Gout

J. T. SCOTT

From the Kennedy Institute of Rheumatology and Charing Cross Hospital, London W6

The pathogenesis of gout is now well recognised as depending on sustained hyperuricaemia, leading in some cases (but only some) to urate crystal deposition and then again to the inflammatory changes of acute gouty arthritis.

Hyperuricaemia

Epidemiological studies have shown serum urate concentrations to be distributed on a normal curve, skewed towards upper values, with those of men lying above those of women. In a recent study in the United Kingdom mean concentrations were $330 \mu\text{mol/l}$ (5.5 mg/100 ml) $\pm$ SD $60 \mu\text{mol/l}$ (1.0 mg/100 ml) for men and $234 \mu\text{mol/l}$ (3.9 mg/100 ml) $\pm$ SD $48 \mu\text{mol/l}$ (0.8 mg/100 ml) for women.¹ Thus it is possible to define hyperuricaemia in statistical terms (2 standard deviations above the mean), but this presents conceptual difficulties in biological terms, especially in view of the skewed distribution. Hyperuricaemia may also be defined in physicochemical terms,² depending on the solubility of urate in plasma at 37°C of about $420 \mu\text{mol/l}$ (7.0 mg/100 ml), but here again there are uncertainties about such influences as protein binding of urate, and certainly prolonged supersaturation may exist without crystal precipitation. For practical purposes, the upper limits of normal may be taken as $420 \mu\text{mol/l}$ (7.0 mg/100 ml) for men and $360 \mu\text{mol/l}$ (6.0 mg/100 ml) for women.

Individual factors contributing to hyperuricaemia consist of (a) those associated with increased formation of uric acid (Table 1), (b) those associated with diminished excretion of uric acid (Table 2), and (c) those in which the exact nature of the association remains uncertain (Table 3). These factors have been extensively described³ and I will not discuss them further. Most patients

Table 1 Some factors associated with increased formation of uric acid

Proliferative haemopoietic disorders: —for example, polycythaemia vera
Specific enzyme abnormalities:
Increased activity PRPP synthetase
Decreased activity HGPRT (Lesch-Nyhan)
Decreased activity glucose- 6-phosphatase
Increased activity glutathione reductase
Drugs:
2-ethylamino-1,3,4-thiadiazole
Methylene blue
Fructose
Diet

Table 2 Some factors associated with diminished excretion of uric acid

Alterations in renal function and fluid volume
Drugs:
Pyrazinamide
Diuretics
Lactic acidemia:
Toxaemia of pregnancy
Exercise
Type 1 glycogen storage diseases
Alcohol
Beryllium disease
Starvation and ketosis
Essential hypertension
Lead poisoning
Hypercalcaemia
Myxoedema

Table 3 Other factors related to uric acid concentrations

Race
Sex
Body weight
Hyperlipidaemia
Intelligence and 'drive'
Mongolism
Psoriasis
Myocardial infarction
Surgery

with primary gout have a genetic tendency to hyperuricaemia (metabolic and renal) to which environmental factors such as diet, alcohol, and drugs may in some cases exert a considerable additional influence.

The management of hyperuricaemia and gout is usually a relatively easy and rewarding therapeutic exercise,⁴ the acute attack responding to colchicine or a wide range of non-steroidal anti-inflammatory drugs, and hyperuricaemia being controlled, if necessary, by uricosuric drugs or the xanthine oxidase inhibitor allopurinol. Currie reported that in general practice in the United Kingdom 45% of patients were receiving continuous treatment with allopurinol compared with only 7% receiving uricosuric drugs.⁵ The remaining 48% were taking no regular drug treatment. In this context the anti-inflammatory agent azapropazone is of some interest: it is effective in the treatment of acute gout and is also a uricosuric agent, though less powerful than probenecid⁶ (C. S. Higgins and J. T. Scott, unpublished observations). Tienilic acid emerged as another drug of great potential value⁷; this drug uniquely combines the properties of a diuretic and uricosuric agent, but it has been withdrawn from study in the United States and Britain after reports of hepatotoxicity.

The question as to whether allopurinol, by controlling urate concentrations, has any effect in preventing deterioration in renal function, is fully discussed in the important and detailed studies of Gibson and his colleagues⁸ who assessed renal function over a two year period in two groups of patients, one receiving colchicine and allopurinol, the other receiving colchicine only. No sequential change was observed in those receiving allopurinol, whereas patients receiving colchicine alone

showed a statistically significant fall in glomerular filtration rate and urine concentrating ability. Inspection of the figures, however, shows that at the onset of the study these values were higher in the colchicine group than in the allopurinol group, concentrations at one and two years closely approximating in both groups, so the question may still perhaps be regarded as open.

