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Factors Inhibiting the Excretion of Uric Acid

Knowledge about the external factors which can impair the excretion of uric acid in man are relevant in at least two fields of activity. In the first place, it has thrown some light on the mechanism of uric acid excretion. Secondly, it is of direct interest to the physician dealing primarily with rheumatic diseases, for many of these factors present themselves as problems in the diagnosis and management of hyperuricæmia and gout. Interest in this aspect of renal physiology is therefore stimulated from purely practical considerations.

Pharmacological agents are the best known of these factors. Most of us have now seen the serum urate elevated, sometimes with the precipitation of acute gouty arthritis, following the use of thiazide diuretics and when such a diuretic has been given to a patient who already has gout, and perhaps some degree of renal impairment, there may be two or three different influences contributing to the hyperuricæmia. Retention of uric acid induced by these drugs is antagonized by uricosuric agents: in such a situation salicylate appears to be the most effective but the high maintenance dosage which is necessary for this purpose makes its use rather impractical. We did, however, use maintenance aspirin therapy in the case of a man whose pulmonary tuberculosis was being treated with pyrazinamide. This is a most potent inhibitor of uric acid excretion and the patient had several attacks of gouty arthritis while taking it. The serum uric acid, which lay between 5·2 and 6·3 mg/100 ml while he was off the drug, rose to 13·5 mg/100 ml when he resumed it. Probenecid achieved only partial control even at a daily dose of 4 g, but 4 g of aspirin lowered the serum uric acid to 4·5 mg/100 ml and up to the time we last heard from him he was taking the combination of drugs without trouble and with no more gout.

It has been suggested (Dollery *et al.* 1960) that certain antihypertensive drugs other than thiazide diuretics also cause uric acid retention, but it is difficult to be sure how much the hyperuricæmia is associated with treatment and how much with underlying hypertension. Uric acid retention is certainly not a property of all antihypertensive agents: Fry & Barlow (1962) studied guanethidine carefully and found no urate-retaining action coincident with satisfactory blood pressure control.

The effect of pharmacological agents is complicated because it varies with dosage and the use of drugs in combination. It has long been known that the renal excretion of uric acid in man is increased by large doses of salicylate and suppressed by small doses, and a similar reversibility of effect has been demonstrated with phenylbutazone, probenecid and sulphinpyrazone, though with the last two drugs the dose producing uric acid retention is so small that it is not a practical problem in treatment (Yü & Gutman 1955, 1959). Conversely, thiazide diuretics given in a large intravenous dose cause a transient increase in uric acid clearance, an effect first shown by Demartini *et al.* (1962). The terms 'uricosuric 'and 'hyperuricæmic' can therefore be applied to a drug only in respect of a particular range of dosage. This paradoxical dosage effect can be attributed to an inhibiting effect on tubular secretion in low dosage which is overcome by a similar effect in higher dosage upon tubular

reabsorption. The interactions between different uricosuric drugs are very complicated and depend on the species examined. In man, for example, but not in the dog, the uricosuria produced by sulphinpyrazone or by salicylate is suppressed when the two drugs are given together, and competition appears to occur not only in relation to renal tubular transport but also for binding sites on plasma protein (Yü *et al.* 1963).

The serum level of uric acid has been known for many years to rise during starvation and ketosis, but until recently the mechanism for this was uncertain. One suggestion has been that depletion of glycogen leads to increased gluconeogenesis with the formation of excess purine breakdown products. But the excretion of uric acid is diminished during starvation, and this is accompanied by a fall in plasma bicarbonate and by the excretion of ketone bodies. Since starvation-induced hyperuricæmia is not affected by the administration of sodium bicarbonate, but rapidly disappears when ketosis is abolished by breaking the fast with a carbohydrate or protein diet, it appeared that ketone bodies might be the direct cause of impaired uric acid excretion. In a recent study (Scott, McCallum & Holloway 1964) the similar effects of starvation and high fat diets were demonstrated in normal volunteers; infusions of β-hydroxybutyrate, which in severe ketosis is the main component of the ketone bodies, were then also shown to depress the clearance of uric acid. There was a significant exponential negative correlation between levels of blood ketones and uric acid/creatinine clearance ratios, which fall by about 50% when blood ketones rise to 10 mg/100 ml. This direct effect of ketones was soon confirmed (Lecocq & McPhaull 1965, Goldfinger *et al.* 1965), and it is likely that β-hydroxybutyrate inhibits tubular secretion of uric acid in a manner analogous to that of lactate (which is α-hydroxyproprionate). The effect can be overcome by uricosuric doses of probenecid and salicylate. Clinical conditions where lactic acid has been thought to cause uric acid retention include pregnancy toxæmia, glycogen storage disease and possibly alcoholic intoxication, though other factors may be operating as well. Ketosis severe enough to cause prolonged hyperuricæmia cannot be common, but acute gouty arthritis has occasionally been precipitated by drastic starvation programmes undertaken for the treatment of obesity (Drennick *et al.* 1964).

