Some historical remarks on microcrystalline arthritis (gout and chondrocalcinosis)

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SUMMARY

The history of microcrystalline arthritis only began in 1961 when Daniel McCarty and Joseph Lee Hollander demonstrated the presence of sodium monourate crystals in the synovial fluid of gouty patients. However, gout is a historical disease, thanks to the descriptions of Hippocrates, Caelius Aurelianus, Soranus of Ephesus and Araeteus of Cappadocia. The relationship between hyperuricemia and gout was first documented in the nineteenth century by Alfred Baring Garrod, who demonstrated deposits of uric acid crystals on a linen thread held dipped in acidified blood (the so-called "thread method"). Gout has always been considered a prerogative of the moneyed classes (arthritis divitum), and history is full of famous gouty personalities, including kings, emperors, popes, commanders, politicians, artists, writers, philosophers and scientists. Another form of microcrystalline arthritis, chondrocalcinosis, was identified as being a rheumatic disorder different from gout in the 1960s. As a specific clinical entity, it was first identified in 1958 by Dušan Žitňan and Štefan Sit'aj in a few Slovak families.

***Key words**: microcrystalline arthritis, gout, chondrocalcinosis, history of medicine.*

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GOUT

Gout has always been the focus of historical interest, and not only for rheumatologists (1). Indeed, there are a number of good reasons to call it a "historical" disease:

a) gout is almost certainly the oldest disease that was correctly recognized in relation to current knowledge;
b) it has always been the best known rheumatic disease, representing until a short time ago a kind of touchstone for other types of arthritis;
c) even some quite recent historical events changed its epidemiology;
d) an unusually high number of historical figures suffered from gout.

According to a historical source, (2) the term "gout" (from the Latin *gutta* or drop) was first used in the thirteenth century by the English Dominican monk Ralph Bocking (also known as Radulphus Bockingus) and by the French historian Geoffroi de Villehardouin (3). It was inspired by the Hippocratic doctrine of humors, meaning the slow dripping of fluids flowing into the joints leading to articular diseases. The Greeks, however, did not have a unique term to describe the disease, and its name changed according to the joint involved: *podagra* (from *pous*: foot and *agra*: trap, i.e. "a trap for the feet"), because it usually involved the first metatarsophalangeal joint, as well as *chiragra*, *gonagra*, *omagra*, if it involved hand, knee and shoulder, respectively.

In modern language, the term "gout" usually has a double meaning: a metabolic disease which causes an expansion of the pool of uric acid, and a rheumatic disease characterized by recurrent flares of acute monoarthritis. As a rule, gout-rheumatic disease is usually caused by gout-metabolic disease (primitive gout), but it can also be due to an expansion of the pool of uric acid, induced by any disease which may interfere with purine metabolism (secondary gout). Conversely, expansion of the pool of uric acid, whatever the cause, can trigger gout-rheumatic disease, but the majority of subjects remain asymptomatic.

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Hippocrates (Figure 1) described some epidemiological features of gout (4), namely that women do not get gout before menopause (29th aphorism) and men *ante usum Veneris*, i.e. before puberty (30th aphorism). As a third concept (28th aphorism), Hippocrates also claimed that eunuchs do not get gout and are also not bald. As a matter of fact, these aphorisms are only valid for primitive gout, while secondary gout, albeit exceptionally, can even occur in children (5) and in women of childbearing age (6).

In the first century AD, Caelius Aurelianus defined a link between gout and excesses in eating and drinking (7). Moreover, his contemporary Gaius Suetonius called gout *morbus divitum* (8), mainly affecting the upper social classes. In the second century AD, Soranus of Ephesus pointed out the possible transmission from one generation to another (9), and Aretaeus of Cappadocia correctly described the acute attack of gout and tophi, and stressed the disease's intermittent course, by reporting that an athlete could win the games at Olympia within a clinical remission interval (10). Finally, in the sixth century AD, Jacob Psychristus introduced *Colchicum autumnale* extracts for therapy of gout flares (11).

Figure 1 - Title page of the "Aphorismi" of Hippocrates (Paris, 1631).

