

Review

A concise history of gout and hyperuricemia and their treatment

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Abstract

First identified by the Egyptians in 2640 BC, podagra (acute gout occurring in the first metatarsophalangeal joint) was later recognized by Hippocrates in the fifth century BC, who referred to it as 'the unwalkable disease'. The term is derived from the Latin word *gutta* (or 'drop'), and referred to the prevailing medieval belief that an excess of one of the four 'humors' – which in equilibrium were thought to maintain health – would, under certain circumstances, 'drop' or flow into a joint, causing pain and inflammation. Throughout history, gout has been associated with rich foods and excessive alcohol consumption. Because it is clearly associated with a lifestyle that, at least in the past, could only be afforded by the affluent, gout has been referred to as the 'disease of kings'. Although there is evidence that colchicine, an alkaloid derived from the autumn crocus (*Colchicum autumnale*), was used as a powerful purgative in ancient Greece more than 2000 years ago, its first use as a selective and specific treatment for gout is attributed to the Byzantine Christian physician Alexander of Tralles in the sixth century AD. Uricosuric agents were first used at the end of the 19th century. In the modern era, nonsteroidal anti-inflammatory drugs are usually the drugs of choice for treating acute gout. Perhaps the most important historical advance in the treatment of hyperuricemia was the development of xanthine oxidase inhibitors, which are effective in reducing plasma and urinary urate levels and have been shown to reverse the development of tophaceous deposits.

Introduction

Gouty arthritis was among the earliest diseases to be recognized as a clinical entity. First identified by the Egyptians in 2640 BC [1], podagra (acute gout occurring in the first metatarsophalangeal joint) was later recognized by Hippocrates in the fifth century BC, who referred to it as 'the unwalkable disease'. Some of Hippocrates' remarkable clinical perceptions in relation to gout are preserved in aphorisms, which are as true today as they were 2500 years ago (Table 1) [2]. Hippocrates also noted the link between the disease and an intemperate lifestyle, referring to podagra as an 'arthritis of the rich', as opposed to rheumatism, an arthritis of the poor. Six centuries later, Galen was the first to describe tophi, the crystallized monosodium urate deposits that can follow longstanding hyperuricemia. Galen associated gout with debauchery and intemperance, but also recognized

a hereditary trait [3] that had previously been referred to by the Roman senator Seneca [4].

The first person to use the word 'gout' to describe podagra (*gutta quam podagram vel artitcam vocant* – 'the gout that is called podagra or arthritis') was the Dominican monk Randolphus of Bocking, domestic chaplain to the Bishop of Chichester (1197–1258) [5]. The term is derived from the Latin word *gutta* (or 'drop'), and referred to the prevailing medieval belief that an excess of one of the four 'humors' – which in equilibrium were thought to maintain health – would, under certain circumstances, 'drop' or flow into a joint, causing pain and inflammation. Later, gout was described by Thomas Sydenham, the famous English physician and proponent of hippocratic medicine, who was himself disabled by gout and renal disease [6]:

"The patient goes to bed and sleeps quietly until about two in the morning when he is awakened by a pain which usually seizes the great toe, but sometimes the heel, the calf of the leg or the ankle. The pain resembles that of a dislocated bone ... and this is immediately succeeded by a chillness, shivering and a slight fever ... the pain ... , which is mild in the beginning ... , grows gradually more violent every hour ... so exquisitely painful as not to endure the weight of the clothes nor the shaking of the room from a person walking briskly therein."