The problem of asymptomatic hyperuricaemia is also one of considerable current interest. Asymptomatic hyperuricaemia has been proposed as a risk factor in (a) gouty arthritis, (b) renal damage, and (c) ischaemic heart disease. There is little doubt that hyperuricaemia must predispose to the development of gout but the figures from the Framingham study,⁹ which indicated a 90% risk in men with serum urate concentrations of over 540 $\mu\text{mol/l}$ (9.0 mg/100 ml) referred to very small numbers of subjects: subsequent observations have indicated that the risk is not so great—for example, only three of 66 such subjects developing gout after four years.¹⁰ In any case, gout can be dealt with if and when it occurs. The problem of renal damage is more difficult, since hyperuricaemia may sometimes lead to the deposition of interstitial urate and renal uric acid calculi. Here again, however, the risk may not be as great as is sometimes feared. The matter is an extremely difficult one to investigate, but it is very fully discussed by Fessel,¹¹ whose studies indicated that azotaemia attributable to hyperuricaemia is generally mild and probably of no clinical importance, at least until serum urate concentrations are very high, and that the risk of urolithiasis is sufficiently low to justify awaiting the occurrence of a stone before lowering the serum urate concentration. There are conflicting findings relating to uric acid as a risk factor in coronary heart disease, but detailed studies^{12 13} indicate that hyperuricaemia is not an independent risk factor after allowing for variables of body weight, blood pressure, and diuretic usage; there is certainly no evidence that reducing the serum uric acid per se decreases the risk of coronary heart disease.

Urate crystal deposition

Table 4 lists some suggested

Table 4 *Mechanism of crystal formation*

1	Supersaturation of serum or synovial fluid with monosodium urate
2	Protein binding of urate
3	Turnover of proteoglycans
4	Temperature
5	Trauma and exercise
6	Altered hydrogen ion concentration
7	Resorption of extracellular fluid
8	Aging and avascularity

mechanisms relating to urate crystal formation. Some of these will perhaps be discussed later in the symposium, but the degree and duration of hyperuricaemia must surely be the most significant influences. This is well illustrated by our experience of a patient who developed the classical neurological features of the Lesch-Nyhan syndrome shortly after birth; diagnosis was confirmed at the age of 9 years by the demonstration of virtually complete absence of erythrocyte HGPRT.¹⁴ Serum uric acid concentration at that time and subsequently was about 720 $\mu\text{mol/l}$ (12.0 mg/100 ml) and urinary uric acid was 10.8 mmol (1800 mg)/24 hours, but for certain reasons the parents decided that he should not receive allopurinol. For 23 years his gross hyperuricaemia remained untreated

Fig. 1 Explosive onset of acute gout with tophaceous deposits in a young man with the Lesch-Nyhan syndrome after 23 years of severe asymptomatic hyperuricaemia.

without the development of any joint symptoms—or, incidentally, any deterioration in renal function or evidence of urolithiasis. Then, suddenly, there was the explosive onset of polyarticular gout with deposition of numerous subcutaneous tophi (Fig. 1), events which the parents finally accepted as sufficient indications for treatment with allopurinol. Why had multifocal urate deposition and inflammation taken place so rapidly after such a long asymptomatic period?

Acute gouty arthritis

Table 5 lists some of the events that have been proposed for the development of acute gouty arthritis. The fact that urate crystals can lie within joints without producing acute inflammation was first brought rather strikingly to my attention by the case of a man with frequently recurrent acute polyarticular gouty arthritis, in whom arthroscopy showed abundant deposits of urate in synovial membrane and articular cartilage, confirmed on biopsy. Control of serum urate concentration by allopurinol produced rapid and complete freedom from symptoms, but appearance on arthroscopy and biopsy six months later was unchanged.¹⁵ Why the urate crystals had ceased to cause inflammation is a mystery, but the studies of Malawista *et al*, who found that the inflammatory response of cells ingesting silica crystals was greater in a medium containing a high concentration of urate than in a control system,¹⁶ may have a bearing on the problem. Certainly crystals have been aspirated from the asymptomatic metatarsophalangeal joints of patients with gout,^{17 18} observations with which my colleagues and I agree.

In the evolution of gout the

Table 5 *Events in acute gout*

1	Crystallisation (or release from tophi)
2	IgG coating
3	IgG coated crystals meet Fc receptors of neutrophils
4	Phagocytosis
5	Release of lysozomal enzymes and cell lysis
6	Activation complement, Hageman factor, kinins and oxygen-derived free radicals

occurrence of acute attacks normally precedes the deposition of clinically evident tophi, usually by a matter of several years. The development of tophi in the absence of acute gout is remarkably rare. With my colleagues Drs Hollingworth and Burry, I saw five patients with such developments,¹⁹ and it was of some interest to us that four of these five patients had varying degrees of renal functional impairment, while the fifth had coexistent rheumatoid arthritis.

