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Gout (A Gibofsky, Section Editor)

Gout and Hyperuricemia: an Historical Perspective

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Opinion statement

Gout is a common disorder of uric acid metabolism. A disease of antiquity its' often dramatic presentation and unique manifestations have been familiar for eons to clinicians and to its sufferers. Effective modern therapies may have downgraded its status, yet it's long, rich history remains a source of fascination, indeed entertainment to those with an interest in the pathophysiology of disease, therapeutic discovery, indeed with the annals of medicine. This paper reviews the history of one of the oldest afflictions of mankind.

George Cruikshank (1792–1878)

Introduction

Gout is a disorder of uric acid metabolism resulting in excessive concentrations of uric acid in the blood. Its course is punctuated by the episodic deposition of urate in the joints of the extremities, particularly the great toe. Affected joints become markedly inflamed and painful, some patients depositing concretions of uric acid (likened to chalk) into the affected joints, known as tophi. Due to its unique presentation, well-established pathophysiology, and effective therapy, gout as a condition is well known to rheumatologists, indeed physicians of every stripe.

With origins in antiquity, gout has not only seized the interest of physicians, but also provoked a voluminous literature, frequently products of its sufferers. Accompanying this written outpouring has been an equally vigorous portraiture depicting the experience with the condition. Coupling these sociological phenomena with its remarkable story of scientific discovery, gout fascinates at multiple levels. This paper reviews the history of this disease emphasizing how clinical observation lead to mechanistic understanding, upon which rationale therapy was developed.

Clinical descriptions

"is the most violent of all joint affections, it lasts long, and becomes chronic… the pain may remain fixed in the great toes … it is not fatal" [1••].

An historical chronology of gout highlighting the important milestones in our understanding of this disorder is shown in Table 1. Although the first

Table 1. A chronology of gout

Archeological finds	7000 (BC)	Urate containing kidney stone in Egyptian mummy; great toe (tophus) of male interred in ancient Egyptian burial ground
Hippocrates	400 (BC)	First clinical description of gout
Aretaeus	200	Proposed a toxin in the blood as the cause
Galen	200	First description of tophi
Alexander of Tralles	600	First to indicate the use of colchicum
Geoffroi de Villehardouin	1200	First use of the term "gout" (*gote*)
Thomas Sydenham	1683	Describes acute and chronic forms of the disease; differentiates gout from other forms of arthritis
Anton van Leeuwenhock	1679	Describes the crystaline nature of tophi
Anton de Storck	1700	Rediscovers colchicine
Benjamin Franklin	1814	Introduced colchicine in the USA
Wollaston	1797	Characterized gouty crystals as uric acid
Garrod	1900	Demonstrated increased uric acid in the blood of patients suffering from gout
Beyer	1947	Synthesized Benemid an inhibitor of uric acid secretion
Rundles, Wyngaarden, Hitchings	1963	Discover allopurinol the inhibitor of xanthine oxidase demonstrating its effectiveness in the treatment of gout
Lesch and Nyham	1964	Describe metabolic abnormality of purine metabolism demonstrating a X-linked recessive inheritance
Teijin Pharma	2009	Febuxostat receives FDA approval
Savient Pharmaceuticals	2010	Pegloticase receives FDA approval

clinical description of this condition is attributed to Hippocrates, important contributions to our knowledge concerning its history have been derived from archeological studies. The oldest recorded example of uric acid deposition is the demonstration of a uric acid contacting renal calculus found in an Egyptian mummy dating back 7000 years [2]. In addition, Smith and Jones (1910) described uric acid accretions in the great toe of an elderly male buried in an ancient Egyptian cemetery, the oldest known example of tophi [3]. While virtually nothing is known concerning the clinical recognition of the disorder in these early times, together these discoveries establish gout as a disease of antiquity. However, the historical record concerning the clinical features of gout, its presentation, and natural course begins with Hippocrates (460–370 BC) in whose writing is found the first description of the condition.