Throughout history gout has been associated with rich foods and excessive alcohol consumption. Because it is clearly associated with a lifestyle that, at least in the past, could only be afforded by the affluent, gout has been referred to as the 'disease of kings'. In some eras gout was perceived as socially desirable because of its prevalence among the politically and socially powerful. In his classic monograph on the history of gout [5], Copeman refers to a comment in the London *Times* in 1900, "The common cold is well named – but the gout seems instantly to raise the patient's social status", and to another in *Punch* in 1964, "In keeping with the spirit of more

Table 1**Five aphorisms of Hippocrates on gout**

Aphorism	Details
VI-28	Eunuchs do not take the gout, nor become bald
VI-29	A woman does not take the gout, unless her menses be stopped
VI-30	A youth does not get gout before sexual intercourse
VI-40	In gouty affections, inflammation subsides within 40 days
XI-55	Gouty affections become active in spring and in autumn

From Hippocrates [2].

democratic times, gout is becoming less upper-class and is now open to all ... It is ridiculous that a man should be barred from enjoying gout because he went to the wrong school."

In earlier times, attacks of gout were also seen as a prophylactic against more serious diseases. According to the writer Horace Walpole [7], gout "prevents other illnesses and prolongs life ... could I cure that gout, should not I have a fever, a palsy, or an apoplexy?"

In recent decades, however, the diet and lifestyle that predispose individuals to hyperuricemia and gout have become increasingly common. The role of excess dietary purines (derived from meat, seafood, and beer) in the development of gout is illustrated by the disparity between the incidence of gout in Asia and Europe. Traditional Asian diets, based on rice and vegetables, are low in dietary purines, and gout has been relatively rare in these cultures. In contrast, European and American diets, which are high in meat and certain seafoods, are associated with hyperuricemia and gout [8,9]. Increasing affluence has also led to an expansion in the number of people following a westernized diet and lifestyle, and this has been paralleled by an increase in the incidence and prevalence of gout worldwide.

Historically, gout has been considered to be primarily a male disease. The fact that women can also develop gout was first recognized during the reign of Nero (AD 54–68) by Seneca, who observed, "in this age, women rival men in every kind of lasciviousness ... why need we then be surprised at seeing so many of the female sex afflicted with the gout?" [4]. In the modern era, although gout remains primarily a disease of men in middle age, it has become increasingly more frequent in women, particularly after the menopause.

Uric acid as a factor in the causation of gout

Antoni van Leeuwenhoek (1632–1723), one of the pioneers of microscopy, was the first to describe the appearance of the crystals from a gouty tophus, although their chemical composition was unknown at that time. He wrote in 1679 [10]:

"I observed the solid matter which to our eyes resembles chalk, and saw to my great astonishment

that I was mistaken in my opinion, for it consisted of nothing but long, transparent little particles, many pointed at both ends and about 4 'axes' of the globules in length. I can not better describe that by supposing that we saw with naked eye pieces from a horse-tail cut to a length of one sixth of an inch."

Fifty-five years later the physician and noted antiquarian William Stukeley, who also suffered from gout, described the crystals from a tophaceous joint [11]. In 1776 the chemical identity of uric acid was first established as a constituent of a renal calculus by the Swedish chemist Scheele [12], and the English chemist Woolaston demonstrated urate in a tophus from his own ear in 1797 [13]. Fifty years later, Sir Alfred Baring Garrod described his famous 'thread test', a semiquantitative method for the measurement of uric acid in the serum or urine; it was the first clinical chemical test ever undertaken [14]. In his remarkable volume *The Nature and Treatment of Gout and Rheumatic Gout* (1859) [15], Garrod stated that, "the deposited urate of soda may be looked upon as the cause, and not the effect, of the gouty inflammation". Experimental support for this hypothesis later came from Freudweiler's demonstration that acute gouty arthritis could be precipitated by the intra-articular injection of microcrystals of sodium urate [16] and from the work of His [17], which demonstrated the formation of tophi following subcutaneous injection of urate crystals. These experiments were overlooked for more than half a century until the publication of a seminal paper by McCarty and Hollander [18], which showed that crystals from the synovial fluid of patients with gout were composed of monosodium urate. Their classic report described the use of compensated polarized light microscopy to examine joint fluid for crystals, and this technique was subsequently used to identify calcium pyrophosphate dehydrate crystals in synovial fluid from the joints of patients with chondrocalcinosis and 'pseudogout' [19].

