GOUT

By R. M. MASON, D.M., M.R.C.P.

Assistant Physician, Department of Physical Medicine, The London Hospital

Gout represents perhaps the most satisfactory of all the rheumatic diseases. It is characterized not only by the severity of the pain of the acute paroxysm but by the complete freedom from symptoms between attacks. Morale is thus not undermined by the constant spontaneous pain experienced, for example, by the rheumatoid arthritic, whilst the dramatic nature of the acute attack and the intensity of the pain provide a co-operative patient. The diagnosis can be supported by an almost specific biochemical estimation, and if a correct diagnosis is made, full use of available drugs will enable satisfactory control of the disease to be achieved in a large proportion of cases.

The Diagnosis of Gout

It is indeed remarkable how the diagnosis of gout is often missed, and perhaps more frequently a diagnosis of gout is made where some other condition exists. This may be due to a failure to recognize the natural history of the disease, which can be conveniently considered as occurring in four stages.

Stage 1. Asymptomatic hyperuricaemia. This may precede the first acute paroxysm by a variable period and is only likely to be recognized by accident or in the asymptomatic relatives of known gouty families. It may, however, lead to error in these patients who, by chance, develop some other form of arthritis. This, in practice, is extremely rare.

Stage 2. Acute mon-articular attacks. Where, as is most commonly the case, the initial attack occurs in the first metatarso-phalangeal joint no difficulty of diagnosis should exist, but where other joints are first involved, such as the knee or wrist, considerable difficulty arises, since the characteristic discoloration of the skin may not occur in the larger joints, or if it does may suggest acute infection. The spontaneous onset, intense pain and complete remission after a brief period are all, however, suggestive features, and the exquisite tenderness with the presence of a dry skin over a hot inflamed joint is also helpful.

Stage 3. Polyarticular attacks with complete re-

missions. After a further variable period multiple joint involvement develops, also often giving rise to diagnostic difficulties. Deposits of urate now begin to develop, both clinically and radiologically.

Stage 4. Chronic gout. Progressive deposition of urate now leads to chronic gouty arthritis with clinically visible or bony tophi. Acute attacks may be superimposed on the chronic arthritis.

The rate of development from Stage 1 to Stage 4 is exceedingly variable. The patient may never indeed pass beyond Stage 2, since intervals of complete remission may last up to 63 years (Bauer, 1943) or, in severe cases, the patient may pass to Stage 4 within a very few years. The diagnosis in Stage 2 must be made in the absence of visible or radiological tophi, and is thus, primarily, clinical. It must be supported by a finding of a raised level of circulating uric acid. A definition of 'normal' depends on the laboratory technique used and whether blood, plasma or serum estimations are made. As a working rule the normal upper limit of uric acid in the blood may be taken as 4 mg. per cent. in males and 3.5 mg. per cent. in females; in the plasma or serum it is 6 mg. per cent. or 5.5 mg. per cent. respectively. It has been stated that some 20 per cent. of cases of gout have a normal reading, but an analysis of 51 readings taken when no drugs were being administered in eight random cases of undoubted gout, reveals that 12 (24 per cent.) fell below normal levels. This is not the same thing as saying that 24 per cent. of patients with gout have normal levels.

It is often stated that blood levels fluctuate with the acute attack, but there is very little data to support this, and for various reasons suitable observations are scanty. Jacobson (1938) and Mason (1951) found slight and inconstant changes only. This is of some interest in connection with the mechanism of the acute paroxysm referred to below.

Treatment of Gout

We have now available several drugs which, used separately or in combination, can provide satisfactory control of the disease. Their selection

DIAGRAM 1.—Serial blood uric acid readings in a case of gout, showing the effect of probenecid G. (fig. 1) 5/24 hours.

for the individual case leaves much scope for clinical judgment and they are of value as research tools. They may be classified as follows:

1. *Specific.* Colchicine.
2. *Uricosuric.* (a) Salicylates.
(b) Probenecid ('Benemid').
3. *Anti-inflammatory.* ACTH.
4. *Unknown.* Phenylbutazone ('Butazolidin').

1. *Specific.* Colchicine, used for some 1,500 years as a specific for the acute paroxysm of gout, remains a most valuable drug even though its mode of action continues to be quite unknown. Its main use is in Stages 2 and 3 for controlling acute attacks, given either orally in 1/60th to 1/120th gr. doses two-hourly up to maximum tolerance at the very outset of the attack and occasionally intravenously, 3 mg. in 3 ml. of sterile water (Graham and Roberts, 1953). It may also be of value as interval treatment in regular doses of 1/120th gr. once or twice daily. Such a regime may reduce the frequency of attacks and does not diminish its efficacy in the acute paroxysm. However colchicine is a mitotic poison and its use in this way

should be cautious and restricted to cases in which the frequency or the severity of the attack justifies its use.

