The Treatment of Gout—1967

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Gout has been known for many hundreds of years, although the modern usage of the word seems to stem from a Dominican monk, Randolphus of Bocking, Chaplain to St Richard, Bishop of Chichester (1197–1258), who referred to 'arthritis with podagra' (Copeman, 1964). Wollaston (1797) provided the first biochemical clue to the disease when he analysed a gouty tophus and discovered it to be urate. The recognition of gout as an articular manifestation of an inborn error of metabolism resulting in hyperuricaemia was due to Garrod, who demonstrated, in 1848, the excess of uric acid in the blood, and later (1863) concluded that the cause of gout was due either to increased synthesis of uric acid or its retention in the blood. Freudweiler (1899) then showed that the injection of microcrystalline sodium biurate would cause an inflammatory reaction, incidentally often producing an encapsulated lesion histologically resembling a tophus. Freudweiler later (1900) demonstrated that the injection of uric acid crystals in suspension into a joint produced an acute arthritis indistinguishable from acute gout.*

While it is true that hyperuricaemia *per se* does not necessarily cause articular gout, it is equally true that joints participating in gout have been repeatedly shown to contain urate crystals (Faires and McCarty, 1961; McCarty and Hollander, 1961; Seegmiller *et al.*, 1962).

The next development was the identification in the joint fluids of patients with an acute arthropathy of crystals that were not consistent with uric acid and were shown to be calcium pyrophosphate dihydrate (McCarty *et al.*, 1962) (i.e. 'pseudogout'). These too were found to produce an acute inflammatory response when injected into joints.

Thus, gout must be classified as a 'crystal synovitis' (Mason, 1966) or 'crystal deposition disease' (McCarty, 1966) and the diagnosis in an equivocal case may be confirmed only after finding the needle-shaped crystals in the joint fluid (Fig. 1). The uric acid crystals are ingested by, or become adherent to, the polymorphs in the joint fluid (Rajan, 1966). The polymorphs then become degranulated, and the granules have been shown to be lysosomal

* One reason why this work has been overlooked may be, as has been suggested by Brill and McCarty (1964), 'the almost unbelievable verbosity and repetition which characterised their articles'.

containing bound acid-hydrolases (Novikoff, 1962). Release of these enzymes from the lysosomes may be one factor responsible for the synovitis.

However, this does not answer the question why a hyperuricaemic in-

Fig. 1. Uric acid crystals (from a tophus)

dividual develops clinical gout, since the incidence of hyperuricaemia is far greater than that of clinical gout. Popert and Hewitt (1962) found that 13 per cent of females and 4·6 per cent of males were hyperuricaemic (above 6 mg/100 ml), although in populations of European stock only 0·5 per cent develop clinical gout (Lennane *et al.*, 1960; Popert and Hewitt, 1962). Thus, in a hyperuricaemic individual there must be a precipitating factor acting to produce gout. Similar manifestations occur in secondary hyperuricaemia due to haematological disorders and the treatment of neoplastic disease.

The essential aim in the treatment of gout must be the correction of hyperuricaemia, since any other type of therapy does not correct the fundamental abnormality.

In practice there are three situations requiring effective treatment:

1. The treatment of the acute attack.
2. Long-term care and the prevention of acute attacks.
3. The treatment of the grossly tophaceous patient.

Of these, 2 and 3 demand the correction of hyperuricaemia.

Treatment of the acute attack of gout with colchicine has been known for some 1,500 years, and it remains a specific remedy. However, it is only comparatively recently that the pathogenesis of the arthritis has been partly understood and that it has been possible to correct the basic metabolic defect of hyperuricaemia.

TREATMENT OF THE ACUTE ATTACK

The acute attack of gout, which classically affects the first metatarsophalangeal joint (podagra) demands immediate relief of pain. It is ironic that our understanding of the action of colchicine has begun when the drug has been superseded by phenylbutazone. Colchicine probably acts by stabilising the polymorphonuclear leucocyte lysosomes, thus preventing some of the release of acid hydrolases (Rajan, 1966), but it has the disadvantage that to be effective it must be given to the limit of the patient's tolerance, and distressing diarrhoea and vomiting often intervene before pain is alleviated.