The rarity of acute gouty arthritis in association with chronic renal failure has been commented on from time to time; it has been thought that perhaps duration of renal disease may have been insufficient to allow crystal deposition and acute gout.²⁰ Our patients with tophi but without acute gout, however, allow speculation as to a further possibility—namely, that hyperuricaemia and crystal deposition occur in patients with renal impairment, but that the inflammatory response is inhibited. Buchanan *et al* showed that skin reactivity to intradermal or subcutaneous injection of urate crystals was depressed in patients with uraemia.²¹ Similarly, the rarity of association of gout and rheumatoid arthritis has been attributed to difference in age and sex distribution and to diagnostic difficulty, but again, it is possible that crystal deposition is taking place in rheumatoid patients with hyperuricaemia but that the inflammatory response is inhibited by factors such as alteration in protein coating,²² synovial hypocomplementaemia,²³ or diminished phagocytic function of polymorphs in the synovial fluid of patients with rheumatoid arthritis.²⁴

References

- 1 Sturge R A, Scott J T, Kennedy A C, Hart D P, Buchanan W W. Serum uric acid in England and Scotland. *Ann Rheum Dis* 1977; **36**: 420–7.
- 2 Wyngaarden J B, Kelley W N. *Gout and hyperuricaemia*. New York: Grune and Stratton, 1976: 21.
- 3 Kelley W N, Weiner I M. *Uric acid. Handbook of experimental pharmacology, Vol 51*. Berlin, Heidelberg, New York: Springer-Verlag, 1978.
- 4 Scott J T. Long term management of gout and hyperuricaemia. *Br Med J* 1980; **281**: 1164–6.
- 5 Currie W J C. The gout patient in general practice. *J Rheum Rehab* 1978; **17**: 205–18.
- 6 Dieppe P A, Doherty M, Whicher J T, Walters G. The treatment of gout with azapropazone: clinical and experimental studies. *European Journal of Rheumatology and Inflammation* 1980; **4**: 392–400.
- 7 Reardon J A, Scott J T. Controlled inpatient study of tienilic acid in treatment of gout and hypertension. *Ann Rheum Dis* 1980; **39**: 367–72.
- 8 Gibson T, Rodgers V, Potter C, Simmonds H A. Allopurinol and its effect on renal function in gout: a controlled study. *Ann Rheum Dis* 1982; **41**: 59–65.
- 9 Hall A P, Barry P E, Dawber T R, McNamara P M. Epidemiology of gout and hyperuricaemia. *Am J Med* 1967; **42**: 27–3.
- 10 Fessel W J. Hyperuricaemia in health and disease. *Semin Arthritis Rheum* 1972; **1**: 275–99.
- 11 Fessel W J. Renal outcomes of gout and hyperuricaemia. *Am J Med* 1979; **67**: 74–82.
- 12 Klein R, Klein B E, Cornoni J, Maready J, Cassel J C, Tyroler H A. Serum uric acid. Its relation to coronary heart disease risk factors and cardiovascular disease. *Arch Intern Med* 1973; **132**: 401.
- 13 Persky V W, Dyer A R, Idris-Soven E, *et al*. Uric acid: a risk factor for coronary heart disease? *Circulation* 1979; **59**: 969–76.
- 14 Bunn D N, Moss I K, Nicholls A, Scott J T, Snaith M L, Watson M R. Clinical and biochemical observations on three cases of hypoxanthine-guanine phosphoribosyltransferase deficiency. *Ann Rheum Dis* 1975; **34**: 249–55.
- 15 Scott J T. New knowledge of the pathogenesis of gout. *J Clin Pathol [Suppl]* 1978; **12**: 204–13.
- 16 Malawista S E, Van Blaricom G, Cretella S B, Schwartz M L. The phlogistic potential of urate in solution: studies of the phagocytic process in human leukocytes. *Arthritis Rheum* 1979; **22**: 728–36.
- 17 Agudelo C A, Weinberger A, Schumacher R, Turner R, Molina J. Definitive diagnosis of gout by identification of urate crystals in asymptomatic metatarsophalangeal joints. *Arthritis Rheum* 1979; **22**: 559–60.
- 18 Roualt T, Caldwell D S, Holmes E W. Aspiration of the asymptomatic metatarsophalangeal joint in gout patients and hyperuricemic controls. *Arthritis Rheum* 1982; **25**: 209–12.
- 19 Hollingworth P, Scott J T, Burry H C. Non-articular gout: hyperuricemia and tophus formation without gouty arthritis. *Arthritis Rheum* 1983; **26**: 98–101.
- 20 Sorensen C B. The pathogenesis of gout. *Arch Intern Med* 1962; **109**: 55–66.
- 21 Buchanan W W, Klinenberg J R, Seegmiller J E. The inflammatory response to injected microcrystalline monosodium urate in normal, hyperuricemic, gouty and uremic subjects. *Arthritis Rheum* 1965; **8**: 361–7.
- 22 Abramson S, Hoffstein S T, Weissman G. Superoxide anion generation by human neutrophils exposed to monosodium urate. *Arthritis Rheum* 1982; **25**: 174–80.
- 23 Hasselbacher P. Immuno-electrophoretic assay for synovial fluid C3 with correction for synovial fluid globulin. *Arthritis Rheum* 1979; **22**: 243–9.
- 24 Turner R A, Schumacher H R, Myers A R. Phagocytic function of polymorphonuclear leukocytes in rheumatic diseases. *J Clin Invest* 1973; **52**: 1632–5.