GOUT
A DISEASE OF DISTINCTION

Associated for hundreds of years with drunkenness and gluttony, but also with genius and sexual prowess, gout has quite a reputation. **Dr Erik Skovenborg** sifts fact from fiction in the long history of a disease – still very much with us – that has been almost as coveted by those who did not have it as cursed by those who did

'Gout is the only enemy that I do not wish to have at my feet'
Reverend Sydney Smith, 1841

Alone among all the mammals, man can suffer from gout. But recent research suggests that the acid that causes such excruciating pain also helps us live longer than any of the others. Even before this comforting discovery, the connotations of the disease were far from being entirely negative. Associated with an affluent, indulgent lifestyle and the pleasures of both the bed and the table, gout has been the disease of the privileged and the powerful. It has also afflicted so many of the most brilliant men of the day – from Leonardo da Vinci and Michelangelo, through Francis Bacon and Isaac Newton, to Milton, Swift and Tennyson – that it has been regarded as synonymous with genius.

As we shall see, there is more than a grain of truth in such theories, though the history of gout shows how wrong most of the medical men have been. The reality – disappointing in some ways, liberating in others – is that the disease owes more to genealogy than to lifestyle, more to blood than to wine.

Cause and effects

The cause, at least the immediate cause, of gout is uric acid – or, more accurately, its salt, crystalline sodium urate. Most of us produce about 750mg of uric acid per day by metabolising proteins – either from ingested food such as meat or from the normal breakdown of body tissue. Most mammals produce the enzyme *Urate oxidase* (Uox) – so ancient that it is present even in bacteria – which catalyses the oxidation of uric acid into highly soluble allantoin. But not we. Millions of years ago in the Miocene epoch, mutations occurred in the Uox gene of our hominoid ancestors that eventually silenced the gene totally. The loss of Uox activity has resulted in a concentration of uric acid in the blood of humans and the great apes that is more than ten times higher than it is in other mammals. High uric-acid concentration carries the risk that urate crystals are deposited in a joint, and it is this that can cause a fit of gout.[1]

Today, gout is still a common medical problem, affecting at least 1 per cent of men in the Western world. And acute gout – characterised by the sudden onset of pain, redness, restricted range of motion and swelling of the affected joint – is not easily shrugged off. The distinguished English physician Dr Thomas Sydenham (1624–89), one of many famous sufferers, captured its full horror in his *Tractatus de podagra et hydrope* (Treatise on Gout and Dropsy), written in 1683:

> *'He goes to bed and sleeps well, but about two o'clock in the morning he is waked by a severe pain seizing either the great toe; more rarely the heel, the calf of the leg or the ancle; this pain is like that of dislocated bones, with the sense of water almost cold, poured upon the membranes of the parts affected [...]; presently shivering and shaking follow with a feverish disposition; the pain is first gentle, but increases by degrees [...] and that hourly, till towards night it comes to its height [...]. Bones of the tarsus and metatarsus [...] it seizes sometimes like the gnawing of a dog, and sometimes a weight, the part affected has such a quick and exquisite pain that it is not able to bear the weight of the bedcloaths upon it nor hard walking in the bedchamber.'*[2]

Sydenham has been dubbed the English Hippocrates. But his Greek namesake was aware of the malady some 2,000 years earlier, and it has fascinated and flummoxed physicians ever since.

The burning pain of acute gout

The Ancient Greeks on gout

'Podagra is the most violent of all joint affections, it lasts long, and becomes chronic [...] the pain may remain fixed in the great toe'
Hippocrates (c.460–c.357 BC)

In the Greek humoral model of disease, health and illness were determined by the balance of the major fluids or humours – blood, choler (yellow bile), phlegm and melancholy (black bile). Hippocrates regarded gout as the outcome of the descent (*rheuma*) of bodily humour, probably phlegm, which swelled the affected joint. The conditions were classified according to the joints affected: *podagra* (foot-grabber), *chiagra* (hand-grabber), *gonagra* (knee-grabber) and the like. Later on, the Latin word *gutta* (a drop) was used for gout – a disease that implies the dropping of fluid matter from the brain to a body part such as the extremities.[3]

Hippocrates was, however, close to the truth in other ways. Levels of uric acid do not rise until puberty in males and menopause in females. The *Aphorisms* of Hippocrates reflect knowledge of these facts: Aphorism number 29 notes that a woman does not take the gout as long as she is menstruating, while Aphorism number 30 states that a young man does not become susceptible to gout until the time of indulging in copulation.[4]

Galen (c.130–c.201 AD) – Greek chief physician to the gladiators in Pergamum and, later on, physician to the emperor Marcus Aurelius – compiled the Hippocratic teachings, adding his own observations. Accurately, he alluded to the role of heredity, observing that those inheriting gout suffered more intensely than those acquiring it.[5] The Greek humoral model of health and disease, and Galen's writings on gout, had a dominant influence on medical theory and practice in Europe for centuries.

