

The Story of Gout

W. S. C. COPEMAN

Middlesex and West London Hospitals, London, England

Introduction

Gout probably has been the best documented of human diseases throughout the ages. This may be because it is easily identifiable, owing not only to the dramatic nature of its sudden painful, acute episodes, but also—which may have pleased the masses—to its tendency to pick out rather important and wealthy victims. For the underdog, seeing that sort of person suddenly and unpredictably incapacitated, with his afflicted foot swathed in monstrous protective bandages, the disease assumed a uniquely comic aspect which has persisted to this day, although never shared by sufferers from what the great Dr. Samuel Johnson described as “the most diabolic [pain] to which man may be subjected.”

Gout was not a word devised by the medical profession, but rather a colloquialism used first by the Teutonic denizens of the northern outposts of the Roman Empire, for what the Greeks termed generically “arthritis,” i.e., disease of the joints. When it affected the great toe, as true gout frequently does (Fig. 1), they termed it *podagra*. The term was based upon the Latin word *gutta* (a drop). According to their humoral hypothesis, phlegm, one of the four constituent humours which made up the human body, could be distilled in excess and would then drop into weakened joint cavities, the distension thus caused producing the great pain and swelling typical of the disease.

The first person in modern times to distinguish between gout and

rheumatic fever as specific entities was the 16th century French Royal Physician Guillaume de Bailleu, also called Ballonius (1642). A little later, the great Thomas Sydenham independently made the same differentiation in his classic and often quoted description, drawing largely upon his own sufferings from the former disease.

The basic cause of the gout, like that of all other disease processes, was believed by most physicians of the early world to lie in an alteration or an imbalance of the body humours (Fig. 2). A modified view is attributed to Aretaeus the Cappadocian (fl. A.D. 135), however, who asserted that “the basic cause of this disease none but the Gods can ever understand.” In the 18th century, the Age of Reason, gen-

eral medical opinion was summarised by Dr. Walter Harris, who wrote that a man may have a “gouty disposition” even when he is free of “actual fits” (diathesis). He thought, moreover, that “The Common Opinion as to Wine and Women is proved unjust and uncharitable.”

Here the matter rested until Sir Alfred Garrod discovered, in 1848, that the “morbid circulating matter” which had always been assumed to be causative of the gouty diathesis was uric acid. The hereditary and seasonal nature of the affliction had been remarked upon by Galen (A.D. 120), the most notable disciple of Hippocrates, who, in his writings 600 years previously, had also noted the association of the acute attacks with various

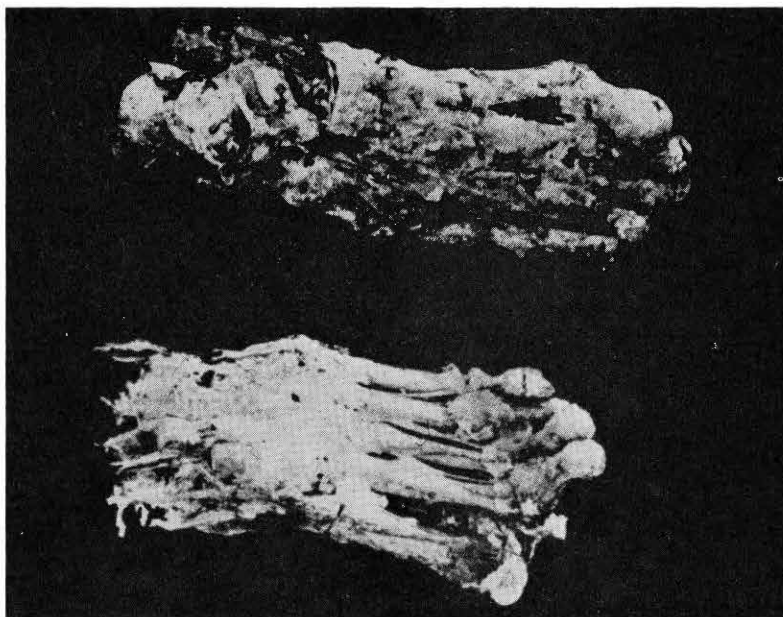


Fig. 1—True gout in the great toes of an ancient Greek.