The occurrence of hyperuricæmia and gout in association with hyperparathyroidism has been noted in recent years though at first regarded as coincidental. Mintz *et al.* (1961), however, found hyperuricæmia in 4 of 8 patients with hyperparathyroidism, and following a study of joint lesions in this condition it was found that the serum level of uric acid was raised in 11 of the 12 patients in whom it was estimated (Scott, Dixon & Bywaters 1964). These patients were selected by a number of factors and the incidence of hyperuricæmia is probably not nearly as high as these figures would indicate. It was noteworthy, however, that 5 of them had acute gouty arthritis and 2 of these were premenopausal women in whom primary gout is extremely rare. Adequate clearance data were not obtained on most of these subjects but such information as was available indicated that hyperuricæmia was due to impaired excretion of uric acid. Many of the patients had impaired renal function as shown by a raised blood urea at some time in the course of the disease, so that diminished glomerular filtration may have been a contributory factor. In others, however, renal function was normal and only slightly impaired and uræmia could not have been a major factor in producing hyperuricæmia. Seven of the 11 patients had radiological nephrocalcinosis and 5 had soft-tissue calcification elsewhere: it is possible that calcium deposition in the renal tubule produces a special type of lesion leading to hyperuricæmia and gout. In this connexion there are several sporadic reports of patients with hyperuricæmia and soft-tissue calcification due to causes other than hyperparathyroidism and we have recently had the care of such a case, a man with hypercalcæmic sarcoidosis who had calcification in various tissues and whose serum uric acid was elevated. Acute arthritis occurring in patients with soft-tissue calcification may of course be calcium pseudogout of the type described by McCarty *et al.* (1962) rather than uric acid gout, a question which can be resolved in individual patients only by crystal identification.

Uric acid retention in another endocrine disorder, hypothyroidism, is another problem now coming under review. Leeper *et al.* (1960) examined the serum uric acid levels in 28 myxœdematous patients and found that most of the males and one-third of the females had a significant degree of hyperuricæmia accompanied by a decreased rate of urinary excretion. Treatment of the myxœdema resulted in a uric acid diuresis and a fall in the serum level. At Hammersmith we recently studied uric acid excretion in a man of 50 with gout and myxœdema. The symptoms of myxœdema had been present for only six months, whereas he had had attacks of acute gout for seven years. There was also a family history of gout. He was therefore considered to have primary familial gout, but it was decided to observe the effect of thyroid treatment on serum

and urinary uric acid levels. This is shown in Fig 1. Treatment with triiodothyronine was accompanied by a fall in the serum uric acid from 8·5 to 6·5 mg/100 ml. Twenty-four-hour urinary uric acid figures rose from about 400 mg to over 600 mg by the fifth week of treatment, then falling to levels only just above those before treatment. The blood urea remained unchanged at 37 mg/100 ml during this period. Creatinine clearance was low at 62 ml/min before treatment and rose only slightly to 69 ml/min. Of some interest is the fact that he experienced two severe attacks of gout in the fourth and tenth weeks of therapy. I managed to trace the hospital records of 3 other patients with gout and myxœdema, all of whom had acute attacks shortly after starting thyroid treatment. The situation is reminiscent of the acute attacks which sometimes occur shortly after the commencement of uricosuric treatment,

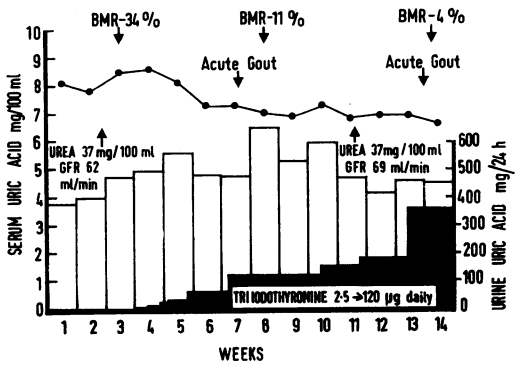

Fig 1 *A B, male aged 49, with gout and myxœdema. Low purine diet. Uric acid figures are weekly means of daily estimation*

possibly related to fluctuating levels of serum uric acid causing dissolution and recrystallization of microtophi. Although in the case described we were unable to demonstrate any marked change in glomerular filtration rate before and during thyroid treatment, there is some evidence that both this and renal plasma flow are usually depressed in myxœdema (Papper & Lancestremere 1961). The study of Leeper *et al.* (1960) did not relate uric acid clearance to other aspects of renal function during the treatment of myxœdema and this clearly requires further investigation.

This short review of various agents and conditions impairing uric acid excretion has not been exhaustive. The striking thing about these conditions is their diversity. There is little doubt that further studies will lead to the discovery of other factors, inborn or environmental, which contribute to renal hyperuricæmia and hence to that heterogeneous group of disorders we call gout.