The Ancient Romans and saturnine gout

'So many poisons are employed to force wine to suit our taste – and we are surprised that it is not wholesome'
Pliny the Elder (23–79 AD)

The Romans were avid devotees of the god of wine, Bacchus, and the goddess of love, Venus. Luxurious foods, however, were for the upper classes of Roman society only, and Musonius (c.20–c.90 AD) made the following observation:

> *'[M]asters are less strong, less healthy, less able to endure labour than servants; countrymen more strong than those who are bred in the city, those that feed meanly than those who feed daintily; and that, generally, the latter live longer than the former. Nor are there any other persons more troubled with gouts, dropsies, colics, and the like, than those who, condemning simple diet, live upon prepared dainties.'*[6]

Lucius Seneca (4 BC–65 AD), referring to the gout as the rosy daughter of Bacchus and Venus, observed that luxurious living had led to its spreading to women because 'in this age women rival men in every lasciviousness [...] why need we then be surprised at seeing so many of the female sex afflicted with gout?'[7]

The Hippocratic writings, compiled by Galen, regarded podagra as a joint swollen by an excessive accumulation of bodily humour. This painful state might result, they thought, from sexual excess or from a sedentary life with too rich a diet, causing 'indigestion' of the humours.[8] What Galen and his colleagues failed to recognise was the risk of saturnism – lead poisoning. The Greek and Romans both used leaden vessels in making

Alcohol was the most ambiguous and vexing of the substances included in the medical debates. Some permitted wine in modest amounts; others decried it altogether

wine, and they even added lead as a preservative or to improve taste.

In a classic experiment, Hofmann, in accordance with the directions of the early Roman writer Columella, boiled various wines with lead to produce *sapa*, the wine syrup used to enhance the colour, sweetness and preservation of wine. Subsequent analysis revealed levels of 390–710mg of lead per litre of *sapa*.[9] In order to know the toxicity of wines treated with *sapa*, it is, of course, necessary to know the proportion in which *sapa* was added to wine. But the lead content of Columella's wines may be estimated at approximately 20mg per litre.

That is very bad, considering the Provisional Tolerable Weekly Intake of 25mg lead per kilogram of body weight given by the World Health Organization.[10] To be on the safe side, a Roman would have to have been content with one small glass of wine per week! He was not, of course. The average consumption of wine in Ancient Rome has been estimated at about 1–5 litres per capita per day, and gross excess was common. Cicero compares the end of a banquet, given by the notorious Verres, to the battle of Cannae, since some were carried away disabled, while others remained in an unconscious state on the field of battle.[11] Besides hangovers, the Roman binge drinkers risked chronic lead intoxication leading to lead nephropathy, a chronic renal disease giving rise to hypertension, hyperuricaemia and gout.[12] In the light of the Roman emperors' predilection to lead-tainted Apician *entrés* and Columellan wine blends, it comes as no surprise that Aulus Corneluis Celsus (c.25 BC–50 AD), a Roman gentleman and author of *De re medicina*, says that most of these rulers suffered from gout.[13]

Aldermanic gout (18th–19th centuries)

'Gout: the sequence of high-living and thorn in the rose of gastronomy, with many years of savoury dinners and fragrant vintages as its genesis and means of evolution'
George H Ellwanger, 1897

From antiquity onwards, Byzantine, Arab and Latin Christian writers used to transmit and gloss ancient Graeco-Roman writings on podagra without, however, developing new ideas of their own. Authors from Hippocrates to Sydenham and beyond asserted, in the words of Sir Richard Blackmore, that 'gout owes its production to the table of the Epicure and the Abuse of delicious wine'.[14] Hence the so-called Aldermanic gout prevalent in the 18th and 19th centuries.

The received wisdom had already been summed up by Thomas Sydenham in his treatise. In the light of his own experience spanning more than 30 years, Sydenham insisted that although gout does not seize only the 'gross and corpulent', nevertheless 'the gout generally attacks those aged persons who have spent most part of their lives in ease, voluptuousness, high living, and too free abuse of wine and other spirituous liquors, and at length, by reason of the common inability to motion in old age, entirely left off those exercises which young persons commonly use'.[15]

Alcohol was the most ambiguous and vexing of the substances included in the medical debates. Some permitted wine in modest amounts; others decried it altogether. Spirits were deemed pernicious, but small amounts of beer were permissible. Among the British physicians engaged in these controversies, Sir Richard Blackmore achieved fame with his *Discourses on the Gout: A Rheumatism, and the King's Evil*. He upheld traditional morality linking gout and gluttony, and he urged patients to pursue 'Abstinence [...] in eating, Temperance in drinking strong Liquors, and proper Exercise'.[16] But unlike his contemporary George Cheyne, who advocated 'total Abstinence from all fermented Liquors, except, perhaps, clear unhopt Small-beer',[17] Blackmore thought wine useful for gouty patients, since 'it aids the concoctive Faculty of the Stomach'. Most doctors, though, tended to agree with the statement of the high priest of gout, Sir Alfred Garrod: 'There is no truth better established in medicine, than the fact that the use of fermented liquors is the most powerful of all predisposing causes of gout.'[18]

Investigating the drinking behaviour of 24 gout patients of today, medical researcher Colin Sharpe found that their average weekly alcohol intake was twice that of the control group, and that about half the patients with gout drank excessively.[19] The drinking habits among the Aldermanic gout sufferers will have been no more temperate, for as Evelyn Waugh writes:

> *'The chief revolution in wine drinking habits came at the beginning of the 18th century, when the Methuen Treaty with Portugal endowed the heavy wines of the Douro with preferential tariff. The immediate effect was not entirely beneficial when men accustomed to their three or four bottles of light claret in the evening began to drink vintage Port in the same measure, and the mahogany gout stools which abound in our country houses are evidence of the price paid for this innovation.'*[20]

Beer drinkers are, and were, also promising candidates for the development of Aldermanic gout. Gibson's modern study of 61 men with gout and 52 control subjects showed that their daily intake of most nutrients was similar, except that patients with gout drank significantly more alcohol. Beer was the most popular beverage, and half of the men with gout drank more than 2 litres of beer daily. The heavy drinkers had a significantly higher intake of purine nitrogen, half of which (0.14g) was derived from beer.[21]

There is more to Aldermanic gout, however, than alcohol, be it beer or wine – namely, feast and fast. The latter was not a favourite of Port-loving squires, but to present-day alcoholics food is often of secondary importance. Fasting is associated with a marked reduction in urinary-acid excretion. When a group of gouty patients fasted for one to two days, the mean increase in serum urate was 2mg/dl; fasting combined with the intake of alcohol was associated with an even larger mean average rise of 2.4mg/dl.[22]

But let us return to feasting and the victims of true Aldermanic gout – the gluttonous Port-loving squires. And feast the squires did; for almost three centuries the consumption of vast meals was habitual. A dinner consisted of at least two services. A

full service had 32 dishes, usually 16 of different meats and as many side dishes.[33] Much more recently, Gerald Rodnan examined the influence of food and drink on a group of seven patients with long-standing gout. Consumption of a single, large, purine-rich meal resulted in increases in serum urate level of 1.3–3.3mg/dl. When the same purine-rich meal was accompanied by copious amounts of spirituous liquors containing 83–198g of alcohol (the equivalent of 1–3 bottles of wine), there was an even greater increase in serum urate level, ranging from 2.0 to 6.1mg/dl. All but one patient experienced a fit of Aldermanic gout during the course of these studies.[34]

A leaden revival

On being asked, 'Have you finished all that Port [three bottles] without assistance?', Sir Hercules Langreish answered, 'No – not quite that; I had assistance of a bottle of Madeira'

In the 18th century, gout rose to almost epidemic proportions. Some have questioned, however, whether the mere exchange of claret for Port was enough to set it off. It is true that Port was being fortified heavily, a habit that started about 1715 'from the unfounded notion', claimed Cyrus Redding in the 1830s, 'that it was essential to their durability'.[35] It is also true that the English gentry enjoyed themselves in drinking it plentifully. In the 1890s, Edward Spencer wrote:

> *'This was the era of the three- and four-bottle heroes of whose deeds I have heard my father speak, almost with bated breath; how, after the retirement of the ladies, to discuss tea and scandal by themselves, the dining-room door would be locked by the host himself, who would pocket the key thereof. Many of the guests slept where they fell, "repugnant to command", like the sword of Pyrrhus; whilst others would be fastened in the interior of their chariots at a later hour.'*[36]

Nevertheless, there have always been defenders of Port, like Edward Bunyard, who wrote in the 1930s: 'Port has been blamed for most of the gout in this country, but with little justice. Did not the eminent Dr Richardson say: "If Port does not agree with you then there must be something wrong with the Port"?'[37] So might it really be that there was something 'wrong' with the Port?

The first statement incriminating lead from wine in gout came from James Hardy, who maintained in the 1770s that 'gout originates from the action of mineral substances, especially those conveyed into the human system by the medium of adulterated wines'.[38] In his book on wines written in the 1860s, James Richmond Sheen included a chapter on the adulteration of wines to lower their acidity:

> *'The ancients, it would appear, were acquainted with this property in lead, for according to Pliny, the Greeks and the Romans improved the quality of their wines by immersing a plate of lead in them. But the object more to be desired by the use of lead was doubtless to lessen the acidity which belonged to the wine, or which it had acquired by keeping.'*

Although Sheen regarded the practice as 'highly reprehensible' and could 'scarcely imagine that any conscientious dealer would resort to so dangerous an expedient', he nevertheless described several tests whereby 'the presence of lead may be easily detected'.[39] Garrod suspected the association between lead toxicity and gout in about a quarter of his patients – some of which were artisans working with lead paints – inferring the cause of the hyperuricaemia to be imperfect secretion of urate by the kidneys.

Because of the distillation process involved in the production of brandy, Port and other fortified wines would be more likely to be contaminated with lead than would non-fortified wines. In a unique study undertaken in the 1970s, Gene Ball obtained four different English Ports made between 1770 and 1820. Each wine was sealed in the original corked bottle without any lead covering. Even so, analysis by atomic emission spectrophotometry showed lead levels ranging from 0.83mg of lead per litre of Port from the 1805 vintage to 1.9mg of lead per litre in Old Canary Wine 1770–1810, compared with an average of 0.16mg of lead per litre in modern Port wine. After the investigation, Ball and his friends drank the remains of the old Port, which they found to be delicious![39]

Now, therefore, we have two culprits lined up for a revival of saturnine gout: a gluttonous intake of meat dishes and an intemperate consumption of alcohol in general and of lead-tainted Port in particular. A large load of purines (from meat and entrails), combined with decreased excretion of uric acid (due to impaired renal function from chronic lead poisoning), is the perfect recipe for an epidemic of gout.