Hippocrates of Cos was a Greek physician in the Age of Pericles (Classical Greece), now regarded as perhaps the most outstanding figure in the history of medicine. Often referred to as the father of western medicine, he is widely known for the Hippocratic Oath which is still recited at medical school graduation ceremonies across the globe. Yet, despite his enduring fame and legacy, little is actually known about his thoughts, writings, and work habits. Among his many contributions to clinical medicine, his observations concerning gout (*the unwalkable disease*) include his five aphorisms, truths which have held for 2500 years (Table 2). With these maxims, Hippocrates bestows the condition a personality—an affliction of mature, sexually active men [4•]. Further, Hippocrates was the first to associate the disease with a specific lifestyle (an arthritis of the "rich"), distinguishing it from rheumatism which afflicted the poor [5] and introduced the term "podagra" signifying the involvement of the great toe, differentiating this presentation of the disorder from "chiagra" (involvement of the wrist) and "gonagra" (involvement of the knee). He further recorded observations concerning the prognosis of the disease observing how, prior to the deposition of chalk (tophi), it was easier to control. Once such deposits had occurred, the condition became more refractory to treatment.

Additional important milestones in the understanding of gout followed. Aretaeus the Cappadocian, a second century physician, anticipated the role of uric acid in this condition when he proposed that a specific toxin in the blood was responsible. In his writings, he expanded the clinical descriptions of Hippocrates, emphasizing the predilection for involvement of the great toe, followed by the arch of the foot, extending thereafter to the ankle. Galen (130–200 AD), the Greek physician and philosopher whose theory of humorism dominated medical science for more than 1300 years, would later provide the first description of the tophus, introducing a term derived from the Greek word meaning rough, crumbling rock [4•]. Perhaps due to Galen's stature and influence, advances in the understanding of gout and doubtless many other conditions hit a standstill, for a gap of 1400 years followed until things changed with the arrival of a great English physician, Sir Thomas Sydenham.

Inserted between Galen and Sydenham was one important development however, and it involved terminology. The first use of the term "gout" is attributed to Geoffroi de Villehardouin, a French historian of repute, who first employed it in his *Histoire de l'empire de Constantinople sous les empereurs francois*, written between 1207 and 1212. In this piece, de Villehardouin relates how the count Hugues de Saint Paul suffered (and died) from *une maladie de gote* (a malady of gout) involving his feet and ankles [6]. His selection of the word

Table 2. The Hippocratic aphorisms on gout

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
VI-55	Gouty affections become active in spring and in autumn

"gout" appeared a good one as, to the present, it has proven a durable choice employed to the present day across many languages: in addition to the English gout, the French speak of goutte, the Spanish gota, the Italians gotta, and the Germans gicht, all referencing the same disorder.

Nonetheless, it was not until the seventeenth century that a wave of advances in the understanding of the condition was to take place. By this time, different forms of the condition were appreciated: "regular" gout (the classic presentation of painful, swollen joints), "irregular" or "visceral" gout (a form affecting internal organs), and a third type "flying" gout (in which pain darted erratically around the body). So, it was at this time that the modern history of gout begins. Thomas Sydenham (1624–1689), a towering figure, was too a sufferer of the disease, provided an unsurpassed clinical description of the condition in his influential *A Treatise on Gout and Dropsy* [7••] (Fig. 1). The physician's art, bedside observation (mixed in this case with personal experience), was Sydenham's stock and trade, and no contemporary did this better. He was the first to recognize the acute and chronic forms of the disease and differentiated gout from other forms of arthritis, a seminal insight. As a sufferer, Sydenham experienced his first attack of gout at age 30, followed by a kidney stone 7 years later; rarely out of pain thereafter, the disease interrupted his career regularly.

With Sydenham, gout as a focal point of attention reached an early apogee, the commentary subsequently muted, as attention shifted from clinical to more fundamental discoveries concerning its pathophysiology.

"The patient goes to bed and sleeps quietly till 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 … immediately succeeded by a chillness, shivering and a slight fever. The pain grows gradually more violent every hour, and come to its height towards evening, adapting itself to the numerous bones of the tarsus and metatarsus, the ligaments whereof it affects; sometimes the gnawing of a dog, and sometimes a weight and constriction of the parts affected, which become so exquisitely painful as not to endure the weight of the clothes nor the shaking of the room for a person's walking briskly therein. Things worsen till after twenty-four hours from the first approach of the fit … the patient is suddenly relieved"

Fig. 1. Sydenham's description.