stresses—chiefly those of a bibulous, gastronomic or sexual nature. He also pointed out correctly that eunuchs and women who had not reached the menopause never fell victim. The distinguished contemporaries of Hippocrates—King Priam of Troy, King Oedipus of Thebes and the hero Achilles—were all, he reported, sufferers from gout. The Roman poet Lucian wrote a popular burlesque tragedy on the powers of the Goddess Podagra and the ineffectiveness of human treatment. Tophaceous deposits were noticed and commented upon by most of the early medical writers, including the second century physician Soranus of Ephesus, who advocated their surgical removal in selected cases. It was the great English chemist William H. Wollaston, F.R.S., who, in the 18th century, was able to demonstrate that a tophus removed from his own ear was composed of uric acid.

Prognosis

With regard to the prognosis of the disease, Aretaeus rightly pointed

out that, once gout is declared in a person, “the disease sticks to him until death.” Hippocrates stated that those affected “who are aged and have tophi in their joints and those who have led a hard life and whose bowels are constipated, are beyond the power of medicine to cure. . . . Persons under other circumstances may be cured by a skillful physician.” He pointed out that the younger the sufferer, the poorer the outlook. These views remained largely unaltered until comparatively modern times, when uricosuric preparations were introduced and the disease process at last became controllable by chemical means. It is interesting to note that 50 years ago most insurance companies took an extremely unfavourable view of the prognosis in victims of gout, whilst today the majority of adult cases are accepted at normal rates. In 1959 John H. Talbott and Abraham Lilienfeld showed that the mortality rate among gouty sufferers in the United States was similar to that in the general population.

Classification

Classification remained simple until the 18th century, because the early Greek writers regarded all affections of joints, except those of directly traumatic origin, as being of the same basic “gouty” nature, despite evidence in the surviving works of Hippocrates that he may have recognised a difference between the syndromes of true gout and rheumatic fever. If Hippocrates did recognise a distinction, it was forgotten by his successors until the 17th century. Even then, Sydenham’s views were not universally accepted, if we may judge from his dry remark, “Doubtless gout and rheumatism were often confounded by the ancient Greek physicians; a point which is still equally applicable to the great pundits of our present day.” Until that time, the generic term used was “arthritis,” and its evident varieties were merely classified according to an anatomical plan: podagra, when it afflicted the foot (Fig. 3); chiagra, the hand; gonagra, the knee; and so on, through-



Fig. 2—Possibly the earliest printed work on gout (1577).

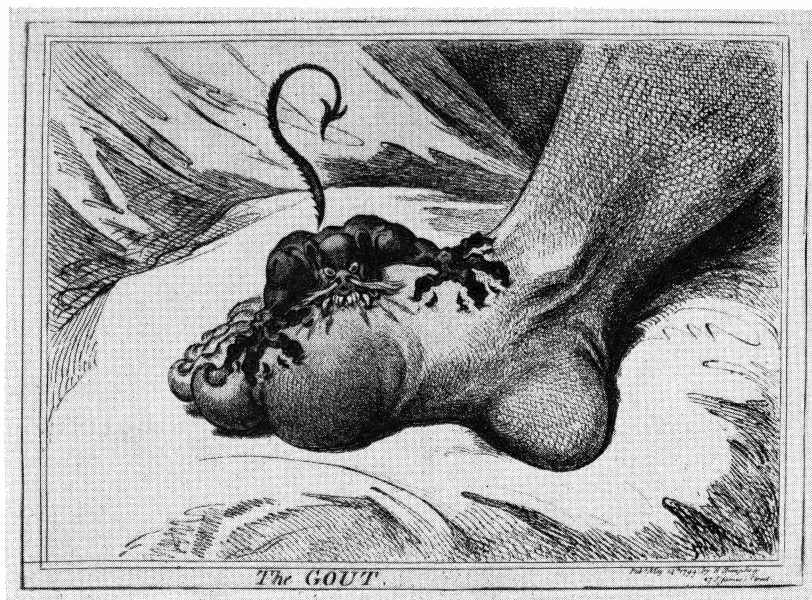


Fig. 3—A personal reminiscence of podagra (1799) by James Gillray.