After such a promising start, however, nothing new was added to our knowledge of the disease for a very long time. Scientific literature continued to discuss gout (there were many writings on such rheumatic disorders throughout the centuries), but the authors while prolific did not write well. Differences between gout and arthritis or rheumatism became increasingly confused and each author interpreted the distinction in their own way. In fact, Soranus of Ephesus (9) had already begun to ignore the distinction between gout and what is now called rheumatic fever. Then, to go from bad to worse, separate distinctions were made between a "hot" and a "cold" gout, (12) and the term "gout" was also used to describe chronic articular diseases. In addition, Rufus of Ephesus introduced the concept of "metastatic" or "visceral" gout in the first century AD (13). The term "gout" for non-articular disorders, which have nothing to do with the classic clinical picture of *podagra*, was often used. From a historical point of view, although very rare, extra-articular equivalents of an acute attack of gout may exist: gouty phlebitis (14), iritis (15), orchitis (16) and pharyngitis (17). Some diseases can also induce secondary gout (18) and there are others that may be associated with primary gout, such as other metabolic diseases (obesity, diabetes, hyperlipemia) (19). These observations do not justify the concept of visceral gout; the only organ that may be directly involved in gout, even from a historical point of view, is the kidney (20).

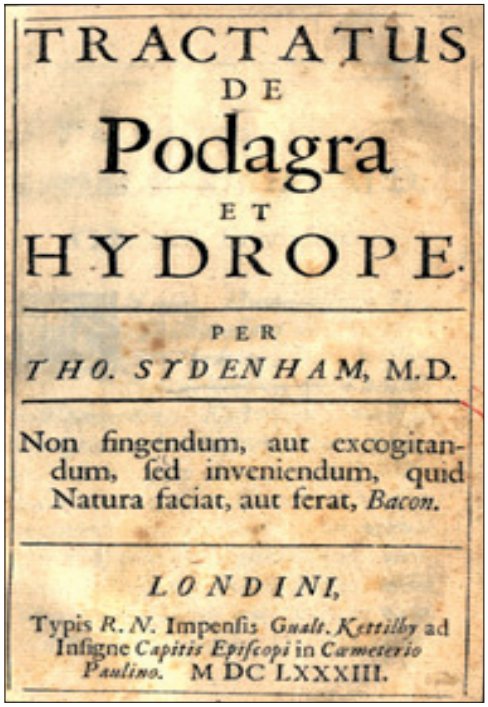
The "modern" history of gout is often associated to Thomas Sydenham (Figure 2) who left a masterly description of the acute attack. (21) The fact that Sydenham had suffered from many such attacks himself

probably helped. Referred to as the English Hippocrate, he also proposed the unfortunate aphorism "*totum corpus est podagra*", which helped to perpetuate the false concept of visceral gout for many generations. It was at the end of the Age of Enlightenment that a discovery opened up a new era in the history of gout. In 1776, a chemist in Stockholm, Carl Wilhelm Scheele, isolated a new substance from some urinary stones (22). The substance was discovered in 1797 by the English chemist William Hyde Wollaston, another gout sufferer, who found it in the material extracted from a tophus of his ear (23). Initially, this material was called "urolytic acid", but already in 1798 the French chemist Antoine de Fourcroy, who identified it as a normal constituent of urine, used the term "uric acid" (24). More than a century earlier, however, Antonie van Leeuwenhoek, the discoverer of the microscope, had observed and described the presence of needle-like crystals in gouty tophi, but he did not identify their nature (25).

It became clear that gout was somehow associated with the accumulation of uric acid. Alfred Baring Garrod, with the murexide test in 1848 (26) and (27) the so-called "thread method" in 1859 (Figure 3), in which uric acid crystals are deposited on a linen thread and held dipped in the acidified blood, first documented that gouty patients are hyperuricemic. In 1913, Otto Folin and Willey Glover Denis began to develop a simple and sensitive colorimetric method (28) to determine uric acid, and this has become a routine investigation ever since.

Garrod, however, did not merely highlight hyperuricemia. He hypothesized (27) that it could be due to increased production or decreased renal excretion of uric acid, as documented one century later by James B. Wyngaarden and his co-workers (29). Garrod also suggested that the acute attacks could be the result of the precipitation of uric acid inside the joint or around it, as demonstrated by Max Freudweiler in 1899 (30).

