Current Practice

JOINTS AND THEIR DISEASES

Management of Gout

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It is nowadays possible to control both the inflammation of acute gouty arthritis and the level of uric acid in the blood with a facility which is considerably in advance of our understanding of some of the pathological and physiological features of the disorder. The time is long past since severe acute attacks and tophus formation progressed in the face of tedious dietary restriction. Proper handling of appropriate drugs should keep most patients entirely free of symptoms.

In making the initial assessment of a patient it must be remembered that there are many causes of hyperuricaemia. For example, has the patient been taking a thiazide diuretic, which raises the uric acid by its action on the renal tubule? Does examination show any evidence—e.g., splenomegaly—of a proliferative disorder of the haemopoietic system, such as polycythaemia rubra vera? Furthermore, in all patients with gout, either primary or secondary, examination of the cardiovascular and renal systems must not be overlooked. Mild degrees of hypertension and nitrogen retention are not uncommon in many gouty patients, and, especially in some young subjects, these may occasionally be severe and require appropriate treatment. Blood count, examination of the urine for protein, and estimation of the blood urea as well of course as the serum uric acid are therefore necessary preliminary investigations.

Apart from consideration of these possible underlying or complicating factors, the treatment of gout falls into two parts—the acute attack and long-term management.

Acute Gout

Treatment of acute gout is directed solely towards relief of inflammation as rapidly as possible. A common error is to begin immediate treatment with a uricosuric drug or allopurinol. It must therefore be emphasized that control of uric acid plays no part in the treatment of acute gout, and attempts to lower the blood level at this stage may well prolong the episode.

Three drugs are effective.

Colchicine.—This drug is best given as the 0.5 mg. tablet. Liquid tinctures or mixtures have nothing to recommend them, and there is no point in using the intravenous preparation, which has the additional disadvantage of being irritant if any escapes from the vein. The usual dose is 1.0 mg. followed by 0.5 mg. every two hours until the attack subsides. The most frequent toxic effect is diarrhoea, but this does not usually occur until a total dose of 5–6 mg. has been taken. There is considerable variation in individual sensitivity, however, and sometimes diarrhoea, nausea, or vomiting precludes the effective use of colchicine.

Phenylbutazone (Butazolidine) should be prescribed in a dose of 200 mg. four times daily until the attack is relieved. Such a dose is rather too high for the long-term treatment of other disorders such as rheumatoid arthritis, but may be safely given for a few days.

Indomethacin.—This is also useful in acute gout in a dose of 25 mg. approximately six times daily.

These three drugs can be used either alone or in combination. They should be administered as early as possible, and a known gouty patient should always keep a small supply of whichever preparation is most effective for his own particular case, so that he can abort an attack directly he notices the first symptoms.

Salicylate is less effective than these three drugs, and is therefore rarely indicated. It should be noted that colchicine and indomethacin do not alter the serum uric acid, whereas phenylbutazone and salicylate do (phenylbutazone is weakly uricosuric; salicylate causes urate retention in low dosage and is strongly uricosuric in high dosage). If there is any doubt about the diagnosis it is therefore advisable to draw blood for a uric acid estimation before any drugs are given.

Acute gout sometimes causes a sizable joint effusion, particularly in the knee. Immediate relief then is given by aspiration of the fluid followed by intra-articular injection of hydrocortisone or prednisolone. This procedure is also of diagnostic value, since microscopic examination of the fluid will demonstrate the presence of urate crystals.

Long-term Management

When the acute attack has been terminated the question of long-term management is considered, with particular reference to lowering the serum uric acid. This is a decision of some importance, because once started such treatment must be continued regularly and indefinitely. It is therefore necessary for both doctor and patient to be convinced of its necessity.

Indications for lowering the serum urate vary slightly with individual cases, but treatment should usually be commenced in one of the following situations:

- (1) Gout with chronic joint changes or tophi.
- (2) Frequent acute attacks.
- (3) Evidence of renal damage.
- (4) Gout accompanied by a considerably elevated serum uric acid—8.0 mg./100 ml. or over—because the disease is then usually progressive, in terms of both the frequency of attacks and the development of chronic joint damage.

In the absence of these criteria—following one or two attacks with only a moderately elevated uric acid—there is nothing lost by awaiting the course of events for a while. In particular, long-term treatment should not be started when there

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is any doubt about the diagnosis. A rare exception is the patient who presents with atypical joint symptoms in the presence of hyperuricaemia, when it may be justifiable to lower the uric acid for some months as a form of therapeutic trial. Such situations are very unsatisfactory, however, and such a step should not be taken before the fullest possible investigation has been carried out. Sometimes a patient with a symptom which is fairly obviously *not* due to gout—such as a frozen shoulder or osteoarthritic hip—is nevertheless subjected to an estimation of the serum uric acid. If there is coincident hyperuricaemia he may be started on urate-lowering drugs, which are then both unnecessary and symptomatically ineffective.

Related to this is the question of asymptomatic hyperuricaemia. In these days of meddlesome investigation it occasionally happens that a serum uric acid is carried out for no valid reason at all. The problem then arises what to do if the level is elevated. In our present state of knowledge it is very doubtful if asymptomatic hyperuricaemia should be treated, though of course with high values one must feel some disquiet about the possible development of joint symptoms or renal disease.