Thus, phenylbutazone has become the first drug of choice in the acute attack (Kidd *et al.*, 1952; Huffman *et al.*, 1954; Mason, 1955; Gutman, 1965). In the short course necessary it has fewer immediate adverse effects and is equally effective. Gutman (1965) found that 79 per cent of acute attacks of gout were ended within 48 hours by phenylbutazone, compared with 80 per cent terminated by colchicine. Phenylbutazone (or oxyphenbutazone) 600 mg should be given on the first two days; and subsequently the dose should be rapidly tapered off. It must be noted that phenylbutazone is effective before its mild uricosuric effect is appreciable (Huffman *et al.*, 1954). However,

when there is a definite contra-indication to phenylbutazone, then indomethacin (up to 200 mg daily) is frequently effective. Failing this, colchicine 1·0 mg stat. and 0·5 mg two-hourly by mouth until gastro-intestinal effects occur or the attack abates, followed by 0·5 mg thrice daily, remains the remedy of choice. Alternatively, intravenous colchicine may be used (3 mg in 20 ml saline, given slowly and with great caution to ensure that the needle is in the vein, since colchicine is a highly irritant substance—maximum dosage 6 mg in 24 hours).

Nevertheless, some attacks of gout are resistant to any of these treatments and then, if the joint affected is accessible, aspiration and the intra-articular injection of a soluble corticosteroid derivative is always useful, and the result may be dramatic. Systemic A C T H 100 units by intramuscular injection daily has also been recommended (Gutman and Yu, 1950) but in the authors' experience is rarely, if ever, required.

LONG-TERM THERAPY

The aim of long-term therapy must be to correct the hyperuricaemia either by promoting renal excretion of uric acid or by inhibiting its synthesis. Thus, further attacks of acute gout will be prevented, and other manifestations of gout, such as the formation of tophi, either periarticular or in the soft tissues of the body, urate renal calculi, and 'gouty nephritis' may be arrested or avoided.

Renal complications of hyperuricaemia may be one of the principal factors determining the form of therapy used. It has been shown (Seegmiller and Frazier, 1966) that urinary calculi may form from uric acid crystals deposited in the renal tubules in subjects with hyperuricaemia and high urinary uric acid outputs. In gouty subjects, crystals of monosodium urate monohydrate may be found in the renal parenchyma (and in tophi) suggesting that these are in equilibrium with the vascular fluids rather than with the urine. Thus, one must determine whether an increased urinary excretion of urate in a given patient is safe; safety can usually be ensured by making the urine alkaline to increase urate solubility, and by giving a high fluid intake.

The normal renal urate clearance is 5–10 per cent of inulin and, since the uric acid concentration in glomerular filtrate equals that of plasma, this indicates that tubular reabsorption must occur (Milne, 1966). Reabsorption is mediated by active transport mechanisms but tubular secretion of urate also occurs. Yu and his colleagues (1959; 1962), from their studies of uric acid excretion and the effect of salicylates on this, concluded that the filtered urate is virtually completely reabsorbed in the proximal tubules and that urinary urate is derived from distal tubular secretion.

Uricosuric Drugs

Uricosuric drugs have been known for over fifty years. Nicolaier and Dohrn (1908) reported that Atophan (phenylquinoline) promoted an increased output of urinary uric acid and salicylates were soon found to be as effective as Atophan (Denis, 1915). Graham (1920) assumed that uric acid deposited in the tissues was in equilibrium with dissolved urate, and thus the value of uricosuric drugs was recognised. However, some of the potentially uricosuric drugs, such as phenylbutazone (Mason, 1954; Huffman *et al.*, 1954), probenecid and salicylates, have a paradoxical effect in that in a low dosage they cause retention of urate, whereas in high dosage they are uricosuric.