It was recognized that gout could be inherited as early as the second century AD by the distinguished Cappadocian physician Aretaeus, who described what he called a gouty 'diathesis' [20]. However, it was to be the 18th century before gout became associated with certain external, and possibly inherited, physical characteristics by the Edinburgh physician William Cullen, who wrote, "The gout attacks men of especially robust and large bodies, men of large heads ... and men whose skins are covered with a thick rete mucosum with coarse surface ... especially men of a choleric-sanguine type ... [whose fathers had suffered]" [5]. In 1771, William Cadogan asked, "If the features of the countenance, the outside of the body, are often hereditary, why not also the inside?" Despite these observations, it was not until 1931 that Sir Archibald Garrod (the son of Sir Alfred Garrod) suggested that gout be included among disorders that could result from 'inborn errors of metabolism' [21], and the first specific purine enzyme deficiency to be associated with a rare type of inherited gout was not described until 1967 [22].

Earlier, Seegmiller and colleagues [23] had described the relative roles of excessive urate production and impaired excretion in the pathogenesis of hyperuricemia.

Treatments for gout through the ages

Although there is evidence that colchicine, an alkaloid derived from the autumn crocus (*Colchicum autumnale*), was used as a powerful purgative in ancient Greece more than 2000 years ago [5], its first use as a selective and specific treatment for gout is attributed to the Byzantine Christian physician Alexander of Tralles in the sixth century AD [5]. Although colchicine was useful for the treatment of acute gout, it was recognized from earliest times that it could cause severe gastrointestinal side effects. Because of the great influence of Thomas Sydenham ('the English Hippocrates'), who rejected all medications that were purgatives as being too toxic for use, colchicine was not used for the treatment of gout for about 150 years [5] until its rediscovery in 1763 by Professor Baron Von Stoerk in Vienna [24]. In the modern era, nonsteroidal anti-inflammatory drugs (NSAIDs) are usually the drugs of choice for treating acute gout, whereas selective cyclo-oxygenase-2 inhibitors and intra-articular or systemic corticosteroids are used less frequently to control acute attacks in patients with relative contraindications to NSAIDs [25].

Although diet has long been recognized as a major causative factor in the pathogenesis of hyperuricemia and gout, dietary restriction or modification as a means of controlling gout and hyperuricemia has been and continues to be largely neglected. AB Garrod was among the first to suggest that hyperuricemia could be controlled by lowering the intake of purine-rich food [26]. This was confirmed by Haig in a series of clinical experiments he conducted on himself from 1894 to 1897 [27], and more recently in clinical physiological studies on patients given purine-free formula diets [28].

Uricosuric agents, which enhance the renal clearance of urate, were first used at the end of the 19th century [29]. See (1877) [30] was able to induce uricosuria and resolution of tophi in a patient with gout by administering large doses of salicylates. However, salicylates have a bimodal effect on urate excretion; at low doses they reduce urate excretion, whereas at high doses (4–6 g/day) they are uricosuric [31]. Salicylates were, however, not long used for treating patients with gout because of the toxicity and impracticality of high-dose therapy, and they were supplanted as uricosuric agents by probenecid [32], sulfinpyrazone [33], and benzbromarone [34]. More recently, the antihypertensive agent losartan (an angiotensin II antagonist) and the lipid-lowering fibrate fenofibrate were shown to have moderate uricosuric effects [35,36], although neither is licensed for the treatment of gout or hyperuricemia.

In most mammalian species that express the enzyme urate oxidase (uricase), which converts urate to the more soluble

and easily excreted compound allantoin, urate levels are low and gout does not occur. In 1957, London and Hudson published the first report of the use of uricase in two individuals: one with a long history of typical gouty arthritis and the other with no medical history of gout [37]. By measuring urinary allantoin and serum uric acid levels, the investigators determined that purified uricase, administered intravenously, has potent uricolytic activity. Infusion of recombinant fungal uricase has also been shown to be effective in preventing acute uric acid nephropathy due to tumor lysis in patients with malignancies [38]. However, the short half-life and potential immunogenicity of fungal uricase limits its prolonged use for treating chronic gout. Phase III trials of a pegylated, recombinant porcine uricase for chronic treatment of gout are currently underway.

