

Developing Treatments



Gout

Gout is a very painful form of arthritis that affects people's joints. It is caused by too much uric acid, a waste product produced by the body. Attacks of acute gout are agonizingly painful, caused by uric acid crystals forming around the sufferer's joints. It usually affects one joint at a time, most often the big toe. Today 90% of gout sufferers are men. Although there is no cure for gout, it can now be controlled very effectively through regular medication.

The word 'gout' was first written in English in the year 1290:

"There cam a goute In is kneo, Of Anguische gret...So longue, that is kneo to swal"

[there came a gout in his knee of anguish great, so long that his knee swelled]

In the past, people associated gout with the wealthy – those that could afford rich food and drink. Famous sufferers of gout include King Henry VIII of England (1491-1547), the famous dictionary author Samuel Johnson (1709-1784), American President Thomas Jefferson (1743-1826), and Joseph Banks, the botanist on Captain Cook's first voyage (1743-1820).

Our stereotype of a gout sufferer as a large red-faced man drinking port mainly comes from the cartoons of the 1700s. However, the Ancient Greeks connected gout and good living over 2000 years before this. Researchers today have confirmed that drinking port and eating too much meat does provoke attacks of gout in some people.

A stereotypical gout sufferer, from *Punch cures the Gout, the Colic and the 'TISICK* (tuberculosis) by James Gillray, published in 1799.



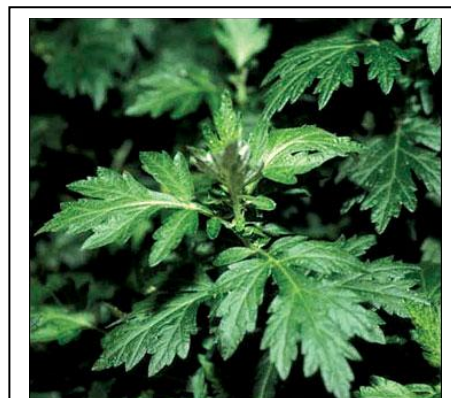
Ancient civilizations

People have recognised gout as a specific disease for thousands of years. Many ancient writers explained gout in ways that still make sense to us today.

The **Ancient Egyptians** identified gout as a disease in around 2650 B.C.

There is prehistoric evidence that people in **Ancient China** treated rheumatic disease, including gout, with acupuncture. They also used “moxibustion”, a technique where they burnt small cones of the dried herb Artemisia on the affected joint.

Both **Ancient Greek** and **Roman** medical writers included gout in their books.



Artemesia

The famous **Greek** doctor Hippocrates (460-375 B.C.) thought gout was caused by too much phlegm settling in the joints. This derived from his belief that every person’s body contained four humours that had to stay in balance to maintain good health – one was phlegm. He called gout “the unwalkable disease” and “the arthritis of the rich”, and blamed it on an excess of wine, food and sex. His observations that gout tends to occur in post-pubertal males and post-menopausal women still hold true today.

The **Roman** physician Celsus (25BC- A.D.50) used the Latin words *podagra* (seizure in the foot) and *chiragra* (seizure in the hand) to describe a gout-like disease.

Galen (129- 216 A.D.) was the first doctor to describe the *tophi* that some gout sufferers experience – lumps of crystallized uric acid under the skin. Aretaeus (1st century A.D.) suggested there was a toxic substance in the blood of gouty patients.

Colchicum

A treatment through the ages

In the **Byzantine** Empire surrounding today’s city of Istanbul, physicians introduced a plant called *Colchicum autumnale*, commonly known as meadow or autumn crocus, as a specific treatment to ease the pain and inflammation of gout. Alexander of Tralles (6th century A.D.) used the corm (bulb) of the plant. Paul of Aegina (7th century A.D.) used infusions of the whole plant. Some sufferers still take colchicine, an active ingredient in colchicum, today.



1) *Colchicum corm*

The whole corms come from a collection of *materia medica* crude drug ingredients formed by John Burges, a physician in the 1700s. The sliced corm comes from a study collection which was used by Dr Stephen I. Anker as part of his pharmacy apprenticeship in 1959.



2) *Later colchicum medicines*

Blair's Gout and Rheumatic Pills claimed to cure gout. The ingredients included colchicum corm.

Wooldridge's Gout and Rheumatic Tincture includes colchichine, alongside potassium acetate, potassium bicarbonate and potassium iodide which were claimed to reduce the acidity of the patient's urine.

1930s, Wooldridge's Medicine Company Ltd.

Colchicum wine, Stafford Allen and Sons Ltd, 1950s

Liquid extract of colchicum corm, Stafford Allen and Sons Ltd, mid 20th century

Eade's Pills contained colchicum corm, extract of colchicum, aloes, and guaiacum resin. They were first made in the 1800s and withdrawn from the UK in 1972. George Eade Ltd, late 20th century South African example.

Gout in Britain

Early ideas and treatments, 1200s-1700s

The word 'gout' comes from the Latin word 'gutta' meaning a drop. This followed from the Ancient Greek idea that every person's body contained four humours that had to stay in balance to maintain good health. Doctors explained that gout was caused when one of the humours "dropped" or flowed into a joint causing pain and swelling. As a result, many people continued to follow the ancient remedies of bleeding and purging to try to restore this balance.

'Gutta' for 'gout' was first used by the Dominican monk, Randolphus of Bocking, the chaplain to the Bishop of Chichester (1197-1258).

