In My Own Time

Gout

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When I qualified in 1941 the treatment of a patient with gout had, as now, two objectives. The first was to relieve the severe pain of an acute attack of gouty arthritis; the second was to prevent further attacks. Colchicine was used for both purposes; in large doses (0·5 mg hourly up to a total of 6 mg or until diarrhoea had been induced, whichever came earlier) for the acute attack, and thereafter 0·5 mg two or three times daily together with avoidance of alcohol and foodstuffs with a high purine content to obviate future recurrences. Judged by the number of patients who relapsed, this treatment was not very effective. In fact, colchicine has no influence on urate metabolism (we thought it might) and does nothing to prevent the development of gouty tophi in the ears, elbows, fingers, and toes or the formation of uric acid renal calculi. Neither we nor our patients had an inkling of the therapeutic advances that lay ahead.

Acute gouty arthritis

As a house surgeon I was taught a cardinal diagnostic feature of acute gouty arthritis. Almost invariably the pain wakes the patient in the small hours of the night or, in less severe cases, is present on waking in the morning. This was striking in the first patient with gout I remember seeing—a plethoric publican whom I was called to see at 3 am—48 hours after his inguinal hernia had been repaired. The inflammation of his big toe was so acute that the warning legendary stories of casualty officers who had incised what they thought was an acute pyogenic abscess with superimposed cellulitis became more understandable.

The second patient I saw with gout had an acute attack in his hand and wrist; the swelling and redness made it hard to say exactly where. He came to the medical sorting department at St Thomas's—a large Victorian tiled room with sturdy practical wooden benches in parallel rows like pews in a church, and facing each row (like a pulpit) a high perched desk for the resident assistant physician and the medical registrar who, in 1944, were the only "senior" MRCP-qualified junior staff. I made the diagnosis on the basis of his previous history. Certainly, I didn't look for crystals of sodium urate in synovial fluid (the only sure way of making the diagnosis nowadays, we are told); to have measured the serum urate concentration or had an *x*-ray examination done would not have been countenanced in those days of clinical acumen. He responded to colchicine. When he returned a week later, as a mark of appreciation he brought me a crab—a rare delicacy at any time, and especially so in the food-rationing days of 1944. Some days later I went shopping in Peter Jones, and standing outside in Sloane Square on the pavement was a strangely familiar figure in dark pink spectacles, a tray of tired matches resting on his chest and a dog-eared notice drawing-pinned to the tray stating "Totally Blind." Strangely familiar, but not identified until my patient came to hospital the next week with complete resolution of his gout and another crab for me. I learnt how to distinguish a cock from a hen crab, when a crab was fresh, and some of the finer points of being a professional beggar.

In those days we instructed the patients about avoiding alcohol, although we then knew nothing about the competitive renal tubular excretion of the alcohol metabolites, lactate and β-hydroxybutyrate, and sodium urate, and lectured them about avoiding foods with a high purine content.

Therapeutic evolution

But therapeutics were advancing. Probenecid, which was first evolved to heighten the blood penicillin concentration in days when penicillin was in short supply, and is still valuable when high levels are required for treating bacterial endocarditis, was found to have a potent uricosuric action and became the standard preventive treatment for gout. Its main side effect was gastric discomfort, but this could usually be avoided by taking the drug with meals sandwiched between the first and second courses—a worthwhile tip that brought comfort to no fewer than three presidents of the Royal College of Physicians.

By 1951, cortisone was widely available and so was phenylbutazone, both with potent anti-inflammatory effect. As a "control," with others of the teaching staff, I sat the final multiple-choice exam in medicine for students of Columbia University when working that year as a postgraduate research fellow in the Presbyterian Medical Centre in New York. One of the questions I got wrong was, "Which of the following is the preferred treatment for an acute attack of gout: (*a*) cortisone, (*b*) colchicine, (*c*) phenylbutazone, (*d*) salicylates ?" To this day, I am not sure which answer the examiners wanted—obviously not salicylates, because in a dose of less than 4 g daily they impede urate excretion, and anyway uricosuric drugs play no part in the treatment of acute gout. The one I chose (cortisone) was not according to the gospel of Goodman and Gilman, and Ed Goodman was the professor of therapeutics at the time.

Cortisone

In practice, cortisone or its modern analogues can, in an emergency and in high dosage, be very effective. Such an emergency arose in an Irish bookmaker with private telephone lines to some of the clubs in St James's Street and Pall Mall. Three days before he was due to leave for a salmon fishing holiday in Connemara he developed acute gout in his right

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wrist. It was redder than his rubicund face, acutely painful, and swollen almost beyond belief. Little short of a modern therapeutic miracle was required if the turf accountant was to hold a rod in his right hand and avoid losing the money he had paid to fish in his homeland.

Five days later a 15 lb salmon in its wicker wrapping arrived in London, a tribute to cortisone and to the bookmaker's skill.

Primary and secondary gout

Biochemists rather than clinicians have advanced gout beyond Garrod's original concept of an inborn error of metabolism. The present division into primary and secondary types, each type being subdivided into overproduction (increased biosynthesis) and underexcretion by the kidneys, is helpful.

Primary gout, whether metabolic in the sense of overproduction or renal, is analogous to Garrod's thinking. Although only one enzyme deficiency has been clearly defined (hypoxanthine-guanine phosphoribosyltransferase deficiency in the Lesch-Nyhan syndrome), it seems highly likely that other inborn errors account for "idiopathic" hyperuricaemia—whether due to increased uric acid production or diminished renal excretion.