If it is decided to lower the serum uric acid this may be done with either uricosuric drugs or allopurinol.

Uricosuric Drugs

These are probenecid (Benemid), or its related compound ethebenecid (Urelim), and sulphinpyrazone (Anturan). The dose of probenecid is 0.5 g.–1.0 g. twice daily, that of sulphinpyrazone 100 mg. three or four times daily, the individual maintenance dose being determined by serial levels of serum uric acid, which should be kept at normal levels. (Normal values depend to some extent on the method used: in general the upper limit is 6.0 mg./100 ml. for men and post-menopausal women, and 5.0 mg./100 ml. for younger women.)

Uricosuric drugs act by inhibiting the renal tubular reabsorption of uric acid, thus increasing the urinary output. The effect is sustained, and, provided administration is continued regularly, attacks of gout become less frequent and eventually terminate, while tophi become smaller. In the early stages of treatment, however, acute attacks of gout may remain troublesome, and it is a good plan to prescribe concurrent treatment with an anti-inflammatory drug for a few months, such as colchicine 0.5 mg. three times daily. Uricosuric agents are usually well tolerated; dyspepsia and rashes are uncommon complications. The development of the nephrotic syndrome has been noted with probenecid, but this is extremely rare.

As noted above, salicylates are uricosuric, but the high dosage necessary makes them generally unacceptable for this purpose. With low plasma levels they actually raise the serum urate, and they also antagonize the action of probenecid and sulphinpyrazone.

Allopurinol

This drug is a powerful inhibitor of the enzyme xanthine oxidase, which mediates the oxidation of xanthine and hypoxanthine to uric acid. It therefore lowers both serum and urinary levels of uric acid.

As with uricosuric agents, the dose depends upon estimations of serum uric acid. It is usually 300 or 400 mg. daily. Allopurinol produces a very rapid fall in uric acid, and attacks of gout in the early weeks of treatment may be frequent and severe. Concurrent colchicine or phenylbutazone is therefore indicated for a few months, and the patient should be warned

of this possibility. There is something to be said for starting with a daily dose of 100 mg., increasing it gradually.

Allopurinol appears to be free of serious side-effects. The theoretical risk of xanthine stone formation has not been found to occur in gout. (It has been reported following the use of allopurinol in the Lesch–Nyhan syndrome, a rare congenital disorder of urate metabolism. Here, however, there is very gross overproduction of purines, and xanthine is not re-metabolized in the normal way.) There was also some initial concern about the possible effect of the drug upon iron metabolism, but this has not turned out to be a problem. Skin eruptions and oedema are occasionally troublesome, and unfortunately these seem particularly apt to occur in patients with renal failure, who constitute one of the groups in which allopurinol is particularly indicated.

In the treatment of early uncomplicated gout there is little to choose between the use of uricosuric agents and allopurinol, both of which are effective in lowering the serum uric acid. Allopurinol is rather more potent than uricosuric drugs, but it has been in use for a far shorter time, so that caution and prolonged observation for late effects are still necessary. There are a number of situations where allopurinol is clearly indicated, either alone or in combination with uricosuric therapy:

- (1) Extensive tophaceous gout.
- (2) Gout where there is known to be gross overproduction of uric acid with high urinary excretion. (However, estimation of urinary urate is not a necessary investigation in most patients with gout.)
- (3) Failure of uricosuric agents to control serum uric acid effectively (but the most common cause of this is failure to take tablets regularly).
- (4) Intolerance to uricosuric agents.
- (5) Gout associated with severe renal failure, where uricosuric drugs become ineffective.
- (6) Uric acid stone formation.

Other measures in gout are of secondary importance. Severe dietary restriction is unnecessary, though it is probably wise to observe moderation with regard to alcohol and high-purine foods, which include sweetbread, liver, kidney, fish-roe, and tinned fish. Gouty subjects tend to be overweight, and this may require attention, which is, however, better deferred until after the serum uric acid has been stabilized, since severe calorie restriction tends to elevate the uric acid and occasionally precipitates attacks of gout. Large tophi can be removed surgically if necessary, but again the serum urate should be satisfactorily controlled beforehand. The question sometimes arises of administering thiazide diuretics to patients with gout who may have, for example, incidental hypertension or heart disease. These diuretics raise the serum uric acid by their action upon the renal tubule: the effect can, however, be overcome by uricosuric drugs or by allopurinol.

Potassium Supplements

In the Today's Drugs article "Hypotensive Drugs—II" (17 May, p. 430) in the section on potassium depletion we stated that "resin-based tablets [of potassium chloride] may pass through the gut unchanged." Later in a footnote to a letter (12 July, p. 118) we stated that the use of the term resin-based was inaccurate. Some uncertainty seems to exist about our advice on potassium supplements, which is as follows:

Potassium supplements to diuretic therapy must be given as potassium chloride. No one preparation will suit every patient, but both wax-based tablets (Slow-K) and effervescent preparations (Kloref, Potassium-Sandoz Effervescent) are effective means of giving the drug.