2. *Uricosuric.* The potential value of uricosuric drugs has long been recognized, particularly since it was realized that uric acid in the solid phase might be in partial equilibrium with dissolved urate (Graham, 1920). Recent work using radioactive isotope techniques, the uric acid being labelled with N_{15} in the first and third positions, has confirmed this (Benedict *et al.*, 1950). By dilution studies these workers were able to measure the total quantity of uric acid present in the body capable of prompt mixing with the injected labelled uric acid, and they termed this the 'miscible pool.' The size of this pool in normal subjects was found to be about 1,200 mg., and this was greatly increased in gouty patients, in one case to as high as 31,019 mg. The very size of this pool suggested that some at least of the uric acid must be in the solid phase, nor was it always in direct proportion to the level of uric acid in the blood.

(a) *Salicylates.* Jennings (1937) first reported

on the value of salicylates in high dosage in causing an increase in uric acid excretion via the kidneys and lowering blood levels. He advocated, however, intermittent administration, i.e. for three or four days each week, and later Marson (1953) demonstrated that this technique is unsatisfactory since during rest periods uric acid retention occurs so that the total urate excretion over a prolonged period is unaffected by such a method. Marson advocated continuous high dosage salicylate administration in the maximum tolerated dose of 60 to 120 gr. a day indefinitely. Salicylism, which may occur early, usually disappears with reduced dosage over a brief period, after which it can again be increased. Maintenance of the blood uric acid level by this means at normal or near normal levels results, he claims, in gradual absorption of tophi (Marson, 1952) and a reduction in the frequency and severity of acute attacks.

(b) *Probenecid*. Recognition of the value of prolonged uricosuria came at much the same time as the development of a new non-toxic uricosuric substance. This followed the incidental finding that caronamide had this effect (Wolfson *et al.*, 1948; Boger *et al.*, 1950). Boger and Crosson (1950) then showed that p-(di-n-propylsulphamyl)-probenecid ('Benemid') had a still greater effect. It acts by interference with renal tubular mechanisms bringing about reabsorption of urate from the glomerular fluid. Many encouraging reports of its use have been published (Gutman and Yü, 1951; Talbott *et al.*, 1951) and Bartels (1955) was even able to entitle a paper 'Gout—now amenable to control' with the prolonged administration of probenecid. There appears to be little doubt that sodium salicylate is more effective in reducing blood levels, the average reduction being to between 60 per cent. and 70 per cent. of pre-treatment values with probenecid and to 50 per cent. with high doses of salicylate. With each drug the maximum fall is observed within a few days and this is usually followed by a slight rise (see Diagram 1), the early fall never being quite maintained. Intolerance occurs in about 30 per cent. of cases and is usually mild. This consists commonly of sensitivity with an urticarial rash or nausea; both usually disappear with reduced dosage. Urate stones are a possibility in view of the uricosuria and a high fluid intake maintaining an alkaline urine is a wise precaution. A curious and interesting observation is the frequent occurrence of acute attacks at the outset of treatment. Gutman and Yü (1951) found that this occurred in six of 18 cases treated with probenecid 2 g. daily, acute attacks developing within the first few days. This observation has been confirmed by Mason (1954) who pointed out that these attacks can regularly occur at a time when the blood level has

DIAGRAM 2. Effect of probenecid ("Benemid") G. 2/24 hrs., in a case of gout, showing the fall in serum uric acid levels with acute attacks occurring when the serum uric acid had been reduced to normal levels.

been brought to normal for the first time, perhaps, for years. Such a case is illustrated in Diagram 2. The general experience, however, seems to be that the likelihood of these attacks tends to pass off after the first few weeks. They can usually be avoided by starting the patient on small doses of probenecid at first.

It is interesting to speculate why these attacks occur, and it may be that if this could be elucidated we should be nearer an understanding of the acute attack. Of interest in this connection are the

findings of Benedict *et al.* (1952). Shemin and Rittenberg (1947) had demonstrated that glycine can be responsible for the nitrogen in the seventh position in uric acid in man, and Benedict and her co-workers were therefore able to identify the uric acid than in normals, and they suggest this source following the administration of isotopic glycine. They produced some evidence that in some gouty subjects there exists a more rapid mechanism for the transformation of glycine into uric acid than in normals, and they suggest that may be via a different metabolic route. Is it possible, therefore, that it is an abnormal precursor of uric acid which is responsible for the acute attack? This would account for the discrepancy between the inactive tophus, where uric acid appears inert, and the intense inflammatory reaction surrounding the site of an attack. It may also account for the lack of correlation referred to between the acute attack and changes in the blood levels and it may be at this point that colchicine acts.

Whatever the significance of these observations they do demonstrate for the first time a clear association between changes in uric acid levels and the acute attack, and it is curious that this should be in the reverse direction to that which would have been anticipated.

No mention need now be made of cinchophen ('Atophan') which is a potentially lethal drug and is entirely replaced by salicylates or probenecid. So far as the writer is aware there is now no indication for cinchophen in medicine.