Hyperuricemia

"First of all 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 by long, transparent little particles, many pointed at both ends and about 4 "axes" of the globules in length, others shorter and a few only half as long" [8••].

The discovery of the role of uric acid in the pathophysiology of gout has its own parallel history, a story that begins with Antoni van Leeuwenhoek of Delft (1632–1723). A Dutch biologist and father of microscopy, van Leeuwenhoek, was the first to observe capillaries, red blood cells, bacteria, protozoa, and spermatozoa accomplishments all the more remarkable because of his lack of scientific training. The above quotation of 1679, excerpted from a letter to Lambert van Velthuysen, is the first description of the contents of the gouty tophus. In a letter to the Secretary of the Royal Society this discovery, another of his originals, was reported in the societies' *Philosphical Transactions of the Royal Society of London* (1685). The actual chemical composition of these "pointed particles" however took another 100 years to elucidate.

Uric acid as a distinct substance was discovered by Carl Scheele (1742–1786). This remarkable Swedish chemist and apothecary has a long list of "firsts" of his own, including the discovery of oxygen (with Priestley) as well as numerous other chemical elements and compounds [9••]. Almost simultaneously another Swede, Tobern Bergman, analyzed a bladder stone finding it composed of the same substance [10]. Neither of these men connected the substance Scheele called "lithic acid" to the condition gout. In the same year, a Scottish physician, Murray Forbes, theorized in his *A Treatise upon Gravel and upon Gout* that if urine contained uric acid, then the blood might too; if so, he astutely posited that uric acid might precipitate in other parts of the body thereby explaining the phenomenon of tophi [11]. Following quickly, upon this supposition, W.H. Wollaston (1797), nephew of William Heberden (of Heberden's nodes), isolated uric acid from a gouty tophus and the urinary concretions. The first to actually examine a tophus, Wollaston with this observation had brought everything together dislodging the long entrenched humoral theories with a chemical basis for the disease, a sentinel moment in the history of this condition [12]. Gout had been reframed.

This rapid pace of discovery proved to be unsustainable; however, as the understanding of the mechanisms of gout would now enter a temporary doldrums, the primary contributions coming from several notable physicians (Parkinson, Scudamore, Gairdner) furthering only descriptive observations. Indeed, the next transformative figure was Alfred Baring Garrod (1819–1909). Trained at the University of London, he was to become physician and professor of therapeutics and clinical medicine at that institution. Knighthood followed (1887), and then 3 years later, he was named physician extraordinary to Queen Victoria, perhaps the most prestigious appointment in the land. It was at the University of London where Garrod conducted his seminal research demonstrating the high levels of uric acid (hyperuricemia) in the blood of those suffering from gout. His ideas, presented in his *The Nature and Treatment of Gout*

Table 3. Garrod's hypotheses

I	In true gout, uric acid is present in abnormal quantities in the blood
II	Gouty inflammation is always accompanied by uric acid deposition in the inflamed part
III	The deposits are crystalline and interstitial
IV	The deposited uric acid is causal, not a consequence of gouty inflammation
V	The inflammation accompanying an episode tends to the destruction of uric acid in the blood and the system in general
VI	The kidneys are implicated in gout
VII	The hyperuricemia is the probable cause of the disturbance that precedes the acute illness
VIII	Causes that predispose to gout do so either through the increased formation of uric acid or lead to its retention in the blood
IX	Acute episodes are caused by conditions that induce a less alkaline condition of the blood; greatly augment the formation of uric acid; or impair the excretion of uric acid via the kidney
X	A no disease but true gout has a deposition of uric acid in the inflamed tissue