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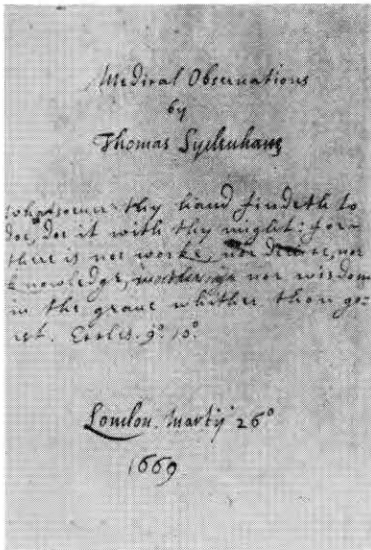


Fig. 4—Sydenham's notebook; in possession of the Royal College of Physicians.

out the joints of the body, and including sciatica. This simple convenient authoritarian method of classification persisted unchanged for the next thousand years, although occasional murmurs of doubt could be heard, as when Dr. Andrew Boorde, who was one of King Henry VIII's physicians, warned (1547) that, despite general belief, "All jointe illnesses are not the goute." He added in an independent vein, "It is extremely difficult for a physician who puts too much trust in what he reads to form a proper decision from what he sees," a sentiment which we can still endorse.

With the 18th century came the fashion started by Carolus Linnaeus, the great botanist, for evolving "systems" of classification. Articular affections received considerable at-

tention from leaders of the profession throughout Europe. Gout then became subdivided into 14 varieties and species with further subdivisions according to its seasonal variations and its association with other disorders. Its visceral manifestations also became more generally known and were classified under the headings "Anomalous," "Irregular," "Retrocedent" or "Misplaced" Gout. Such classifications, however, perpetuated the belief that gout was the basic prototype of all joint affections other than those attributable to rheumatic fever or Sydenham's further indeterminate class of "scorbutic affections of the joints." It was just over a century ago (1859) that Garrod (who should be known as the "Father of Modern Rheumatology"), as the result of his studies



Fig. 5—"Comfort in the Gout" (J. Rowlandson, 1785).

in morbid anatomy, was able to differentiate between the clinical entities of rheumatoid arthritis, for which he suggested the name, and osteoarthritis. Modern classification of joint affections has become complicated once more with the identification of an increasing number of disease processes. The system most generally accepted is the one proposed by the A.M.A., which seems sufficiently flexible to accommodate further increases in knowledge as they occur and includes the various types of gout currently recognised.

Pathology

The pathology of gout began to arouse interest subsequent to the acceptance of Thomas Sydenham's reintroduction of sound observational medicine into England towards the end of the 17th century. He clearly and unambiguously described the clinical features of gout and its associated pathology, such as tophus formation ("stony concretions like unto chalk") in the tissues around joints and in the cartilage of nose and ear, leading to chronic and sometimes crippling conditions—e.g., urinary stone, heart disease and apoplexy (Fig. 4). His influence quickly spread throughout Europe with the help of such distinguished admirers as the Dutchman Hermann Boerhaave and his pupils William Cullen and Sir John Pringle of Edinburgh and, later, Gerard Van Swieten and Baron Anton Von Stoerk of Vienna. Increasing interest in the pathology of gout coincided with the development of the microscope and the general introduction of postmortem examination, which, until that time, had been discouraged by the Church. This conjunction of circumstances culminated in the first great work on morbid anatomy (1761) produced by Giovanni Morgagni, the Italian founder of that subject. His description of the pathology of gout was carried further by Jean Bichat, the father of

French scientific medicine, in his splendid work *Anatomie Pathologique* of 1825.

The interesting "mediaeval" character, Paracelsus, half alchemist-quack and half genius, was the first to suggest that gout might not be a product of humoral derangement, but might instead be a "tartarous" chemical abnormality; proof was lacking, however. The first step towards an accurate metabolic conception of the disease was taken when the Swedish apothecary Karl Wilhelm Scheele discovered uric acid (1776) in the course of chemical researches carried out after business hours in the kitchen of his herb shop. The next step was Wollaston's discovery, noted above, that gouty tophi contained uric acid. It was this knowledge which led to Garrod's demonstration (1848) that uric acid was the *éminence grise* behind the various manifestations of gout. For that purpose, he devised his famous "thread test," one of the first bedside chemical tests ever used for diagnostic purposes.