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Dr J E Seegmiller (*Bethesda, USA*): At Bethesda we have seen one patient with hyperparathyroidism and hyperuricæmia who developed acute gouty arthritis. Dr Kleinenberg at Johns Hopkins Hospital has also seen a similar patient. In the patient that we had the opportunity to see briefly in Bethesda, we performed uric acid-inulin clearance ratios before parathyroidectomy with the full expectation that the serum urate would return to normal after the parathyroidectomy, which it failed to do. There seemed to be no real change in the uric acid-inulin clearance ratio following parathyroidectomy in this particular patient. I wondered if Dr Scott had any comparable data in his much larger series that would shed some light on this subject, and what this means if his data should agree with ours.

Dr Scott: With regard to the question which Dr Seegmiller raised about the effect of parathyroidectomy, in only one patient was there a convincing fall in the serum uric acid after operation. In most of them, as far as we could see, the serum urate level remained about the same, and some of them required uricosuric treatment. I think this fits in with Mintz's study, where he infused Parathormone without finding that this had any effect on uric acid excretion, and I think, too, it supports the idea that the hyperuricæmic effect is due to actual nephrocalcinosis, rather than just to the presence of a raised serum calcium level.

Dr V L Steinberg (*London*): I have recently had a patient under my care whose parathyroidectomy was followed some years later by clinical gout. When I saw him his plasma calcium, phosphate and phosphatase were all quite normal. He still had hyperuricæmia with clinical gout. His renal function was normal and there was no nephrocalcinosis. He had punched-out areas in his big toe, which on biopsy contained a deposit of uric acid.

Professor E G L Bywaters (*Taplow*): Professor Milne, are secretion and reabsorption the properties of the same cell of the same segment, or of different segments, and has this ever been looked at instead of following the filtrate down the tubule, following the blood along from the glomerulus, looking at the blood concentration of urate?

I also want to ask about the correlation, if any, between the traditional role of alcoholism in gout, and the acute effects of alcohol. These are two quite different things and many people try to put them together, but I am sure that even in a chronic alcoholic his lactate does not, over the twenty-four hours at least, reach the levels necessary to retain the urate to the extent required for gout.

Professor Milne: The segmental location has been chiefly done by the somewhat dubious and admittedly inaccurate method of stop-flow analysis, and I believe that the loci in the proximal tubule for secretion and reabsorption are at least in adjacent segments. They are very close, but I do not think that one can go farther than that. Obviously, to show them up in segments as close as this you need to put in inhibitors such as pyrazinamide to inhibit secretion and then show up the locus of reabsorption. Examination of blood in the kidney is very much more difficult technically, and I think that relevant micro-puncture studies have only been done in the vasa recta.

With regard to alcoholic intoxication, I would entirely agree that the main effects on uric acid clearance have been shown by acute and almost paralysing levels of alcoholic intoxication. They are very well shown by intravenous infusion of pure ethanol in saline. I see no reason why gout should be precipitated in the chronic tippler who keeps a very low level of alcohol in his blood through the day. But I think that such individuals are rare – alcoholism in my experience is often a chronic affair interspersed with acute exacerbations, and I see no evidence whatsoever for the traditional implication that certain specific alcoholic drinks are great producers of gout. I am thinking of port, of course, although many famous gouty characters in history have also been famous port wine drinkers.

Dr Seegmiller: Dr Rodnan and Dr Machlachlan, at our gout symposium at Princeton, presented some interesting evidence that bears on this subject. They had found that in addition to the lactic acidæmia produced by alcohol infusion, there was a marked increase in serum concentration of β-hydroxybutyrate as well. This provides another chemical mediator of the uric acid retention produced by ethanol.

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Urinary Hydrogen Ion Excretion in Patients with Uric Acid Calculi

Patients with uric acid calculi usually have a persistently acid urine (under pH 6·0), and their tendency to form calculi can be reduced by oral administration of substances which render the urine more alkaline, such as sodium citrate or bicarbonate. The importance of urine pH in the genesis of stones lies in the pK of uric acid, which is 5·7. In urines more alkaline than pH 5·7 biurate is present in greater concentration than uric acid, but in more acid urines uric acid predominates. Uric acid is much less soluble than biurate and calculi are therefore more likely to form in urines of pH 5·7 or under.

Recently Henneman *et al.* (1958, 1962) investigated a group of patients with uric acid calculi and found that their urinary excretion of ammonium was less than that of titratable acid. Most healthy subjects excrete more ammonium than titratable acid, and Henneman was therefore led to postulate that defective renal elaboration of ammonium is the fundamental defect responsible for uric acid stone formation. Such a defect, he reasoned, would lead to a more acid urine because the hydrogen ion produced by metabolism would be excreted as titratable acid rather than as ammonium.

It has been known since the observations of Henderson & Palmer (1915) that patients with