and Rheumatic Gout, were published the same year (1859) as Darwin's *Origins of Species*. Here, he introduced his famous uric acid "thread test," a simple method for the demonstration of uric acid in the blood [13••]. Adducing evidence both experimental and clinical, Garrod (foreshadowing Koch' s postulates, 1884) developed a set of hypotheses that remain so fundamental to the modern understanding of this disease as to justify their enumeration here (Table 3). The stage was now set for new investigators who would unravel the mysteries of the disease. This required the input of biochemists on the forefront of biochemical and pharmacologic aspects of purine metabolism. Emil Fischer (1852–1919), a Noble Prize recipient, demonstrated that uric acid was a purine compound [14••]. Later, Folin and Denis (1913) described a colorimetric method for the measurement of uric acid in the blood, fostering more research in to this disease [15]. Indeed with what seemed a near complete understanding of the disease, the focus of the 20th century has been the treatment of the condition. Before going there, however, a number of important discoveries of the modern era are worthy of inclusion.

Here again a Garrod enters, this time Archibald, the son of Alfred, a distinguished physician-investigator in his own right. Also knighted in his lifetime, he was appointed the Regius Professor of Medicine at Oxford succeeding the iconic William Osler. Now regarded as the "father" of metabolic medicine, he presented a new view of gout as well as other conditions. Garrod suggested that gout was an inherited disorder, an "inborn error of metabolism", an appellation familiar to physicians of the present day. Indeed with this powerful conceptualization, Garrod introduced the era of molecular medicine. Important contributions to the understanding of purine metabolism were to follow, the work of a number of investigators. Of particular interest was Garrod's discovery of the first inherited abnormality of purine metabolism (Alkaptonuria).

In 1965, Michael Lesch, a medical student, and William Nyhan, a pediatrician, described a metabolic abnormality of purine metabolism, the absence of the salvage enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT), the clinical consequences of which are profound [16•]. The resulting accumulation of uric acid results is a condition characterized by self-mutilating behaviors (lip and finger biting), neurological symptoms (facial grimacing,

involuntary writhing, poor muscle control) and a moderate impairment in intellectual capacity; megaloblastic anemia is also frequently seen. Lesch-Nyhan syndrome (LNS) is a rare disease (1/380,000 births) produced by mutations in the HGPRT gene located on the X chromosome (Xq26). Complete [17] and partial [18] deficiencies of HGPRT have been described explaining the variation in the severity of the disease. As an inherited X-linked disorder, it affects males; women are generally asymptomatic carriers. The diagnosis is suspected in children exhibiting psychomotor delay in the first year of life in association with hyperuricemia or an elevated uric acid/creatinine ratio; the diagnosis is confirmed by enzymatic (HPRT) determinations. Treatment targeting the uric acid overproduction (allopurinol) is effective at controlling such manifestations as gouty arthritis, tophi, and kidney stones; unfortunately, it does not control the behavioral and neurological phenomenon. Nonetheless, many patients now live to adulthood. More recently, a near converse disorder of enzymatic (PRPP) overactivity has also been described [19].

Treatment

Hermodactylon confestim minuit dolores[1]

Another important chapter in the history of gout is how it has been treated over the ages. Early approaches dating to Hippocrates emphasized the role of diet recommending barley water, purging (*white hellebore*), and counterirritation such as scorching the veins contiguous with the affected joint, an early form of pain management. Galen later added bleeding, a favored accompaniment to his therapies. The approaches of these authorities dominated the therapeutic landscape for the next 1000 years.

As indicated in Table 1, the first historical reference to a more "pharmacological" approach to the treatment of gout surfaces in the works of Alexander of Tralles (sixth century), a Byzantine physician who reported on the salutary powers of hermodactyl (the finger of Hermes quoted above), a drug derived from colchicum (*Colchicum autumnale*). Although confusion exists concerning terminology and botanical sources, it is remarkable that colchicine (in an ancient formulation) appears first and remains a mainstay of our armamentarium to the current day [20, 21•]. The term "colchicum" references the ancient Black Sea district Colchis, the original source of the plant species from which it was obtained. An alkaloid composed of a complex ring, colchicine is obtained from the seeds and corn of *Colchicum autumnale*, a bulb also know as "autumn crocus" or "wild" or "meadow saffon" [20]. The toxicity of colchicum was well known to physicians of the time. Dodoems for instance describes that among its effects, it may *stirreth up tossing, wamblings, windinesse, and vomting and subverteth and overturneth the somacke*, acknowledging side effects of colchicine well known to a present day clinician [22]. Indeed, its cathartic effects fit well with the humoral theory of disease; its mechanism presumes the facilitation of the evacuation of evil humors.