Phenylbutazone is uricosuric only when the plasma concentration of the drug is greater than 10 mg/100 ml; thus requiring an oral dosage of more than 600 mg/day, which is not acceptable for long-term therapy. Lower dosage produces urate retention, as occurs with small doses of probenecid infused at less than 0·4 mg/minute (Huffman *et al.*, 1954; Yu and Gutman, 1955).

Klemperer and Bauer (1944) reported that salicylates in a dosage of 5–6 G/day produced increased urate excretion due to a raised urate/inulin clearance ratio and attributed this to the inhibition of tubular reabsorption of urate. Similarly, they showed that 1–2 G/day of salicylate caused retention of urate, and this dose of salicylate abolished the uricosuric effect of probenecid when the two drugs were given together.

Yu and Gutman (1959) repeated these experiments and found that dosages of 3 G/day of salicylate or more were required to enhance uric acid excretion. The uric acid excretion was further enhanced by alkalinisation of the urine, which increased free urinary salicylate levels, or reduced by acidification of the urine, which diminished the urinary salicylate level. On the assumption that filtered urate is virtually completely reabsorbed in the tubules and that excreted urate is normally derived from tubular secretion they concluded that the latter was more sensitive to inhibition by salicylate. Thus, low concentrations of free salicylates in the urine may suppress tubular secretion only and lead to a net decrease in urinary urate, while high concentration of free salicylate suppresses both tubular secretion and reabsorption, leading to a net increase in urate excretion.

More recently Oyer *et al.* (1966) have shown that phenylbutazone can block the expected uricosuric effect of salicylates in high dosage.

Thus, in view of the paradoxical uricosuric effect of salicylates, the effect of low-dosage salicylates on probenecid, the effect of phenylbutazone on salicylate-induced uricosuria, together with the adverse effects of long-term high dosage salicylate therapy, it is probably advisable to avoid the use of any salicylate-containing preparation in the gouty subject unless one can

rely on a continued high intake. There is now no place for the age-old remedy Mist. colchicum et salicyl.

(*a*) *Probenecid* (Benemid. p-(di-*n*-propylsulphamyl)-benzoic acid) was shown in 1950 (Boger *et al.*) to increase plasma levels of penicillin and P A S. This substance, like previous benzoic acid derivatives, such as Carinamide, was later reported to be an effective and potent uricosuric agent (Bishop *et al.*, 1951b). As this finding was complementary to the view that prolonged uricosuric treatment was beneficial in gouty subjects, probenecid soon became the uricosuric drug of choice. The miscible pool of uric acid has been shown by N^{15} labelled uric acid techniques to be approximately 1·0 to 1·2 G, in the normal adult (Benedict *et al.*, 1949; Geren *et al.*, 1950; Bishop *et al.*, 1951a), but may rise as high as 31 G in gouty subjects (Benedict *et al.*, 1950). This supports the view that any method of increasing uric acid excretion is of value in gouty subjects. In 1955, Bartels published his results on probenecid therapy and concluded that gout was 'now amenable to control' with prolonged use of the drug.

Probenecid has been shown to act as an inhibitor of renal tubular activity (Bishop *et al.*, 1951b). It probably acts in the same way as high doses of salicylate, and inhibits both tubular reabsorption and secretion of uric acid, with a resultant net loss of urate. Marson (1954) compared the action of sodium salicylate with probenecid in gouty subjects and found that sodium salicylate (gr 60–120 daily) lowered the serum uric acid to 50 per cent of the pre-treatment level, whereas probenecid (2 G daily) lowered the serum uric acid to 68 per cent. Benedict *et al.* (1950) recorded a case whose miscible uric acid pool was reduced from 31 G to approximately 2 G by uricosuric doses of salicylate. Bishop and his colleagues (1951b) showed a similar effect with probenecid.

Benedict and his colleagues (1950) divided the miscible uric acid into three categories: in plasma, in non-plasma body water, and solid, as in tophi; they concluded that it was the uric acid in the solid phase that was subject to wide excursions in response to therapy. However, it has been adequately demonstrated on many occasions that uricosuric therapy lowers plasma uric acid levels. Since it is this level that determines the susceptibility of the individual to articular gout and other complications such as interstitial nephritis, uricosuric drugs have the effect of protecting the patient against these events and also reduce the body's content of uric acid contained in tophaceous deposits (Fig. 2).