Kidneys, gravel and stones

'People wish their enemies dead – but I do not;
I say give them the gout, give them the stone!'
Lady Mary Wortley Montagu

It is no coincidence that the substance used as a basis for the first analysis of uric acid by Carl Scheele in 1776 was a bladder stone. The risk of kidney-stone disease is almost twofold in men with gout compared to those without (15 per cent versus 8 per cent). And in the days before treatment was available, one in four severely afflicted gout patients died from kidney failure.

In 1549, Michelangelo wrote: 'We are now certain that I'm suffering from the stone, but it's a small one and thanks to God and to the water I am drinking [from the spa town of Fiuggi], it's being dissolved little by little so that I am hopeful of being free of it.' Michelangelo suffered from gravel in his urine, which turned into kidney stones in 1549; he seems to have developed gouty arthritis in 1555.[39]

Sydenham also suffered from both conditions and died from one of them. He experienced his first attack of gout at the age of 30. Seven years later he developed kidney stones, for which he took liberal quantities of small beer, and subsequently he was rarely out of pain. He died at the age of 65 in his home in Pall Mall. The cause of death was renal failure from gouty nephropathy and renal calculi.[32]

Kidneys have two essential roles: as well as removing waste products from the blood, producing urine, they regulate the blood levels of many important molecules, including uric acid. But while behaviour can affect their performance, so too can genetics. 'Gout loves ancestors and genealogy,' wrote the Reverend Sydney Smith, himself a sufferer. 'It needs five or six generations of gentlemen or noblemen to give it its full vigour.'[33] Gout is actually 90 per cent a disease of genetics, and 10 per cent a disease of lifestyle. The genetic key rarely lies in uric-acid production per se; the decisive factor is rather how well the kidneys manage to excrete the uric acid. Variations in the recently identified URAT1 gene, leading to the higher retention of urate, may be the culprit responsible for the predisposition to gout that a son may inherit from his gouty father.[34]

MYTHS AND FACTS ABOUT GOUT

'If your Physitian thinke it not good that you drinke wine, or eate such and such meates, Care you not for that, I will finde you another that shall not be of his opinion'
Michel de Montaigne (1533–92)

Myth: Gout is yesterday's news.
Fact: The prevalence of gout is rising worldwide for a number of reasons:

- The dramatic rise in the number of obese people;
- The increases in high blood pressure;
- The increasing use of thiazide diuretics;
- The introduction of Western dietary habits to many developing countries;
- A decrease in the intake of low-fat dairy products. (RJ Johnson & BA Rideout, 'Uric Acid and Diet: Insights into the Epidemic of Cardiovascular Disease', *New England Journal of Medicine* 350 [2004], 1071–73.)

Myth: The intake of alcoholic beverages may increase the level of serum uric acid.
Fact: The increase in serum uric acid per serving per day is:

- Beer: 0.46mg/dl;
- Liquor: 0.29mg/dl;
- Wine: 0.04mg/dl.

The study producing these results was performed in moderately drinking men and women; the possibility that wine drinking may have an effect on uric acid level at a higher consumption cannot be ruled out. (HK Choi & G Curhan, 'Beer, Liquor, and Wine Consumption and Serum Uric Acid Level: The Third National Health and Nutrition Examination Survey', *Arthritis & Rheumatism* 51 [2004], 1023–29.)

Myth: Drinking alcohol to excess increases the risk of gout.
Fact: Compared with men who did not drink alcohol, the risk of gout was trebled in men drinking more than five beers per day. The increase in risk per drink per day was 17 per cent. The increase in risk of gout varied among the individual alcoholic beverages.

- Beer: increase in risk per serving per day – 49 per cent;
- Spirits: increase in risk per serving per day – 15 per cent;
- Wine: no increase in risk with increasing levels of wine consumption.

Beer is the only alcoholic beverage acknowledged to have a large purine content; however, male 'wine drinkers' may be different from 'beer drinkers' in other ways. (HK Choi, 'Alcohol Intake and Risk of Incident Gout in Men: a Prospective Study', *The Lancet* 363 [2004], 1277–81.)

Myth: Beer contains substances that may be harmful to patients with gout.
Fact: Beer has a high purine content, predominantly as readily absorbable guanosine. The average purine nitrogen content of seven British beers was 22.2mg/litre. Of this, 61 per cent was present as guanosine, and similar values were seen for Guinness. The total purine nitrogen and guanosine content of lager was slightly lower. Cider contained negligible quantities of purines. The average purine nitrogen content of American beers was found to be 22.3mg/litre, of which guanosine comprised 71 per cent. (T Gibson, 'Beer Drinking and Its Effect on Uric Acid', *British Journal of Rheumatology* 23 [1984], 203–09.)