Colchicine was rediscovered by Baron Anton de Storck, physician to Maria Theresa of Austria in the mid 1700s, although he used it for its diuretic properties in the treatment of dropsy rather than gout [23]. Its acceptance at that time was muted by the authoritative Thomas Syndenham who cautioned against its use. Wider recognition of its efficacy however developed as a result of another preparation; the use of which caught fire at this time.

Eau medicinale, the brainchild of a Nicholas d'Husson, a former French army officer was touted to purify the blood serving as a panacea relieving… *generally all those maladies resulting from a corruption of the blood or humors, above all when these have not become too chronic and when nature is still strong enough to act conjointly with the remedy* [20]. Gout, of course, was among the conditions it was purported to ease. Despite controversy regarding its efficacy—patients loved it, physicians did not—by the early 1800s, the use of *eau medicinale* was mushrooming, its celebrity helped along by the testimonials of *persons of considerable rank and consequence* [20]. Finally, in 1814, came an announcement. The active ingredient of *Eau medicinale* was found, none other than hermodactyl, or the root of *C. autumnale*, that is colchicine [24]. Although the veracity of this finding was immediately challenged, the episode served to resurrect colchicine, *eau medicinale* soon fading from favor. That same year, Benjamin Franklin, a notable sufferer of gout, brought a similar elixir, *L'eau d'Husson*, back from France for the treatment of his condition [25]. Subsequent analysis proved the compound to be colchicum. The name colchicine was soon proposed by Geiger [26].

These elixors were of course just examples of the therapies of the day. As can be imagined, in this golden age of quackery, countless remedies were promoted, the range of which is near cosmic: heat (sand), cold, various caustics and counterirritants, ointments as well as magnets, even sparks [5]. Auguring a contemporary craze, an early exercise machine, the Gymnasticon, was purported by its inventor (Francis Lowndes) to help those suffering with *gout*, *palsy*, *rheumatism*, *debility*, *contraction* (http://en.wikipedia.org/wiki/Gymnasticon).

More than a century passed before the next major therapeutic advance. Initially developed as an inhibitor of the renal excretion of penicillin, probenecid was found to inhibit the tubular reabsorption of filtered urate suggesting a role in the treatment of gout. Gutman et al. demonstrated its clinical benefit in chronic tophaceous gout [27••]. Following this discovery, a major therapeutic breakthrough came with the observation that the hypoxanthine analog allopurinol was a potent xanthine oxidase inhibitor, work for which Hitchings and Elion were awarded the Nobel Prize (1988). Initially used to reduce the hyperuricemic-uricosuric effects of chemotherapy in the treatment of leukemia, its potential role in the treatment of gout was immediately appreciated and confirmed [28•, 29], closing the historical loop initiated by Alfred Garrod 100 years before. To the present, allopurinol remains the bedrock therapy for the prevention of gout, urate lithiasis and as an adjunct to cancer therapy.

Not to be forgotten are the anti-inflammatories. Acetylsalicylic acid (ASA, Aspirin), another therapeutic compound with roots in the Old World, had been employed in the treatment of gout (and other rheumatic diseases) for years. Indeed as early as 1877, the uricosuric effect (with the resolution of tophi) of ASA were reported in a patient treated with large doses of salicylate [5] [30]. By the mid 20th century, however, new anti-inflammatory agents were added to the armamentarium, notably corticosteroids, adrenocorticotropin, and a new class of drugs based on cyclooxygenase-1 inhibition (COX-1). More recently, two new agents have been developed for the treatment of gout. Febuxostat (Uloric), a new

xanthine oxidase inhibitor, is considered a second-line drug after allopurinol and pegloticase (Krytexxa), a more novel therapy. A pegylated recombinant uricase, pegloticase metabolizes uric acid to allantoin a substance more soluble than uric acid and thus less likely to precipitate. As an infusion therapy, its use is currently restricted to individuals intolerant or refractory to the other options.