Subsequently, much further light was thrown upon the metabolic complexities of gouty metabolism as the result of the monumental work of the German chemist Emil Fischer (1852-1919), who first established the relationship of uric acid to purine protein bodies. He worked out the family tree of gout and showed that the purine nucleus was the common ancestor of all the metabolic products of the disease. This was the scientific foundation of our present improved understanding of the disease process, which has been facilitated by advances in such important aids as micromethods of blood analysis and isometric labelling.

Treatment

The general plan of treatment for gout systematised by the Hippocratic physicians was based upon their conception of humoral pathology and varied very little until

comparatively recent times. Its objective was to evacuate the offending matter from the body through all available routes by purging, sweating, diuresis and bleeding. The system would then have to be built up by proper diet and exercise so that the humoral defects would right themselves and the body would act, henceforth, as its own physician. With minor and fashionable variations, that system of management altered but little until the middle of the last century (Fig. 5).

The modern treatment of gout depends upon the use of powerful anti-inflammatory substances to subdue its acute episodes. More basically important, however, are the long-term measures which must also still be used between attacks, with the objective of lowering the blood level of uric acid and so, in time, preventing further attacks. Such "interval treatment" may have to be maintained almost permanently in certain patients by means of both medication and regime.

Of the anti-inflammatory substances used for the former purposes, colchicine is still probably the most specific. Until 1884 this alkaloid was obtained from the corm of the autumn crocus, *Colchicum autumnale* (Fig. 6). It was known by the name of hermodactyl to the ancient Greeks, who employed it as a powerful purgative. As purgation was considered by them to be the easiest and best method of eliminating the "peccant gouty humour," they evidently obtained good therapeutic results, although there is no convincing evidence that they recognised the specific effect of hermodactyl upon the disease. During the Middle Ages polypharmacy became the fashion, but small amounts of hermodactyl were still used in purgative prescriptions throughout Europe. It was Sydenham who eventually decided that purgation was inappropriate as a therapeutic measure in gout. Such was his influence that

the use of substances for catharsis, including colchicum, was discontinued for the next 200 years. As alternative treatment, dietetic measures, bleeding, blistering, diuresis and sweating, together with moderate physical exercise and a quiet routine life, were reverted to with some degree of success. The names of the English physicians William

Cadogan, George Cheyne and William Heberden were particularly associated with such regimes during the 18th century.

Reintroduction of colchicum for the treatment of gout is generally attributed to Von Stoerk of Vienna (1763). It seems, however, that he advocated its use principally for the treatment of oedema

of cardiac origin; its value in the gout remained forgotten until a French quack introduced his secret remedy L'Eau d'Husson about 1780. This enjoyed immediate success among the many distinguished sufferers in Europe. The Prince Regent of England, the "First Gentleman of Europe," was a great sufferer, but his physicians refused to allow him to obtain a supply, as it was a "patent medicine of unknown composition." Eventually, he used his royal prerogative, saying, "Gentlemen, I have taken your half-measures long enough to please you. . . . From now on I shall take colchicum to please myself." As he had previously been ingesting 1,200 drops of laudanum daily without relief of pain, the immediate results of the beneficial effect of colchicum were felt indirectly throughout the Continent. The success of this medicament led to a spate of other secret remedies such as the famous "Portland Powder," but none of them achieved permanent success. It is a curious fact, however, that although most of the world's leading physicians thereafter adopted the use of colchicum, an influential minority, which included the celebrated Frenchman Armand Trousseau, held out against it in the belief that its use would merely suppress the acute manifestations by driving them into other parts of the body, thereby increasing the underlying visceral gravity of the disease.

Other substances of quite recent introduction which are used in gout for their anti-inflammatory and analgesic properties are: a) phenylbutazone compounds; b) indomethacin; and c) steroid hormones, although these are now seldom employed.