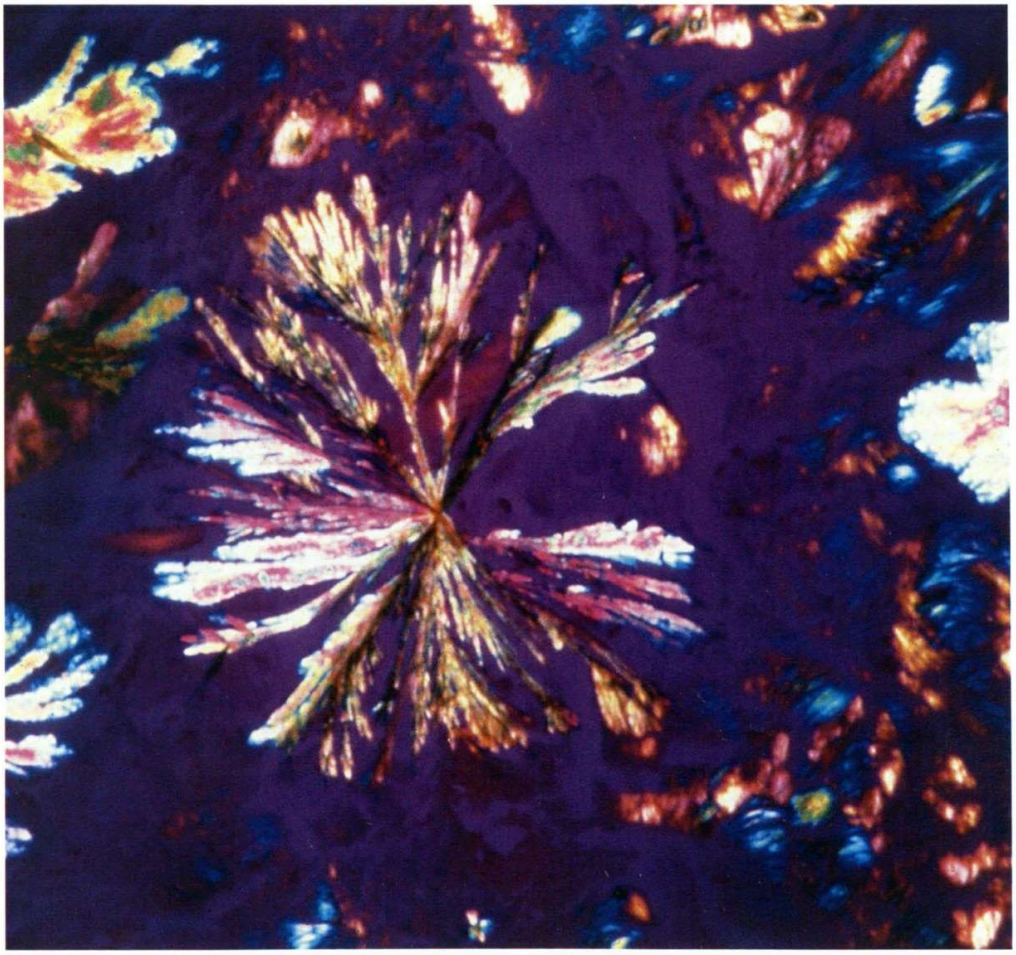
Myth: High blood levels of uric acid are a problem, even if there is no gout.
Fact: Hyperuricaemia is defined as a serum uric acid concentration greater than 7mg/dl, the approximate level at which urate is supersaturated in blood plasma. Up to a serum urate level of 9mg/dl, the risk of gout during a five-year period is very modest.

Serum urate level (mg/dl)	5-year cumular incidence of gout (%)
<7.0	0.5
7.0–7.9	2.0
8.0–8.9	4.1
9.0–9.9	19.8
>10.0	30.5

Whenever hyperuricaemia is encountered, its cause should be determined if possible. Problems such as hypertension, obesity, diabetes, kidney disease, alcoholism and hyperlipidaemia should be addressed. Therapy of hyperuricaemia, however, is not warranted in the asymptomatic patient. (EW Campion, 'Asymptomatic Hyperuricemia', *The American Journal of Medicine* 82 [1987], 421–26.)

Myth: Gout is rare among women.
Fact: The male:female ratio ranges from 7:1 to 9:1. The kidneys of healthy women eliminate uric acid more effectively than those of healthy men until menopause, since oestrogen stimulates urinary uric acid excretion. The sex difference in the 25–29 age group is 31 per cent (5.25 versus 4.00mg/dl), while in the 55–59 age group the difference is only 16 per cent (5.43 versus 4.67mg/dl).

Myth: Gluttons eating large meals rich in meat and fat have increased risk of gout.
Fact: Each additional daily serving of meat is associated with a 21 per cent increase in the risk of gout; and each additional weekly serving of seafood is associated with a 7 per cent increased risk of gout. Neither consumption of purine-rich vegetables nor total protein intake increases the risk of gout. A significant decrease of gout risk was seen with a high intake of dairy products, especially low-fat milk and low-fat yogurt.



Photomicrograph of crystalline sodium urate, the immediate cause of gout

Photography: Wellcome Library, London

Myth: Patients with established gout must adhere to a strict diet low in purines.