Because the efficacy of salicylate is offset by the disadvantages already recorded, probenecid has become the drug of choice in uricosuric therapy, in a dosage of 0·5 G twice to four times daily. Adverse effects are not common, and

usually mild, e.g. gastro-intestinal disturbances or transient skin rashes. As with the other uricosuric drugs increased urinary uric acid concentration may, particularly in the presence of a concentrated or acid urine, lead to crystal deposition in the renal tract. Thus, renal colic, haematuria, the passage of

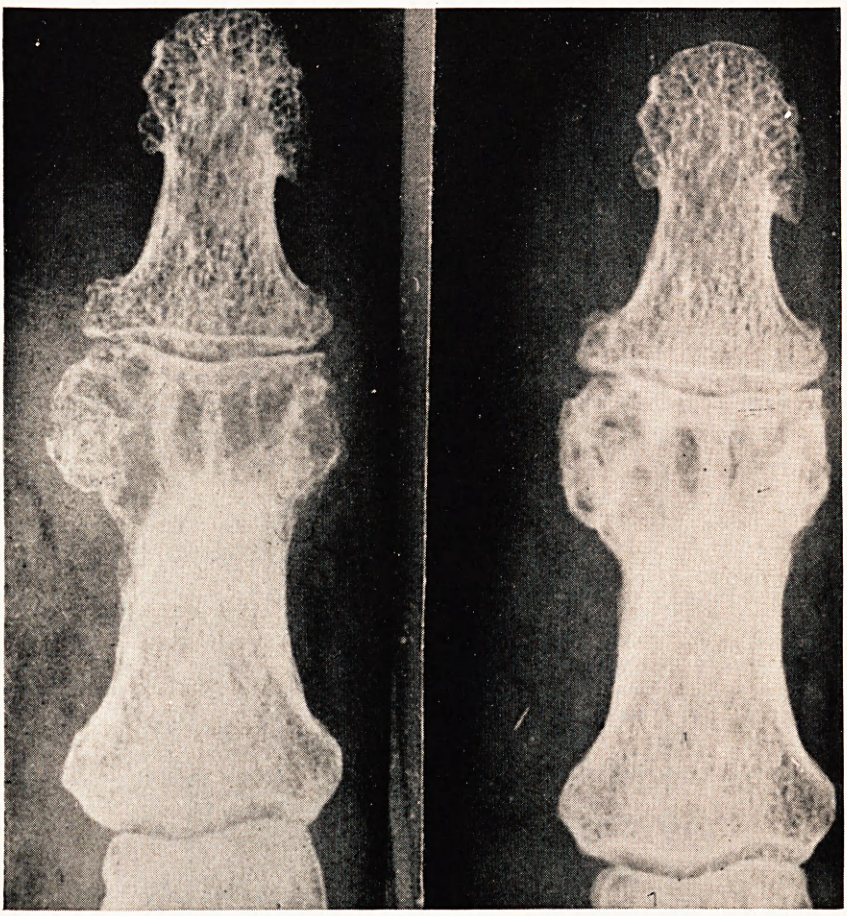

Fig. 2. Resolution of bony tophus during uricosuric therapy
(*a*) Before treatment (*b*) After eighteen months

gravel, or indeed anuria, may occasionally occur as a direct result of this therapy.

(*b*) *Sulphinpyrazone and Ethebenecid.* Other uricosuric agents have been developed. Sulphinpyrazone (Anturan) and ethebenecid (Urelim) are as effective as probenecid and much less expensive; on this basis alone one can recommend ethebenecid as the uricosuric drug of choice.