Perhaps the most important historical advance in the treatment of hyperuricemia was the development of allopurinol, the first xanthine oxidase inhibitor [39]. George Hitchings and Gertrude Elion were awarded the 1988 Nobel prize in medicine for their work in developing allopurinol, azathioprine, and five other drugs. Allopurinol has since become the most frequently used uric acid lowering drug in clinical practice. Xanthine oxidase inhibitors, which act by inhibiting the synthesis of uric acid from hypoxanthine and xanthine, are effective in reducing plasma and urinary urate levels and have been shown to reverse the development of tophaceous deposits. Oxypurinol, the active metabolite of allopurinol, can be obtained for compassionate use in some countries [40], and febuxostat, a novel selective inhibitor of xanthine oxidase, has recently completed phase II [41] and phase III [42] clinical trials, which have shown it to be highly effective in lowering uric acid levels in patients with chronic gout and hyperuricemia.

Asides on the influence of gout on American political history

William Pitt: gout, taxes and the American colonies

The disabling gouty arthritis of the British statesman William Pitt the Elder was a major factor in Britain's loss of the American colonies. It was during one of Pitt's gout-related absences from Parliament that the Stamp Act (1765) was passed, which forced the unwilling colonists to pay a tax, determined by the British Parliament, to defray the costs of defending the colonies against French attack. Upon recovering from his gout, Pitt succeeded in getting the Act repealed with the famous words, "The Americans are the sons, not the bastards, of England. As subjects, they are entitled to the right of common representation and cannot be bound to pay taxes without their consent." Unfortunately, during another of Pitt's absences due to an episode of gout, Lord Townshend persuaded Parliament to levy a heavy duty on colonial imports of tea to raise the necessary revenues. This precipitated the Boston Tea Party in 1773, and the rest is history! (From Copeman [5].)

Figure 1



By Royal Authority. A new way of mounting your horse in spite of the Gout. George Cruikshank, 1799.

Franklin, Jefferson, and the Comte de Vergennes: pivotal figures during the American Revolution whose relationships were crystallized by their gout affliction

Gout played a role in the outcome, as well as the origins, of the American Revolution, the signing of the Declaration of Independence, and the ratification of the Constitution. Benjamin Franklin – the only person to have signed all three founding documents of the USA – suffered from severe gout, as did Thomas Jefferson and the Comte de Vergennes, a French nobleman who was instrumental in obtaining the money to finance the Revolution. Reportedly, Franklin was so severely afflicted by gout that he was carried by convicts in a sedan chair to the Constitutional Convention. Some have speculated that these pivotal figures in American history had such strong connections because they were all sufferers of gout. (From Schwartz [1].)

John Hancock may have used gout for political leverage

By 9 January 1788, five of the nine required states had ratified the Constitution. One notable holdout was Massachusetts, whose governor, revolutionary leader John Hancock, was unable to make up his mind on the Constitution and took to his bed with what was seen at the time as a convenient case of gout. Later, after being tempted by the Federalists with the vice presidency, Hancock experienced a miraculous cure and delivered his critical block of votes. On 6 February, with the Federalists agreeing to recommend the addition of a bill of rights, Massachusetts ratified the Constitution by a slim margin. (From the National Archives [43].)

Conclusion

With a history spanning more than 2500 years, gout is among the oldest recognized diseases. Its profound impact on patient quality of life, as illustrated in memorable medical

Figure 2



The Gout, James Gilray, 1799.

cartoons and images (Figs 1 and 2), has even influenced historical events (see Historical asides, above).

During the past 50 years advances in understanding the causes and pathophysiology of hyperuricemia and gout, have led to the development of effective therapies. As a result gout has become a paradigm for the rational treatment and prevention of a chronic rheumatic disease.

Competing interests

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