Grahame R, Scott JT. Clinical survey of 354 patients with gout. *Ann Rheum Dis* 1970;29:461-8.

²⁰ Hall AP. Correlations among hyperuricemia, hypercholesterolemia, coronary disease and hypertension. *Arthritis Rheum* 1965;8:846-52.

²¹ Myers AR, Epstein FH, Dodge HJ, Mikkelsen WM. The relationship of serum uric acid to risk factors in coronary heart disease. *Am J Med* 1968;45:520-8.

²² Medalie JH, Snyder M, Groen JJ, Neufeld HN, Goldbourt U, Riss E. Angina pectoris among 10,000 men, 5 year incidence and univariate analysis. *Am J Med* 1973;55:583-94.

²³ Klein R, Klein BE, Cornoni JC, Maready J, Cassel JC, Tyroler HA. Serum uric acid. Its relation to coronary heart disease risk factors and cardiovascular disease. *Arch Intern Med* 1973;132:401-10.

²⁴ Bunn DN, Moss IK, Nicholls A, Scott JT, Snaith ML, Watson MR. Clinical and biochemical observations on three cases of hypoxanthine-guanine phosphoribosyltransferase deficiency. *Ann Rheum Dis* 1975;34:249-55.