Fact: In the past, strict 'low-purine' diets were employed with the expectation of a modest 10–15 per cent reduction in the serum uric acid level. The purine content of the diet does not usually contribute more than 1.0mg/dl to serum uric acid concentration. (BT Emmerson, 'The Management of Gout', *New England Journal of Medicine* 334 [1996], 445–51.) 'Low-purine' diets are unpalatable, and the fact remains that 'there is more pleasure in fondling with the minor vices than in courting the virtues, especially in peccadilloes of eating and drinking; the seductive call of the palate is always far easyer to obey than the duty-call of the stomach'. (George H Ellwanger, *Meditations on Gout* [Charles E Tuttle Co, Vermont; 1968], p.99; reprint of an original 1897 work.)

Low-purine foods are often high in carbohydrate and saturated fat. In a study of overweight male gout patients, adherence to a diet with calories restricted to 1,600kcal a day with 40 per cent derived from carbohydrate, 30 per cent from protein and 30 per cent from fat resulted in weight loss of 7.7kg (17lb), a significant decrease of uric acid level and a decrease in the frequency of monthly attacks from 2.1 to 0.6. (PH Dessein et al, 'Beneficial Effects of Weight Loss Associated with Moderate Calorie/Carbohydrate Restriction, and Increased Proportional Intake of Protein and Unsaturated Fat on Serum Urate and Lipoprotein: A Pilot Study', *Annals of Rheumatic Diseases* 59 [2000], 539–43.)

The quest for a cure

'Let all men know that I alone of gods
Do not relent or yield to remedies'
The goddess Podagra

Celsus recommended regular exercise and a light diet to keep podagra at bay.[35] But when it was a question of cure rather than prevention, his rather more drastic therapeutic suggestions were in accordance with the principles laid down by Hippocrates and Galen: blood-letting, diuretics, emetics (including sea sickness) and hot fomentations to get rid of gouty humours. These measures became standard medical practice, and, with one notable exception, no advances in therapy were made in Europe until the 19th century.

The exception to the rule of futile therapeutic treatments was *Hermodactyl*, recommended by Alexander of Tralles in the 6th century. Due to the alkaloid colchicine, obtained from the seeds of *Colchicum autumnale* (autumn crocus), the drug has powerful purgative properties.[36] It also has an anti-inflammatory effect, most patients having some pain relief after 18 hours and diarrhoea after 24.

Due to severe side effects, colchicum fell into disuse, and physicians such as Sydenham dismissed *Hermodactyl* as a fearsome purgative. It was, however, reintroduced as a treatment for gout by Nicholas Husson, a French army officer who, in the 1770s, concocted a panacea that he called *eau médicinale*. Favourable effects on several gouty eminences were reported in 1811 by John Ring.[37] And in 1817, the gouty Prince Regent finally became aware of the value of colchicum, telling his doctors: 'Gentlemen, I have taken your half measures long enough to please you [...] from now on I shall take the *eau d'Husson* to please myself.'[38]

In 1884, colchicine was synthesised and dispensed as pills. Wine lovers, however, might prefer to take it in wine, as the *vinum colchici* described by Edward Spencer:

> *'With a view of shewing the wholesomeness of Sherry it is stated, by no less an authority than* The Lancet, *that it is the only wine enjoined in the preparations of the wines of the British Pharmacopoeia. Therefore it is certain that the sufferer from gout, for whom* vinum colchici *is prescribed, may swallow a proportion of the juice of the grape, and, possibly, a hair of the dog which bit him. This naturally recalls the old story of the Sherry which was sent to a former Lord Chesterfield as a panacea for his ailment, and the curt reply sent: "Sir, I have tried your Sherry and prefer the gout."'*[39]

More effective, safer treatments have become available only relatively recently. In 1951, Probenecid was found to accelerate the excretion of uric acid, and in the same year the synthesis of Phenylbutazon started the era of effective non-steroidal anti-inflammatory drugs. Finally, in 1966, Allopurinol was introduced, a drug that inhibits the formation of uric acid in the body.[40]

Venus, the mother of Podagra

'Venus cannot to the gout give birth
Unless Bacchus has defiled her first'
Joannes Cohausen, 1745

Although cures for gout were sought from Ancient Greek times onwards, and generations of sufferers must have longed to be rid of it, even they might have accepted that it had its compensations – that there could be pleasure in the acquiring of it, and even in the carrying of it, thanks to some of its reputed side effects.

The Ancient Greeks mythologised gout in the great toe as the goddess Podagra, born from the seduction of Aphrodite by Dionysus (known to the Romans as Venus and Bacchus). In other words, gout results from the combined effects of wine and venery – a dictum that stood as medical fact for centuries.

The Dutch physician Nicolaas Heinsius (c.1656–1718) gave the dictum a novel cause-and-effect twist in his *Curious Treatise on the Podagra and the Gout in General*:

> *'Although these two weaknesses, the practice of venery and intemperateness, are most relevant to the gout problem, nevertheless, for the time being this disease should rather be considered the mother of these emotions than these emotions the mother of the gout.'*

Heinsius marvels that 'even though the most terrible pain sometimes began in the midst of coition, they would [...] still maintain their thoughts on the loving embrace of their wives or other loved persons'. He explains why 'although the weakness of their bodies and the painful symptoms of the gout have hindered them in many ways [...] they yet could fulfil their burning desires. The cause thereof is to be sought in the sharp and fickle nature of the gouty matter, which unites with the animal spirits, which then together pleasurably permeate the sexual organ [...]. This stimulus is especially potent in those who are affected by a hot gout.' Heinsius even cites the following case study:

> *'The women who have gouty husbands can speak of their sexual prowess from the closest experience [...]. I have known a sturdy housewife who already had a third husband, and during lovemaking frequently says that in case she should again be widowed and should marry for a fourth time, she would only take a man who has podagra. This was because her first husband, who was afflicted with the disease, had given her as much enjoyment in a week as either of the last two had been able to give her in nearly a month.'*[41]

A woman's guilt, if any, lay only in prolonging her lover's gout attack by acceding to his carnal demands instead of frustrating her own desires.[42]

The alleged libidinous effect of gout attracted even more interest in popular literature, though Heinsius was not the only

Gout has been associated with heightened intellectual powers as well as sexual ones, and in the former case probably with stronger reason

serious medical man to support such a view. The 18th-century Scottish physician John Brown wrote that 'gouty persons are so addicted [to venery], and so exceed others in power, that in the middle of a very bad fit, they are not sparing of it'.[43] Brown's contemporary John Hill, a Westminster apothecary and playwright, also disagreed with the ancient conception of sexual activity as a cause of gout; indeed, sexual bans seemed to him particularly unjust: 'Why should any suppose the gouty person denied, in moderation, this supreme delight of the human being? Of all men nature prompts him to it most; and here it is no false stimulation: the construction of the body, which makes him liable to gout, gives him also peculiar strength.'[44]

As for other aspects of the disease, however, such theories are probably a little wide of the mark. For centuries, gout was the disease that conferred high social status and implied distinction. Men in positions of power – almost always the best aphrodisiac – often take the liberties that their status affords. That may be the rather more sober reality behind the myth placing Podagra as the daughter of Bacchus and Venus.

Gout and genius

'This disease [...] destroys more rich than poor persons, and more wise men than fools'
Thomas Sydenham

Gout has been associated with heightened intellectual powers as well as sexual ones, and in the former case probably with stronger reason. In *A Study of British Genius*, Havelock Ellis writes that gout 'occurs so often, in such extreme forms, and in men of such pre-eminent intellectual ability, that it is impossible not to regard it as having a real association with such ability'. Among 1,030 persons selected for 'genius' from the 66-volume *Dictionary of National Biography*, he finds gout mentioned in the entries on 53 of them – more than any other disease. 'Moreover,' Ellis continues, 'the eminence of these gouty subjects is as notable as their number.'[45]

The astonishing cast of characters on the arts side includes Samuel Johnson, William Cowper, Edward Gibbon, John Milton, Henry Fielding, William Congreve, Horace Walpole, Tobias Smollet, Jonathan Swift, Samuel Coleridge, Alfred Lord Tennyson, Joseph Conrad and many more. On the science side are Francis Bacon, Sir Isaac Newton, William Harvey, Thomas Sydenham, Benjamin Franklin, John Wesley, William R Hamilton and Charles Darwin. Leonardo da Vinci could claim a place on both lists.

Gout was also present in several key figures in the formation of the United States of America: John Locke (whose philosophical writings on human rights influenced the participants in the Constitutional Convention in Philadelphia), John Hancock (the revolutionary leader and the first to sign the Declaration of Independence in 1776), Benjamin Franklin (the only person to sign all three founding documents of the United States), George Mason (the father of the Bill of Rights, the first ten amendments to the United States Constitution, added in 1791) and Thomas Jefferson (the third president of the United States, 1801–09).[46] On the other side were King George III (the British monarch) and William Pitt (the British prime minister). It was during Pitt's absence from Parliament during a fit of gout that his colleagues put a heavy colonial duty on tea to raise revenue. This provocation, as the Americans saw it, eventually resulted in the Boston Tea Party of 1773, when Bostonians raided British ships in the harbour and tipped tea chests into the sea.[47]

Although it is easy to see how the link was made, the correlation is actually not so much between gout and genius as between the level of uric acid in the blood and intelligence. A large serving of roast beef washed down with copious amounts of porter by a man with a disposition to gout will result in a significant increase in serum uric acid level – and most often an acute attack of podagra as well. 'On Monday the 15th I dined and drank rather too freely at M Darcy's,' Benjamin Franklin admitted. 'Tuesday morning I felt a little pain in my right toe.'[48] Such periods of 'pre-attack hyperuricaemia' have been described as stimulating for the brain. Evelyn Waugh, for example, writes:

> *'Port, and the very finest Port at that, can be slightly deleterious. Its charm insidiously invites excess, and excess of Port, though not in itself harmful, sometimes discloses latent infirmities. The heavy Port drinker must be prepared to make some sacrifice of personal beauty and agility. Its martyrs are usually well content with the bargain and in consolation it may be remarked that a red nose never lost a friend worth holding and that by universal testimony the sharpest attacks of gout are preceded by a period of peculiar mental lucidity.'*[49]

More recent research affords some support for this belief. In a comparison of a group of 100 business executives of various ranks with 40 staff members at the Royal Edinburgh Hospital, the mean serum uric acid level of the executives was significantly higher (6.0mg/dl) than the mean staff member level (4.5mg/dl). The executives in the top echelon had the highest serum uric level, 6.23mg/dl, compared to a mean level of 5.75mg/dl for 'middle' and 'junior' groups.[50] A series of studies like the one above was reviewed by Jack L Katz and Herbert Weiner in 1972. Most, although not all, of the work reviewed appeared to show a positive relationship between intelligence, drive, achievement, ratings for leadership etc and serum uric acid level.[51]