Almost immediately after probenecid was introduced in the treatment of gout it was observed that acute attacks could occur in the first few days of therapy, Fig. 3 (Mason, 1954). This may be the result of rapid mobilisation

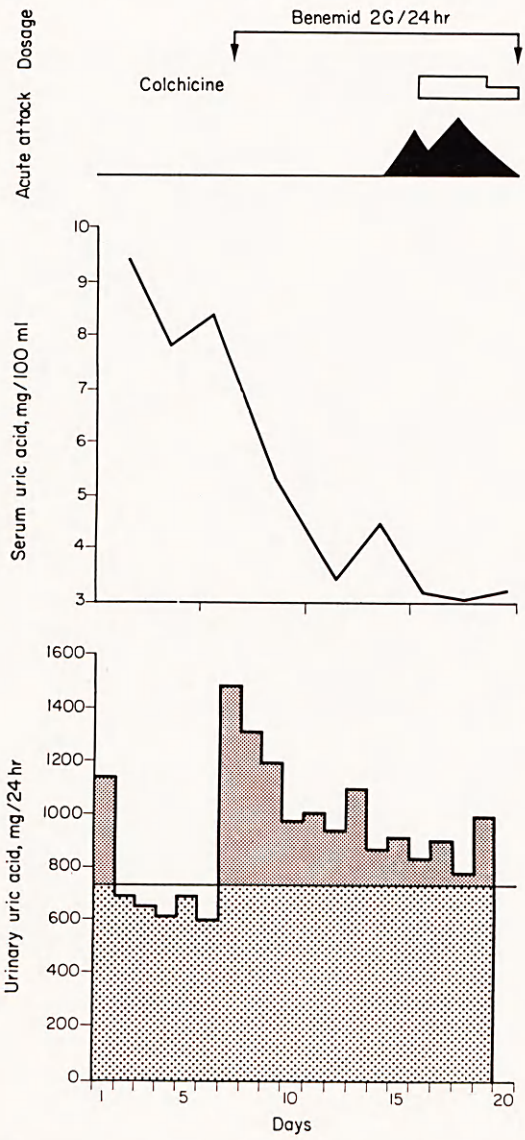

Fig. 3. Serum uric acid and urinary uric acid findings during nineteen days' observation showing acute attack following start of therapy with probenacid (Mason, 1954)

of urate in the body, probably from the 'solid phase', and for this reason uricosuric therapy should be started slowly, and combined with the prophylactic use of colchicine.

Thus, the standard, and probably most useful, treatment for the long-term care of gout is ethebenecid 1 to 2 G daily (or probenecid 1 to 2 G daily) in divided doses together with colchicine 0·5–1 mg daily. On occasions, the combined preparation of Colbenemid (colchicine 0·5 mg + probenecid 0·5 G) may be appropriate and simple. This regime will reduce the severity and frequency of acute attacks and often reduce the size of tophi.

The Inhibition of Urate Synthesis

The search for cytotoxic drugs effective in the chemotherapy of malignant disease produced a series of pyrazolopyrimidine derivatives. These were found to be ineffective (Robins, 1956) or hepato-toxic (Skipper *et al.*, 1957; Shaw *et al.*, 1960). However, some of these substances were found to inhibit xanthine oxidase activity *in vitro* and, in particular, an isomer of hypoxanthine, 4-hydroxypyrazolo-(3,4-d)-pyrimidine (allopurinol-Zyloric) (Fig. 4) was found to be both a potent inhibitor of, and a substrate for this enzyme (Lorz