Finally, a word about diet and lifestyle. The role of excessive alcohol and certain foods, specifically those containing excess purine, has been recognized for centuries. That for much of history only the affluent could afford such luxury may be in part responsible for the epidemiology of the disease. Although modern therapy has significantly diminished the therapeutic importance of lifestyle modification, observations concerning global shifts in the distribution of gout continue to support a central role for such lifestyle influences in the genesis of the condition [31, 32].

Notable victims

Morbus dominorum et dominus morborum [33][2]

It is readily acknowledged that an attack of gout is a memorable experience, the condition indeed for some debilitating. Yet, gout may have achieved its renown, not so much for how but rather who it affected. So colorful is this history that no review is complete without a commentary concerning its prey.

Gout has long been associated with the great, the glamorous, and the gentile. Historically considered an ailment of the elite (*a monarch among maladies*), the upper crust sufferers (almost always men) approached the condition as a natural accompaniment to a life of accomplishment. Often anticipated with a touch of pride, the malady was borne with stoicism, considered virtually a "life cycle" for those of a certain station. Gout, as a subject for discourse in the lay and medical literature, trumped many of its competitors, some of which carried more ominous and fearful implications. Fever, inflammation, and dropsy are just a few of the disorders that might have competed for the attention of earlier commentators. Yet, no other disease caught the public's notice as gout did, owing no doubt to the memorable nature of its symptoms and perhaps because of who its sufferers were. The idea that they lived to recount their experiences (and did so prolifically) may have also played a role. Indeed this fact, that gout rarely kills, may have accounted for a widely held belief in its capacity for *inoculating against worse* [5]. According to this conception gout provided resistance to the many other more serious conditions and, as such, was viewed as protective—*nature's way of throwing off peccant humors* [34]. Taking this to its extreme, some even challenged the designation of gout as a disease.[3] It was a blessing in disguise.

A vast and graphic portraiture was also stimulated. Usually satirical in nature, gouty sufferers are the subject of thousands of woodcuts, line engravings, and color prints, a visual history championed by Gerald Rodnan [35, 36] and his well known print collection. Easily accessed via the American College of Rheumatology (ACR) website (www.rheumatology.com), when seen in its entirety, the collection emerges as a unique genre of medical caricature.

Among the well to do, gout showed no prejudice [37]. Statesmen, royalty warriors, scientists, artists, theologians, men of letters, and even physicians were not spared of its spleen. Indeed such individuals are responsible for the colorful

descriptions of the disease, some employed to the present day. Descriptions of an acute attack, likening the experience to *walking on my eyeballs* [38] or *so exquisitely painful as to not endure the weight of the clothes* [39] are familiar to modern day students and practitioners. The list of memorable sufferers is enumerable. Familiar afflicted personages include: the statesmen Benjamin Franklin, Thomas Jefferson, and William Pitt; royalty with Queen Anne of Scotland, England and Ireland, and Charles V, the Holy Roman Emperor; the warriors Alexander the Great and Charlemagne; the artist Leonardo da Vinci; John Calvin and Cotton Mather, theologians; and such distinguished men of letters as John Milton, Samuel Johnson, and Martin Luther. Scientists including Charles Darwin, Carl Linnaeus, and Isaac Newton also suffered from the disease. Physicians too were not spared with such notables as William Harvey, John Hunter, and Thomas Sydenham developing gout in their lifetime; William Osler was too stricken ("I cannot take a glass of champagne without feeling it in my great toe"). Given the collective accomplishments of this arbitrary and much abridged list of the afflicted, the upper class notion of gout is readily understood, as is its perceived desirability. This is indeed a club to which one would aspire membership.

In closing, an historical discussion of gout should not neglect the contributions of several 20th century commentators. Notable among these are Copeman whose book *A Short History of the Gout and the Rheumatic Diseases* was influential [40]. Rodnan and Benedek, quoted here, were also prodigious reporters. Further, a recent textbook provides a succinct and useful historical review [41•]. One source, however, stands alone.