The secondary form of gout is a more modern condition that has largely emerged during my professional life time, and it is usually iatrogenic. The breakdown of purines may be so great in the effective present-day treatment of leukaemias, reticuloses, and lymphomas that the normal metabolic pathways are overloaded, hyperuricaemia results, and there is danger of renal damage. In other instances, secondary gout may be induced as a consequence of diminished urate excretion by the kidneys and not as a result of excessive uric acid production. This rarely occurs in chronic renal failure of any cause; more often it occurs in patients taking thiazide diuretics. These widely used agents, by their action on the renal tubules, often induce a degree of hyperuricaemia. Clinical gout may develop—and not only in those who already have a propensity to primary gout.

Thus the various factors that influence the serum urate concentration have suggested, particularly to the pharmaceutical industry, logical points in the overall metabolic scheme that might be influenced with the prospect of reducing hyperuricaemia. Restriction of the dietary purine load is a time-honoured step, but one which when considered quantitatively in relation to the large uric acid pool in the body can only be of modest importance. Alcohol, or rather its metabolites, impair the renal excretion of urates. Port probably has its reputation for inducing gout because in the past it was drunk in large quantities, and today is drunk at the end of a meal, before and during which other alcoholic drinks have been served.

Prevention

Today the main objective is to prevent attacks of acute gouty arthritis, the deposition of gouty tophi, and renal damage by obviating hyperuricaemia. Probenecid (Benemid) and sulphinpyrazone (Anturan) are effective uricosuric agents. For many years we were happy with probenecid; it has a long record of safety and it is still a most valuable drug. When there is some renal insufficiency it is not always effective, any more than sulphinpyrazone is. The advent of a drug—a xanthine oxidase inhibitor—that impaired uric acid synthesis, had considerable scientific appeal and today allopurinol (Zyloric) plays a major part in preventive treatment. Scientifically, one should be able to decide which cases should be treated with a metabolic inhibitor—which is certainly the case in patients being treated for leukaemia—and which with a uricosuric drug, but in primary gout the art rather than the science of medical practice requires that all these agents are available. Some patients find one more effective than another (success largely depends on maintaining a normal urate concentration), and some experience side effects (mainly indigestion or rashes) with one and not with another.

Patients with primary gout must learn, and often do the hard way, that once the diagnosis of gout has been firmly established, lifelong treatment is called for. We have no evidence yet whether or not such treatment will influence the increased incidence of cardiovascular disease in gouty patients. Inevitably any lifelong treatment calls into question the long-term safety of the drug being used. Happily the track records of probenecid, allopurinol, and sulphinpyrazone need cause us no concern on that score.

The treatment of an acute attack of gouty arthritis nowadays relies on anti-inflammatory drugs. Colchicine is often effective, but associated diarrhoea makes it less acceptable to the patient than phenylbutazone, oxyphenbutazone, or indomethacin. It is interesting that the cause of the pain in a joint affected with gout is attributable to the release of prostaglandins from leucocytes that have ingested microcrystals of sodium urate. Indomethacin is an inhibitor of prostaglandin synthetase, and is certainly very effective in relieving gouty pain. But, again, the art of medical practice has shown that some patients find one of these agents more helpful than another, and the physician must not be rigidly committed.

No single discovery has revolutionised our understanding or the treatment of gout. The remarkable progress has been a team effort, and a multifaceted one at that. The honours go to the biochemists and the pharmaceutical industry; intellectual satisfaction and understanding to the clinicians; most important of all, the benefits go to the patients—and they are many.

A final word about colchicine. It is an old drug, used for centuries, but until recently we have not understood its pharmacological action. Colchicine diminishes leucocyte migration and we now know that leucocytes and the liberation of prostaglandins after phagocytosis of sodium urate crystals are probably the cause of the acute pain in gouty arthritis. Colchicine still plays a vital part in the management of the patient with gout. Sudden changes in the plasma urate concentrations, upwards or downwards, may precipitate sodium urate crystals. Hence allopurinol or uricosuric agents given to prevent attacks of gout may induce exactly what they are intended to prevent. The wise doctor during the initial weeks of treatment with allopurinol or probenecid or sulphinpyrazone will give colchicine 0·5 mg twice daily. And the prudent patient will carry colchicine or indomethacin to take at the first twinge of gouty pain.

Is rubella vaccination contraindicated if someone else in the household is already pregnant?

Although vaccine-related cases after poliomyelitis have been recorded, so far as I am aware this does not occur with rubella vaccination. So I see no reason for withholding rubella vaccination if one person in the household is already pregnant.

Are general adenopathy and arthopathy recognised symptoms of rubella in a 12-year-old?

Arthralgia or arthritis is said to occur in about 15% of adults with rubella and may occur in children, but it is rare.[1] It usually subsides in a few days but may persist for several weeks. Enlargement of the lymph nodes is usually confined to the neck, especially the suboccipital group, but not always: the nodes in the axilla and groin are occasionally enlarged. Textbooks of paediatrics and infectious diseases are noticeably reticent about lymph node enlargement other than in the neck, but they all imply that the enlargement *may* affect other areas. The clinical diagnosis of rubella is not always easy, for a rubella-like rash, with or without affected joints, can be caused by infectious mononucleosis and many other viruses, or by drugs. The fact that the malaise lasted for three weeks would favour the diagnosis of infectious mononucleosis, but could perhaps be related to the arthritis if the diagnosis was indeed rubella.

[1] *British Medical Journal*, 1973, **4**, 186.