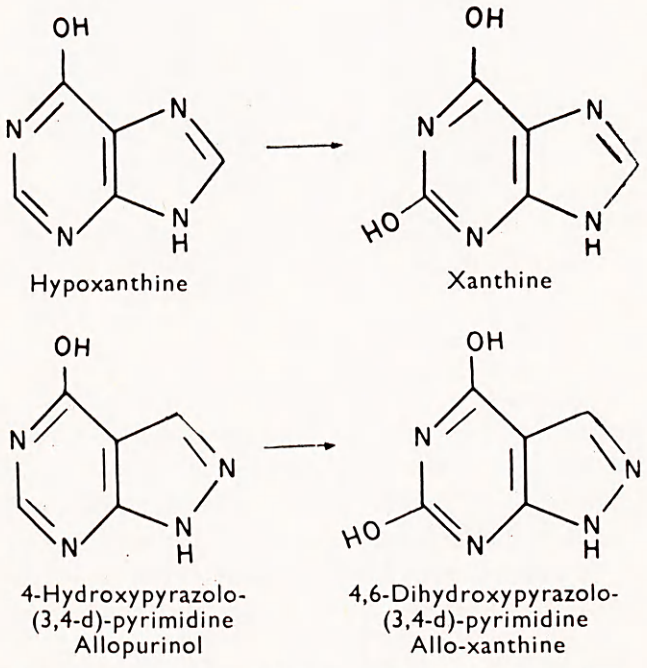

Fig. 4. Structural formula of oxypurines and oxypyrazolo-pyrimidines

and Hitchings, 1956; Elion *et al.*, 1964). Thus, allopurinol by the action of xanthine oxidase, is converted to allo-xanthine (4,6,dihydroxypyrazolo-(3,4-d)-pyrimidine) which is still a xanthine oxidase inhibitor (Elion *et al.*, 1964). This substance was then used in the treatment of leukaemia in an attempt to prevent the conversion of 6-mercaptopurine to inert 6-thiouric acid, in which reaction xanthine oxidase is effective (Rundles *et al.*, 1963; Elion *et al.*, 1963 a,b). Rundles *et al.* (1963) noted that in those patients with

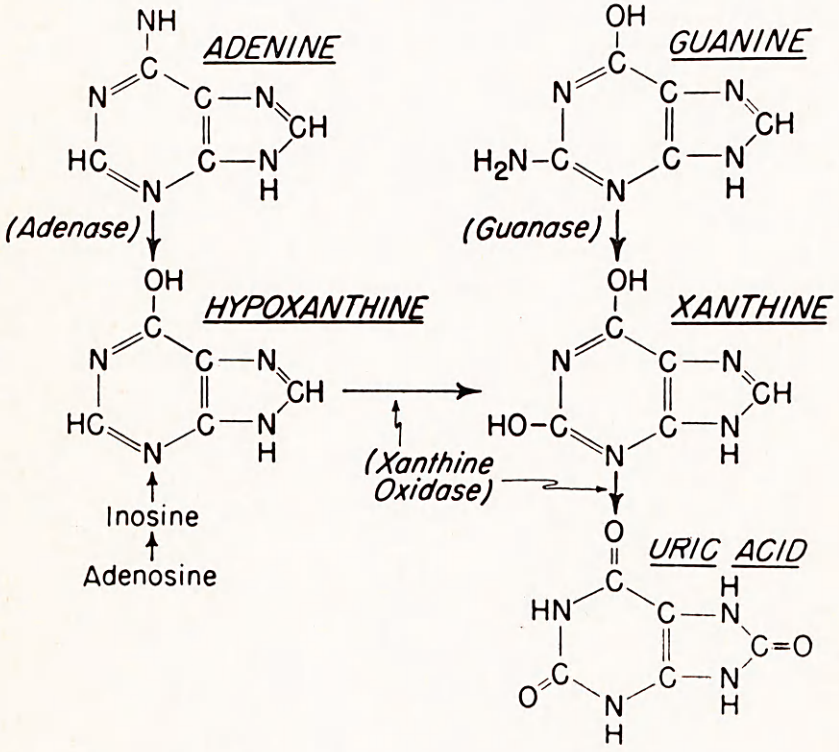

Fig. 5. Uric acid synthesis

leukaemia and hyperuricaemia treated with a combination of 6-mercaptopurine and 4-hydroxypyrazolo-(3,4-d)-pyrimidine (allopurinol), urinary and serum uric acid levels declined, an effect not obtained by the use of 6-mercaptopurine alone. This inhibition of activity is illustrated in Fig. 5.