Since the 1998 publication of Porter and Rousseau's *Gout*: *The Patrician Malady* [42••], no attempts to summarize the history of this condition can stand beyond the shadow of this remarkable work. Comprehensive, erudite, and rich with insight, it is an essential reading for those curious about the historical origins of the disease. The summation presented herein, pale in comparison, nonetheless offers a précis of the high points of a fascinating story. At the beginning, ancient descriptions establish gout as among the oldest diseases of mankind. Following a time honored path of medical detection, its slow unraveling begins with clinical observation, more nuanced with successive telling, its sociological allusions adding characters and color. Basic science, when it finally had the tools, entered uncovering the crystalline nature of the disease, identifying the crystals involved and, with the advent of modern techniques, defined the metabolic nature of the disease. Directed therapies, based on modern principles of pharmacology, soon followed, and once incorporated into medical practice, this regal disease was permanently tamed. Perhaps the story is over but, as a paradigmatic case of medical discovery, the allure of its history will likely embrace the generations to come.

> *Next Gout appears with limping pace,*
> *Pleads how he shifts from place to place,*
> *From head to toe how swift he flies,*
> *And ev'ry joint and sinew plys,*
> *Still working when he seems supprest,*
> *A most tenacious stubborn guest. [43]*

6. Notes

1. Translates as "the finger of Hermes immediately relieves pain."
2. Translates as "lord of disease and disease of lords."
3. "I believe the gout a remedy and not a disease, and being so no wonder there is no medicine for it". From: Walpole to Sir Horace Mann, 25 July 1785, quoted in Copeman (www.rheumatology.com).

Compliance with Ethics Guidelines

Conflict of Interest
C. Ronald MacKenzie declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Hippocrates, on the afflictions of the parts. See Hippocrates, Aphorisms, in vol. 4 of Hippocrates (1923–31).
2. Kittredge WE, Downs R. The role of gout in the formation of urinary calculi. J Urol. 1952;67:841.
3. Smith GE, Jones FW. The archeological survey of Nubia, report for 1907–89, Vol. 2. Cairo, National Printing Department: 1910, pp. 44 and 269.
4. Porter R. Gout: framing and fantasizing disease. Bull Hist Med 1994;68.
5. Nuki G, Simkin PA. A concise history of gout and hyperuricemia and their treatment. Arthr Res Ther. 2006;8(1):1–5.
6. Neuwirth E. Milestones in the diagnosis and treatment of gout. Arch Int Med. 1943;72:377–87.
7. Sydenham T. A treatise of the gout and dropsy. London: GGJ.J Robinson. W. Otridge, S Hayes and E Newbery. 1683.
8. McCarty DJ. A historical note: Leeuvenhoek's description of crystals from a gouty tophus. Arthritis Rheum. 1970;13(4):414–18.
9. Scheele KW. Examen chemicum calculi urinarii. Opusula 1776;2:73.
10. Bergman TO. A dissertation on elective attractions. Translated by the Translator of Spallanzani's Dissertations. Trans. Thomas Beddoes. 1785. London: J. Murray.
11. Forbes M. A treatise upon gravel and upon gout. 1793. London: T. Cadell.
12. Wollaston WH. On gouty and urinary concretions. Philos Trans R Soc Lond. 1797;87:386.
13. Garrod AB. The nature and treatment of gout and rheumatic gout. 1859 (First ed), 1863 (2nd ed), 1876 (3rd ed). London: Walton & Maberly; London: Longmans, Green.
14. Fischer E. Untersuchungen in der puringruppe. New York: Springer; 1907.
15. Folin O, Denis A. A new (calorimetric) method for the determination of uric acid in the blood. J Biol Chem. 1912–13;13:469.
16.• Lesch M, Nyhan WL. A familial disorder of uric acid metabolism and central nervous system function. Am J Med. 1964;36:561.

A seminal discovery in the discovery of uric acid mediated diseases.