In the meantime, knowledge of chemical and biochemical properties of uric acid had also advanced. In 1871, the Swiss Johann

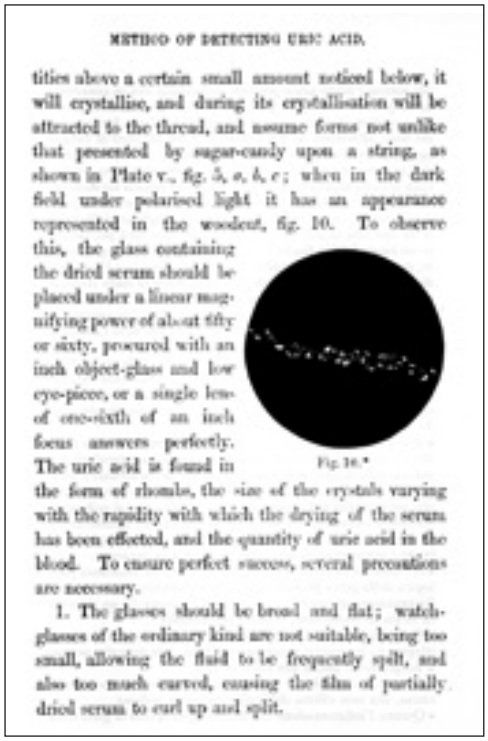

TRACTATUS
DE
Podagra
ET
HYDROPE.

PER
THO. SYDENHAM, M.D.

Non fingendum, aut excogitandum, sed inveniendum, quid Natura faciat, aut ferat, *Bacon.*

LONDINI,
Typis *R. N.* Impensis *Gualt. Kettilby* ad Insigne *Capitis Episcopi* in *Cœmeterio Paulino.* M DC LXXXIII.

Figure 2 - Title page of "Tractatus de Podagra et Hydrope", Thomas Sydenham (London, 1683).


METHOD OF DETECTING URIC ACID.

tities above a certain small amount noticed below, it will crystallise, and during its crystallisation will be attracted to the thread, and assume forms not unlike that presented by sugar-candy upon a string, as shown in Plate v., fig. 5, *a*, *b*, *c*; when in the dark field under polarised light it has an appearance represented in the woodcut, fig. 10. To observe this, the glass containing the dried serum should be placed under a linear magnifying power of about fifty or sixty, procured with an inch object-glass and low eye-piece, or a single lens of one-sixth of an inch focus answers perfectly. The uric acid is found in the form of rhombs, the size of the crystals varying with the rapidity with which the drying of the serum has been effected, and the quantity of uric acid in the blood. To ensure perfect success, several precautions are necessary.

Fig. 10.*

1. The glasses should be broad and flat; watch-glasses of the ordinary kind are not suitable, being too small, allowing the fluid to be frequently split, and also too much curved, causing the film of partially dried serum to curl up and split.

Figure 3 - The "thread method" to determine uric acid in blood (Garrod, 1859).

Friedrich Miescher reported that the cell nucleus consists of nucleoproteins (31) which can be divided into proteins and nucleic acids. Shortly after, the German Albrecht Kossel obtained the purine bases by hydrolysis of nucleic acids (32). Finally, in 1898, Emil Fischer showed that uric acid is derived from the oxidation of purine bases (33), thus representing their terminal catabolic product. There were three main developments in the twentieth century.

1) Radioisotopes were first used to study purine metabolism in 1943 (34). Radioisotopes made it possible to identify the origin of all atoms in the purine ring (35) and to measure such parameters as the pool of miscible uric acid and its turnover (36).
2) In 1961, Daniel McCarty and Joseph Lee Hollander discovered sodium monourate crystals in the synovial fluid of gouty patients using polarized light microscopy (37). Immediately after, Jarvis Edwin Seegmiller and his research team showed that these crystals can trigger an inflammatory reaction (38). These data, besides shedding light on the pathogenesis of acute attacks of gout, opened up a new chapter in rheumatology: crystal-induced synovitis or microcrystalline arthritis (39).
3) Lesch-Nyhan syndrome was identified (40). This is a disorder of purine metabolism, different from gout, characterized by hyperuricemia and severe neuropsychological disorders, including coreoathetosis, oligophrenia, and self-aggressive behavior. In 1967, Seegmiller *et al.* (41) found that this syndrome was due to the complete deficiency of hypoxanthine-guanine-phosphoribosyltransferase (HGPRT) and William Kelley and co-workers (42) identified a partial deficiency of the same enzyme in a subset of gouty patients.