Since then, allopurinol has been used in several series of gouty subjects (Yu and Gutman, 1964; Hall *et al.*, 1964; Rundles *et al.*, 1966: Scott *et al.*, 1966; Delbarre *et al.*, 1966; Kuzell *et al.*, 1966) and shown to be effective in the reduction of both serum and urinary uric acid, with a coincidental rise in urinary xanthine and hypoxanthine. It should be noted that the total excretion

of urate, xanthine, and hypoxanthine during allopurinol treatment may not reach the equivalent of pretreatment levels in excretion of these substances especially in the 'hyperexcretors' of uric acid (Yu and Gutman 1964; Rundles *et al.*, 1963; Rundles *et al.*, 1966; Hitchings, 1966). There is some evidence that suggests this is due to either a possible effect of allopurinol on the feed-back mechanism controlling the early reactions in urate synthesis (McCollister *et al.*, 1964), or the re-utilisation of xanthine and hypoxanthine in purine

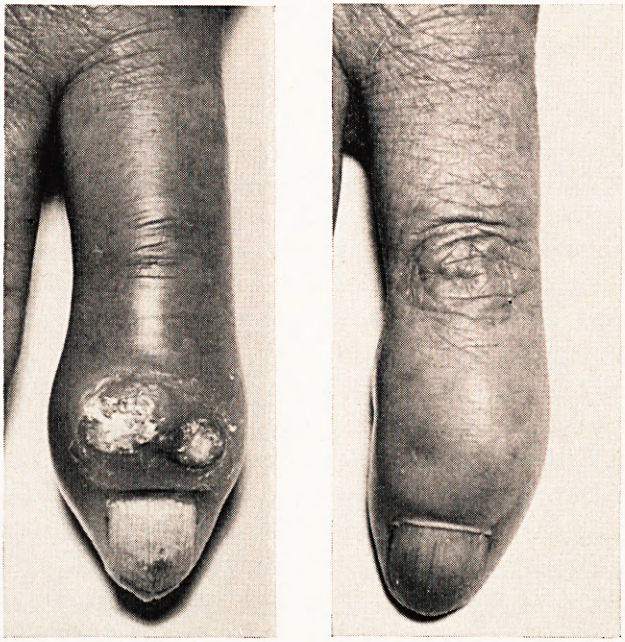

Fig. 6. Reduction in size of an ulcerated tophus during the first ten months of allopurinol therapy

synthesis (Wyngaarden and Ashton 1959; Pomales *et al.*, 1963; Pomales *et al.*, 1965; Rundles *et al.*, 1966).

Thus, mobilisation of 'solid phase' urate deposits can be achieved in addition to a reduction of urate synthesis, and urinary excretion is changed to a combination of urate and the more soluble xanthine and hypoxanthine. Hence, attacks of gout may be fewer, tophi diminished (Fig. 6) and the likelihood of urate calculi decreased, all possibilities that have been shown to be facts.

While allopurinol has not yet become the drug of choice in the treatment of gout there are seven well-defined criteria for its use:

1. Where traditional uricosuric therapy is not tolerated by the patient.
2. Where traditional uricosuric therapy has failed.
3. In the grossly tophaceous patient.
4. Where there is renal disease preventing adequate urate output.
5. The presence of calculus renal disease.
6. Secondary hyperuricaemia due to haematological disorders.
7. In patients with neoplastic disease where cytotoxic therapy or radiotherapy is proposed, with the danger of massive uric acid production and excretion. In these cases it is recommended that allopurinol should be given before cytotoxic therapy is started (Watts *et al.*, 1966; DeConti and Calabresi, 1966).

Almost identical criteria have been put forward by Scott (1966).