17. Seegmiler JE, Rosenbloom FM, Kelly WN. Enzyme defect associated with a sex-linked human neurological disorder and excessive purine synthesis. Science. 1967;155:1682–84.
18. Kelley WM, Rosenbloom FM, Henderson JF, Seegniller JE. A specific enzyme defect in gout associated with overproduction of uric acid. Proc Natl Acad Sci U S A. 1967;57:1735–39.
19. Sperling O, Eliam G, Persky-Brosh S, et al. Accelerated erythrocyte 5′-phosphor-ribosylpyrophosphate

synthesis. A familial abnormality associated with excessive uric acid production and gout. Biochem Med. 1972;6:310.
20. Hartung EF. History and the use of colchicum and related medications in gout. Ann Rheum Dis. 1954;13:190–00.
21.• Rodnan GP, Benedek TG. The early history of antirheumatic drugs. Arthrit Rheum. 1970;13(2):145–65.
Rodnan and Benedek are amongst the most prodigious of the modern contributors to the historical discourse concerning gout. This paper was chosen simply to highlight these investigators. Anything written by them having to do with gout is worth exploring.
22. Dodoens R. A new herball or historie of plants. Translated by Lyte H, Edm. Bollifant, London, 1595, pg 424.
23. von Storch A. An essay on the use and effects of the root of the colchicum autumnale, or meadow-saffron. T Becket and PA DeHondt, London, 1764.
24. Want J. Composition of eau medicinale. London Med Phys J. 1814;32:312.
25. Want J. The use of Colchicum autummale in rheumatism. Med Physiol J (Lond) 1814;32312
26. Geiger PL. Ober einige neue giftige organische Alkalien. Liebig's Ann Pharm. 1833;269:1833.
27. Gutman AB, Yu TF. Benemid, (p-[di-n-propylsulfamyl]-benzoic acid) as uricosuric agent in chronic gouty arthritis. Trans Assoc Am Phy. 1951;64:279.
28.• Wyndaarden JB, Rundles RW, Silberman HR. Control of hyperuricemia with hydroxypyrazolpyrimidine, a purine analogue which inhibits uric acid synthesis. Arthritis Rheum. 1963;6:306.
Another seminal paper concerning the development of the modern treatment of gout.
29. Rundles RW, Wyngaarden JB, Hichings GH, Elion GB, Silberman HR. Effects of a xanthine oxides inhibitor on thiopurine metabolism, hyperuricemia and gout. Trans Assoc Am Physicians. 1963;76:126–40.
30. See G. Etudes sur l'acid salicylique et les salicylates: traitement du rhumatiswme aigu et chronique, de la goutte, et de diverses affections du system nerveux sensitive par les salicylates. Bull Acad Med Paris. 1877;6:689–06.
31. Zollner N. Influences of various purines on uric acid metabolism. Bibl Nutr Dieta. 1973;19:34–43.
32. Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Purine-rich foods, dairy and protein intake, and the risk of gout in men. N Eng J Med. 2004;350:1093–03.
33. Scholtens M. The glorification of gout in 16th to 18th century literature. CMAJ. 2008;179(8):804–5.
34. Letters of Edward Gibbon(n.4),2:239.
35. Rodnan G. A gallery of gout. Arthritis Rheum. 1961;4:27–46.
36. Rodnan G. A gallery of gout. Arthritis Rheum. 1961;2:176–94.
37. Newcombe SD, Robinson DR. Brief history of gout. In: Newcombe SD, Robinson DR, editors. Gout: basic science and clinical practice. New York, Heidelberg, Dordrecht, London: Springer; 2013.
38. Smith S. Letter to countess gray. Lady Holland, ed. (1855), ii.565.
39. Sydenham T. "On Gout". In: The works of Thomas Sydenham, Vol. II, pp.123-62. London Sydenham Society. 1984. Reprint: Classics of Medicine Library.
40. Copeman WSC. A short history of the gout and the rheumatic diseases. Berkeley: Univ Calf Press; 1964.
41. Newcombe DS, Robinson DW. Gout: Basic science and clinical practice. 2013, Springer.
42.•• Porter R, Rousseau GS. Gout: The patrician malady. New Haven and London: Yale University Press; 1998.
An extraordinary retelling of the history of gout. If one reads this book there is no need to read any other historical reference to this condition.
43. John G. Fable XLVII, from the poems of John Gay, ed V.A. dearing. Oxford: Clarendon; 1974. p. 364–5.