3. *ACTH*. There are many reports of the striking effect of ACTH administration in acute gout (Hellman, 1949; Margolis and Caplan, 1950; McEwen and Bunim, 1950; and many others). Initial reports which suggested that ACTH administration and sharp withdrawal might precipitate an attack of gout have not been confirmed, but it is probably wise to continue ACTH administration until the attack period is over, and it may be necessary to cover ACTH withdrawal by colchicine administration. The use of ACTH to precipitate an attack as a diagnostic measure has not proved of value.

4. *Phenylbutazone*. There is general agreement that phenylbutazone ('Butazolidin') is of value in acute gout. Its effect is often rapid (Kuzell *et al.*, 1952; Kidd *et al.*, 1952) although its mode of action is obscure. It is a mild uricosuric agent (Mason, 1954; Huffman *et al.*, 1954), but this, as already mentioned, is not associated with effectiveness in acute attacks and its clinical effect occurs before any uricosuric action could have taken place, since this requires a fairly high (10 mg. per cent.) blood level. Whether this is due to an anti-inflammatory action (if it has such an effect), or is

purely analgesic or is due to some unknown action on uric acid metabolism remains obscure. It is, nevertheless, often useful where colchicine fails and if ACTH is not convenient. For chronic gout phenylbutazone is also helpful, although the potential dangers place it below the salicylates and probenecid, which should be tried first. It is, however, undoubtedly a useful addition to the therapeutic armory.

Conclusions

With these drugs available there is no doubt that we are now in a position to provide adequate control of the disease in many cases. Colchicine remains the drug of choice for occasional episodes in Stage 2 or 3. If oral colchicine is inadequate, intravenous colchicine, phenylbutazone or ACTH are indicated. Where deposition of uric acid begins, in Stage 3 or 4, probenecid or salicylates should be taken as interval treatment indefinitely. With the use of these uricosuric drugs, dietary and alcoholic restrictions are no longer as necessary as previously and widespread empirical restrictions are certainly not justified.

The exact nature of the underlying metabolic defect of gout remains unknown.

Acknowledgment

We wish to acknowledge permission from *The Annals of Rheumatic Diseases* to reproduce Diagram 2.

BIBLIOGRAPHY

- BARTELS, E. C. (1955), *Ann. int. Med.*, **42**, 1.
 BAUER, W. (1943), *New Eng. J. Med.*, **229**, 583.
 BENEDICT, J. D., FORSHAM, P. H., ROCHE, M., SOLOWAY, S., and STETTEN DE W. (1950), *J. Clin. Invest.*, **29**, 1104.
 BENEDICT, J. D., ROCHE, M., YU, T. F., BIEN, E. J., GUTMAN, A. B., and STETTEN DE W. (1952), *Metabolism*, **1**, 3.
 BOGER, W. P., BEATTY, J. O., PITTS, F. W., and FILIPPIN, H. F. (1950), *Ann. int. Med.*, **33**, 18.
 BOGER, W. P., and CROSSON, J. W. (1950), *Amer. J. Med.*, **9**, 35.
 GRAHAM, G. (1920), *Quart. J. Med.*, **14**, 10.
 GRAHAM, W., and ROBERTS, J. B. (1953), *Ann. Rheum. Dis.*, **12**, 16.
 GUTMAN, A. B., and YU, T. F. (1950), *Amer. J. Med.*, **1**, 35.
 HELLMAN, L. (1949), *Science*, **109**, 280.
 HUFFMAN, E. R., WILSON, G. M., SMYTH, C. J., and HELLER, R. (1954), *Ann. Rheum. Dis.*, **13**, 317.
 JACOBSON, B. M. (1938), *Ann. int. Med.*, **11**, 1277.
 JENNINGS, G. M. (1937), *Rep. on Chr. Rheum. Dis.*, **3**, 106.
 KIDD, E. C., BOYCE, K. C., and FREYBERG, R. H. (1952), *Ann. Rheum. Dis.*, **3**, 23.
 KUZELL, W. C., BROWN, B., and MANKLE, E. A. (1952), *J. Amer. Med. Ass.*, **149**, 720.
 MARGOLIS, H. M., and CAPLAN, P. S. (1950), *Ibid.*, **142**, 356.
 MARSON, F. G. W. (1952), *Brit. J. Radiol.*, **25**, 539.
 MARSON, F. G. W. (1953), *Quart. J. Med.*, **22**, 331.
 MASON, R. M. (1951), *Proc. Roy. Soc. Med.*, **44**, 283.
 MASON, R. M. (1954), *Ann. Rheum. Dis.*, **13**, 120.
 MASON, R. M. (1954), *Brit. med. J.*, **1**, 788.
 SHEMIN, D., and RITTENBERG, D. (1947), *J. Biol. Chem.*, **167**, 875.
 TALBOTT, J. M., BISHOP, C., NORCROSS, B. M., and LOCKIE, L. M. (1951), *Trans. Ass. Amer. Phys.*, **64**, 370.
 WOLFSON, W. Q., COHN, C., LEVINE, R., and HUDDLESTON, B. (1948), *Amer. J. Med.*, **4**, 774.