Allopurinol has been used in doses from 200 to 600 mg daily, but in most patients 300 to 400 mg daily in divided doses is adequate. Adverse effects are usually mild, consisting of transient skin rashes and gastro-intestinal disturbances, which resolve when the drug is stopped. Acute attacks of gout frequently follow the start of treatment with allopurinol (Rundles *et al.*, 1966) so it is a wise precaution to administer colchicine or phenylbutazone prophylactically. Liver function has been studied in patients treated with allopurinol, and Scott and his colleagues (1966) reported a rise in serum alkaline phosphatase and bromsulphthalein retention in their patients. However, this was also found in those patients treated with conventional uricosuric drugs and there was no significant difference between the two groups. Rundles and his colleagues (1966) found no evidence of liver dysfunction in an exhaustive study of forty-six patients. Powell and Emmerson (1966) reported that in animal experiments hepatic iron deposition was significantly increased and, since the enzyme xanthine oxidase is effective in iron metabolism, this raises the question of possible defects in iron metabolism arising, although none have been recorded in man (Heberden Society symposium, 1966). There have been two reported cases of bone marrow depression in patients taking allopurinol but without a definite causal relationship (Irby *et al.*, 1966). Similarly, one case of peripheral neuropathy has been reported (Glyn and Crofts, 1966).

Other hypothetical complications of allopurinol therapy may be the accumulation of the urate precursors, xanthine and hypoxanthine, the interference with other metabolic reactions, and the release of enzyme control systems so that new enzyme may be manufactured sufficiently fast for allopurinol to be ineffective. As yet, no such complications have been observed (Hitchings, 1966).

Finally, a major practical problem is the decision when to institute a

life-time of treatment aimed at the correction of hyperuricaemia. We suggest that such treatment should be undertaken if the attacks of acute gout are of sufficient frequency and severity, if the serum uric acid is greater than 8 mg/100 ml or causing systemic effects, and if tophi are present.

THE GROSSLY TOPHACEOUS PATIENT

The problem of the grossly tophaceous patient is not simply one of the prevention of attacks but also the dissolution of the large urate deposits that produce functional and cosmetic disability, and that may ulcerate and become infected. A patient with enormous deposits amounting to many grammes of urate presents a formidable problem for which the only solution used to be surgical removal of the more obvious superficial tophi. Now it is possible to use a combination of uricosuric therapy and allopurinol to promote the secretion of increased quantities of urate while simultaneously suppressing urate synthesis. By this combination many tophaceous deposits may be made smaller or even to disappear.

DIET

For many years patients with gout have been subjected to low purine diets to reduce the amount of purine metabolism and urate synthesis. It is known that high purine intake may slightly raise the serum uric acid, which may be sufficient to produce the manifestations of gout in a patient who is already mildly hyperuricaemic. Marson (1953) compared the serum uric acid levels in eight patients (seven of whom were hyperuricaemic) taking, alternately, high and low purine diets. The difference in serum acid uric on these diets varied between nil and 3·0 mg/100 ml (mean 1·3 mg/100 ml). The lowering of purine intake in an overtly gouty subject probably has little effect in comparison with that of potent uricosuric drugs and allopurinol. It is recognised that acute alcoholism produces hyperuricaemia and it still seems wise to counsel moderation in alcoholic intake, together with the obvious advice to avoid specific drinks the patient knows, from experience, will precipitate acute episodes.

CONCLUSION

The treatment of gout has made considerable advances in recent years and it is now possible to control the disease more effectively. It must be stressed that the basic object of long-term treatment is to correct hyperuricaemia. Failure of treatment is almost always due to the failure of the patient to persist with treatment when he finds himself free from attacks of acute gout. Adequate indoctrination is mandatory as an essential part of treatment.

The basic essentials in the treatment of gout may be summarised:

The Acute Attack

(*a*) Phenylbutazone is the drug of choice.
(*b*) Indomethacin is also an effective remedy.
(*c*) Colchicine is effective but its adverse effects make it less useful.
(*d*) Salicylates should be avoided in all gouty subjects.
(*e*) The resistant case may respond to intra-articular corticosteroids or intramuscular A C T H.

Long-term Care—metabolic control of hyperuricaemia is essential

(*a*) Uricosuric therapy with ethebenecid, probenecid or sulphinpyrazone combined with cholchicine as prophylaxis against acute attacks.
(*b*) Suppression of urate synthesis with the xanthine oxidase inhibitor, allopurinol, in certain cases.

The Grossly Tophaceous Patient

(*a*) Combined uricosuric therapy and allopurinol is indicated.
(*b*) Tophectomy may be required.

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