Genius is not a product of gout, but it may be that the uric acid, the gouty poison, acts as a real aid to intellectual achievement. Dr Egon Orowan of the Massachusetts Institute of Technology (MIT) has pointed out that uric acid is chemically related to compounds, including caffeine, that stimulate the cerebral cortex, which is more highly developed in man than in lower animals. Accordingly, the constant stimulus of uric acid may have played a decisive part in the intellectual development of higher primates, and the mutations that led to the loss of *Urate oxidase* may, therefore, have been a vital step in the evolution of man.[52]

As well as in creating human life, uric acid appears to have played a crucial role in extending it

Gout and the secret of longer life

'They give the sick man joy, and praise
The Gout that will prolong his days'
Jonathan Swift

As well as in creating human life, uric acid appears to have played a crucial role in extending it. Even earlier commentators, who knew nothing of uric acid, believed there to be a positive relationship between gout, health and longevity. Quite apart from gout's alleged beneficial side effects, they rated it among the preferable disorders, in that it attested basic soundness of constitution – quite unlike 'wasting conditions' such as consumption (tuberculosis). Accordingly, caution had to be exercised when seeking a cure. Moreover, it was believed that gout represented a kind of overflow pipe – nature's means of evacuating poisons.

Much conventional wisdom, therefore, held gout to be all for the best. For many centuries, when death was a frequent visitor, gout was thought a painful but welcome prophylactic against diseases that killed. In the 17th century, Gilbert Sheldon, archbishop of Canterbury under Charles II, was reported to have offered £1,000 to any person who would 'help him to gout' to protect his health.[53] And in the 18th century, Abraham Buzaglo wrote in his treatise on the subject, 'No disorder whatever will affect them while they labour under the gouty fit.'[54]

Uric acid, even when it is below the concentration needed to cause gout, is even more beneficial than any earlier writers could ever have realised. In humans, urate is extensively reabsorbed through URAT1, the very efficient urate transporter in the human kidney; only around 10 per cent of the filtered load of urate is excreted, which is another reason why humans have higher urate levels than other mammals. This raises the question of why humans require such an effective urate-reabsorption mechanism in their kidneys.

The answer, it seems, is that it helps prolong our lives. The theory of ageing is based on the premise that the maximum life span of a given species increases as the aerobic metabolic rate at rest decreases and body size increases. The long-living turtle is famous for its low metabolic rate, while long-living whales and elephants are very large animals. A low metabolic rate retards the production of toxic reactive oxygen species (ROS), that attack and damage proteins, lipids and DNA. The life of a cell critically depends on powerful antioxidant systems against ROS, and oxidative stress occurs whenever the production of damaging ROS exceeds the capacity of the antioxidative defences.

There are, however, exceptions to the rule. Theoretically, birds should sustain greater ROS damage compared with mammals due to their higher body temperatures and much higher metabolic rates. Yet birds have great longevity for their body size; a 20g mouse that lives three years experiences about one twentieth of the oxidative burden of a 20g canary that lives 20 years. The magic molecule that lets birds get away with their burning fire of ROS is uric acid, one of the most potent scavengers of ROS.[55] In birds, uric acid is bound to a protein in their kidneys, resulting in a soluble compound. This is why birds can tolerate their very high uric acid levels – and grow very old.

Uric acid works all right in birds, but what about humans? For mammals, and especially for primates, an interspecies comparison yields a positive correlation between serum uric acid concentration and species life span, with man coming out in front. The positive relationship has been ascribed to the antioxidative capacity of uric acid that comprises 30–65 per cent of the ROS-scavenging capacity of blood plasma.[56] In an experiment at Copenhagen Muscle Research Centre, muscle samples were obtained before and after exhaustive cycling exercise; results of biochemical analyses indicated that uric acid is oxidised to allantoin in the muscle during exercise, probably due to the generation of ROS during exercise. The study demonstrated for the first time the ROS-scavenging activity of uric acid in working human muscle.[57]

All tissue compartments contain uric acid as a replenishable antioxidant. The major site of production of uric acid in the cardiovascular system is the vessel wall; the ROS activity is localised chiefly in the endothelial cells. Interestingly, a recent study showed that treating ischaemic heart-disease patients with allopurinol, a drug that decreases the uric acid level in the body, in no way improved outcome; rather, the damage to the heart muscle increased significantly.[58]

The disappearance of *Urate oxidase*, the uric-acid-degrading enzyme, and the evolution of URAT1, the uric-acid-retaining transporter, were both crucially important in producing the high levels of uric acid in humans. In combination with genetic or environmental factors, uric acid can be detrimental when it accumulates at high levels, as gout sufferers down the ages testify. But even they might agree that gout is a risk well worth running when a longer life for all of us is the upside. And especially when sex and wine do not, after all, seem to increase the risk, longer need not mean sadder in those terms. As people have thought for thousands of years, even if not always for the right reasons, gout, or at least the possibility of it, is both a bane and a boon. ■

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