For the long-term control and management of gouty arthritis, in addition to instituting dietetic regime it was necessary to find substances capable of lowering the level of the uric acid present in the sufferer's blood stream. The first

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Fig. 6—Colchicum, or the Meadow Saffron. From a French herbal.

substance of this type was cinchophen (atophan) which was synthesised as early as 1887 in Germany and was introduced into clinical medicine for this purpose by W. Weintraud of Berlin in 1911. For a time it served its purpose, but eventually its often dangerous side effects severely limited its use. The only alternative was sodium salicylate which for this purpose, however, had to be given in a dosage so high that most patients were unable to tolerate it for long.

It was not until 1948—exactly a century after the discovery of uric acid as the *fons et origo* of the gouty state—that a satisfactory uricosuric substance was discovered, as a side issue, during the course of experiments designed to broaden the spectrum of penicillin. In that year William Q. Wolfson and his colleagues noted that carinamide, given in doses of 10-20 gm, would lower the blood level of uric acid whilst increasing total urinary excretion. This dosage level proved too high for safety, however, and it was not until its synthetic progeny probenecid was developed in 1951 that these results could be obtained with comparative immunity from side effects. In 1959 benemid was introduced into clinical practise and since then has proved to be a safe and effective uricosuric agent. Synthetic variants continue to be added to our therapeutic armamentarium for inducing a prolonged negative uric balance in the body.

In 1966 a new type of substance, allopurinol, was introduced which, by enzyme action, is able to effectively suppress the synthesis of uric acid in the body and eliminate purines in their intermediate synthetic stages of xanthine and hypoxanthine, a process which does not appear to be followed by unwanted side effects. An impressive secondary result of allopurinol administration is the gradual reabsorption of fully formed tophi.

Other methods of treating gout

which have had their vogue at times throughout the ages include magic symbolism, use of the lodestone (magnetism), counterirritation such as produced by burning flax (moxa) or the cautery, hypnotism, hydrotherapy and use of electric currents. The earliest use of electrotherapy was described by the Roman physician Scribonius Largus (A.D. 46), who said that, "For any type of gout . . . a live black torpedo fish should be placed under the feet. The patient must stand on a moist shore washed by the sea, and he should stay like this until his whole leg up to the knee is numb. . . ." This treatment was later the subject of a commentary by Galen.

Medicinal "specifics" were a legitimate part of the stock-in-trade of many celebrated physicians in the past for the treatment of a number of diseases, including the gout. Most of these specifics, including the "Gout Cordial" advocated by Hermann Boerhaave, the "Batavian Hippocrates," contained, among other ingredients, white hellebore (*Veratrum album*) or guaiacum bark. The hosts of itinerant quacks and empirics who perambulated Europe also used mineral substances such as antimony, arsenic and mercury which could be—and often were—highly dangerous. During the acute phase of a gouty attack, opiates would naturally be called for by the sufferer, although, strangely, most orthodox medical opinion during the 17th and 18th centuries frowned on the practise, as it was thought that the disease would only be temporarily mitigated and would be likely to recur thereafter in a more malignant and lasting guise. The custom of hot and cold bathing practised by the ancient Greeks led directly to the later development of the various mineral water spas which attracted the wealthier sufferers for treatment during the 18th and 19th centuries—and still do. To Paracelsus, who first suggested a chemical origin for the disease, these

healing springs represented nature's laboratories, revealing to men the hidden virtues and powers of the *vix medicatrix naturae*.

The use of external applications was universal during the Middle Ages and the Renaissance, and secret recipes for such unguents and plasters, if the ingredients were sufficiently exotic or expensive, were often used as gifts by supplicants to ingratiate monarchs and potentates. During the 18th century, however, external remedies were considered undesirable, as they tended to "fix the inflammation" in the affected joints; a policy of laissez-faire concerning the outside of the body was considered preferable.

It is interesting to note that the treatment of gout—the best documented disease of mankind and one which, Sydenham remarked, ". . . destroys more rich than poor persons, and more wise men than fools"—remained basically unchanged from the earliest days until the first quarter of the last century.

Wine

From early times it had been remarked that the stresses put upon metabolism by heavy eating or drinking would often culminate in an episode of gout. Hippocrates and his followers, therefore, placed great importance upon moderation in both food and wine. Curiously, he believed that the heavier, sweeter wines of Salerno and the South were to be preferred.