From an epidemiological viewpoint, there have been periods throughout history in which the prevalence of gout was consid-

Tabella I - Famous people affected with gout.

Kings, emperors and governors	Popes and religious reformers	Political leaders and military commanders	Writers, philosophers and artists	Scientists and physicians
Asa	Pius III	William Cecil Burghley	Quintus Horatius Flaccus	William Harvey
Alexander the Great	Julius II	Francis Bacon	Publius Ovidius Naso	Thomas Sydenham
Hiero of Syracuse	Julius III	Oliver Cromwell	Martial	Isaac Newton
Ptolemaeus II Philadelphus	Clement VIII	Philip Chesterfield	Desiderius Erasmus of Rotterdam	Giovanni Battista Morgagni
Octavian Augustus	Innocent X	William Pitt the elder	Michelangelo	Benjamin Franklin
Charlemagne	Clement XII	Horatio Nelson	Thomas More	Carl von Linné
Charles VIII of France	Pius VIII	William Pitt the younger	Michel de Montaigne	Jöns Jacob Berzelius
Henry IV of France	Martin Luther		Pieter Paul Rubens	Jean-François Champollion
Louis XIII of France	John Calvin		John Milton	
Louis XIV of France	John Wesley		Gottfried Leibnitz	
Louis XVIII of France			Henry Fielding	
Charles X of France			Denis Diderot	
Henry VII of England			Immanuel Kant	
Henry VIII of England			Johann Gottlieb Fichte	
George IV of England				
Holy Roman Emperor Charles V				
Holy Roman Emperor Philip II				
Piero di Cosimo de' Medici ("The Gouty")				

ered to be very high, and others in which the disease seemed almost to disappear. High prevalence corresponded to periods in which a civilization reached its peak, or rather, to times when a community lost the drive to increase its power and prosperity and tended to sit back and enjoy its achievements. Two typical examples are the late Roman Empire, especially when compared to the Republican period, and England at the turn of the eighteenth and nineteenth centuries, the so-called "golden age" of gout (43). In contrast, the incidence of gout attacks declined significantly during the First (44) and Second (45) World Wars, although since the nineteenth century its prevalence had, in any case, shown a steady decrease (46).

In ancient times, gout was called *arthritis divitum* and was a prerogative of the moneyed classes or, at least, of those who "ate at the lord's table", i.e. cooks, butlers, coachmen. Today, at least in the affluent West, gout has been "democratized" (45). History is full of famous gouty personages, including kings, emperors, popes, commanders, politicians, artists, writers, philosophers and scientists (Table 1) (47-49).

One might ask if there is a reason why so many celebrities were gouty. No doubt most of them were part of the wealthy class, and also famous for the way in which they dedicated themselves to the pleasures of the table. However, it would be incorrect to suspect that they all, including such "temperate" personalities as John Calvin or Immanuel Kant, were prone to 'binge' eating.

In 1927, the British psychologist and writer Havelock Ellis hypothesized a relationship between uric acid levels and intelligence quotient asserting that, even if genius is not a direct consequence of gout, it is still possible that the "poison" of gout, i.e. uric acid, may stimulate intellectual capacity (50). The title of Ellis's assay, "A Study of British Genius", speaks for itself in what the author wanted to prove! Moreover, some decades later, a number of epidemiological surveys showed that this assumption may not be completely without foundation. These investigations were probably suggested by another interpretative hypothesis, based on more concrete evidence. In fact, in 1955, Egon Orowan pointed out that:

1) among the most developed mammals, primates and man have lost the uricase activity of the liver because of a genetic mutation, thus resulting in much higher uric acid levels compared with other species;
2) methylated purines (caffeine, theophylline, theobromine) have a stimulating action on higher brain functions, in particular attention span and power of concentration (51).

The results of these epidemiological surveys are not sensational, but they are unique. In fact, a significant correlation between uric acid levels and degree of intelligence has been highlighted, as measured by the Army Classification Battery (52). A similar correlation has been observed between uricemia and high social status in a group of managers, scientists, craftsmen and students (53), as well as in university professors, considering qualities such as initiative, success, and trend to leadership (54).

Obviously, these results require further confirmation and for the moment, every attempt at interpretation is hazardous (55). The most obvious objection, namely oligophrenia of Lesch-Nyhan despite very high levels of uric acid, now has a clear explanation. In fact, the nervous tissue does not have all the enzymes for the *de novo* purine biosynthesis and can meet its requirements of purine nucleotides only through the so-called "salvage pathway" (56). The most important enzyme of this pathway, i.e. HGPRT, is precisely that lacking in Lesch-Nyhan syndrome. Another objection is more substantial (57): behavioral and psychological qualities putatively related to uric acid levels are now prominent in females and sometimes more evident before puberty, conditions in which uricemia is physiologically low.

But the story continues. Gout is now well-known, but obviously there is still something that eludes us. The Ancient Greeks were not mistaken when they called it a "trap" and to argue that "only the Gods know its cause" (2)!

CHONDROCALCINOSIS

When McCarty and Hollander demonstrated the presence of crystals of sodium monourate in the synovial fluid of gout in 1961 (37), they also observed 2 cases in which crystals had different features at polarized microscopy. Shortly thereafter, 6 other similar cases were described (58). In all 6, the clinical picture was characterized by recurrent episodes of acute monoarthritis, justifying the term "pseudogout", while the radiological investigations showed calcific deposits in articular cartilage and meniscal fibrocartilage. From a chemical viewpoint, these microcrystals were shown to be composed of calcium pyrophosphate (59). This new disease had many similarities with gout, and was, therefore, included in the group of "microcrystalline arthritis" (39). These were still "heroic" times; to demonstrate the validity of the hypothesis, one of McCarty's co-workers was injected with the crystal material into one of his joints, where an inflammatory reaction occurred (60).

A similar radiological picture had been described in 1958, under the term "chondrocalcinosis", by Dušan Žitňan and Štefan Sit'aj, who observed it in several members of several Slovak families of Hungarian ethnic origin (61). The clinical manifestations, however, were different from those observed in patients by McCarty and Hollander (37), mimicking, besides gout, osteoarthritis, rheumatoid arthritis, and Charcot's arthropathy (62). In addition, many patients were quite asymptomatic.

Chondrocalcinosis and pseudogout were, therefore, different aspects of the same disease and were soon joined under the name "pyrophosphate arthropathy" (63) or "calcium pyrophosphate crystal deposition disease" (64), even if the term "chondrocalcinosis" was that usually used.

Chondrocalcinosis can be either idiopathic, as a sporadic or a familial disorder, or associated to other diseases, including hyperparathyroidism (65) and hemochromatosis (66). The existence of a familial chondrocalcinosis, although rare, is one of the most interesting aspects of this arthropathy which because of this, and in contrast to gout, could be defined a "geographical" disease. Until 1997 (67), about 100 family groups had been described, including 600 patients, scattered around the world. There are, however, some intriguing clusters: the two countries where the most numerous reports have been made are Spain (124 patients, belonging to 48 families) and Chile (127 patients, belonging to 22 families), both countries of Hispanic ethnicity. These are followed by Slovakia (33 patients belonging to 8 families) and Italy where three familial branches are known (total 8 patients) (68).

From a historical viewpoint, it is interesting to go back and investigate what was known about chondrocalcinosis before its identification, mainly on the basis of radiological and autoptic investigations. Some radiological reports date back to the 1920s and 30s. Jacques Calvé and Marcel Galland described a calcification of intervertebral discs in 1922 (69), and Felix Mandl the calcifications of the articular cartilage in 1927 (70). However, the most interesting case, in whom the articular calcifications corresponded to a painful and swollen knee, was reported by Kort Werwath in 1928 (71).

Autopsy reports of putative chondrocalcinosis provide the oldest proof. In 1842, Robert McLeod identified the presence of a white powder on the surface of articular cartilage (72) and in 1854, according to a report by Paul Dieppe and Michael Doherty (73), Robert Adams, a Dublin surgeon, described a patient with a chronic rheumatic disease showing calcifications of the semilunar fibrocartilages of the knee (74).

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