In 1688 the French wines popular in England began to be fortified with brandy as a preservative, and the incidence of gout markedly rose. According to one authority, "Burgundy is, of all wines, the most certain fuel to the gout." In 1703 gouty Queen Anne of England concluded the Treaty of Methuen whereby port wine was substituted for the French wines. It became very popular, according to Richard Mead, "as an antidote

to the damp climate and fogs of England, the inhabitants being at that time unaware of the canker that lurks in every glass for the gouty subject." From the time of the legendary invention of champagne by a French Benedictine monk in 1718, there was almost unanimous agreement within the Faculty that this wine above all others would precipitate attacks of gout. The 19th century gave rise to considerable learned and pseudo-learned literature upon the subject. In a lighter vein one may quote a letter of James Russell Lowell from Boston. He wrote: "I call my gout the unearned increment from my grandfather's madeira, and think how excellent it must have been—I sip it from the bin of fancy, and wish he had left to me the cause instead of the effect." As Benjamin Franklin pointed out, the truth of the matter, if we exclude those rare persons who have an allergic sensitivity to certain wines, may have been enunciated by Thomas Sydenham when he said (1682), "If you drink wine you get the gout; if you do not drink wine—the gout has you."

Historic Effects

Reference was made earlier to the effect that gout appears to have exercised upon world affairs. Several of the great Renaissance Italian Medici rulers who were sufferers serve to illustrate the association between outstanding ability and gouty diathesis which has been remarked upon throughout the ages. Of "Piero il Grotto" (Peter the Gouty) it was written that his disease "caused him often to leave the affairs of his state to others less worthy." The great Holy Roman Emperor Charles V, who suffered his first attack at the age of 28, eventually was forced to the unprecedented step of abdicating in favour of his son Philip II of Spain, who married Mary Tudor, Queen of England, and, in turn, died crippled of the same complaint.

Had not the great Lord Burghley, Chancellor of England, himself been incapacitated with an attack of the same disease, he would have been able to prevent that marriage which brought such misfortune to his country.

The well-known 17th century statesman Sir William Temple pointed out that the gout often affected the outlook and policy of rulers, saying, "I have seen the councils of a very great country (France) grow bold or timorous according to the fits of gout on its Governor." A final example, nearer home, may be of interest. It concerns the English Prime Minister, William Pitt, First Earl of Chatham, who by 1763 had concluded successfully the seven years' struggle with France for the sovereignty of the New World. The cost of such victory was high, and it was thought that the Colonies should share it. So, taking advantage of Pitt's absence during an attack of gout, Parliament passed the Stamp Act, which threw much of the expense upon the American Colonies—without their consent, however. On his return Pitt indignantly had it repealed, but during a further attack of gout his colleagues substituted a heavy colonial duty on tea to raise the revenue required. This culminated in the famous Boston Tea Party with its well-known results. Pitt was abetted in his peaceful efforts by his gouty American friend and colleague Benjamin Franklin, who was said to have introduced the first corms of colchicum into the colonies on his return to Philadelphia, where he wrote his well-known and amusing *Dialogue between Benjamin Franklin and the Gout*. It is interesting to speculate on the relationship our two great countries would be enjoying had the rediscovery of colchicum for the treatment of gout been advanced by 25 years and the War of Independence therefore not taken place!

It had long been suspected that gout might be a disease of varying

origins, but it has only been during the present century that primary or acquired gout and hereditary gout have been clearly defined and differentiated. A considerable number of secondary types are now recognised. Several are of iatrogenic nature, whereas others result from disorders of the blood, the bone marrow and the metabolism, as well as from associated specific defects such as those in the Lesch-Nyhan Syndrome of children. Increasing knowledge of gout's chemical secrets, however, is resulting in improved treatment, and we can now assert that gout is perhaps the disease of which we have the most detailed specific understanding and the most effective control. With cooperation from the sufferer and a mild dietary regime, we can now prevent any damage which has already occurred from progressing and, thus, avoid recurrent or progressive deterioration. In almost every case we can now terminate the occurrence of the painful acute attacks by use of modern chemotherapy.