3) Nicholas Culpeper, writing in 1653, suggested Tartar Pills of Quercetanus, and Blessed Pills to treat gout. Both types of pills acted as a purge, following the ancient tradition of ridding the body of toxins. A treatise on gout by a French physician Theodore Turquet de Mayerne, dated 1677, also recommended purges, including Cochia Minor Pills, which were made from aloes, scammony, colcyinth, oil of cloves and syrup of buckthorn.

P: BENEDICT, *Pilulae Benedictae*, Blessed Pills jar, 1720-1740

P: COCH: MIN, *Pilulae Cochiae Minores* Cochia minor pills jar, 1750-1770



Medical men also suggested different plant-based remedies:



Horse radish *Armoracia rusticana*

If bruised and laid to a part grieved with the sciatica, gout, joint-ache or hard swellings of the spleen and liver, it doth wonderfully help them all.

Nicholas Culpeper, 1653

Wild strawberry *Fragaria vesca*

By the 1700s, Swedish botanist Carl Linnaeus (1707-1778) claimed that his strawberries-only diet had cured his gout.



Gout-herb *Aegopodium podagraria*

Also called ground elder.

'the very bearing of it about one eases the pains of the gout and defends him that bears it from the disease.'

Nicholas Culpeper, 1653

Meanwhile in Europe, Lorenz Fries, writing in 1518 had a different suggestion for an internal and external treatment:

Roast a fat old goose and stuff with chopped kittens, lard, incense, wax and flour of rye. This must all be eaten, and the dripping applied to the painful joints.

William Shakespeare's recommendation seems to be to avoid doctors:

One that's sick o' th' gout, had rather Groan so in perplexity than be curs'd By th' sure physician death. Cymbeline, 1611

4) Thomas Dover (1660-1742) invented his **Dover's Powders** to treat the pain caused by gout. The main ingredients were powdered ipecachuana and opium. Dover gave the original recipe in his book *The Ancient Physician's Legacy to his Country* (1732). He made the claim for his medicine that "in two or three Hours, at farthest, the Patient will be perfectly free from Pain."

Dover's Powders, mid-1800s

From a medicine chest

The stereotype Suffering from gout in the 1700s



Our image of a gout sufferer as a male wealthy glutton probably stems from the caricatures of the 1700s. In 1771, William Cullen wrote “The gout attacks men of especially robust and large bodies, men of large heads.”

Some historians have argued that, as gout was mainly a disease suffered by men in power with extravagant lifestyles, poorer people aspired to say that they suffered from it too.

Recently medical researchers confirmed that darker coloured alcoholic drinks are more likely to trigger acute attacks. This means that the popular 1700s drinks of port, claret, burgundy and porter were likely to have increased people’s suffering.

In addition to the ancient theories of balancing the body using sweating, bleeding, purging and blistering, scientists became interested in other “lifestyle” treatments.

5) *The Botanic Macaroni*, probably drawn by Robert Dighton, published 1772

Joseph Banks, the botanist on Captain Cook’s first voyage to Australia, was a gout sufferer. This cartoon shows him with a massively swollen leg. Banks took a rhubarb preparation to purge his system, but also made trips to Bath to take the waters.

Spa treatments were popular in the 1700s, and were advised by leading doctors including William Cadogan in *A dissertation on the gout, and all chronic diseases* (1771) which went through nine editions in 2 years. Samuel Johnson (1709-1794) treated what he believed to be gout by soaking his feet in cold water. Dr William Heberden the Elder (1710-1801) thought that ocean bathing along with the fresh air and sunshine it would bring would be more beneficial than spa bathing.

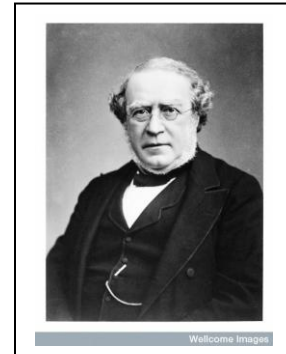
Dr William Stukeley (1687-1765) and doctors in the 1700s believed that diet and exercise could play a part, and that a balanced lifestyle was important:

The golden medium seems right for gout in every thing, liquor, eating, exercise, evacuations. Drink above water, below the strength of wine ie small beer.

The science

Starting to understand the disease

Sir Alfred Garrod (1819-1907) first identified uric acid as the “specific morbid humour” that caused gout. He also devised the uric acid thread test, which depended on the crystallization of urate (one of the forms of uric acid) on linen thread. In his milestone book *The Nature and Treatment of Gout and Rheumatic Gout* published in 1859, he wrote:



‘the deposited urate of soda may be looked upon as the cause, and not the effect, of the gouty inflammation.’

Earlier scientists began to investigate gout in detail when technology allowed them to do so. In 1679, Antoni van Leeuwenhoek (1632-1723), inventor of one of the first microscopes, first described the appearance of the crystals from a gouty *tophus* (lumps of crystallized uric acid under the skin). In 1797, the English chemist William Wollaston demonstrated urate in a tophus from his own ear.

Medical men continued to advise that patients should follow a diet that avoided urate-forming items. Reverend Sydney Smith (1771-1845) wrote in 1829, likening food and wine to beautiful women:

‘The sufferer must enter into a solemn pact with his stomach to relinquish all serious flirtation with the sirens of the kitchen and the houris of the wine cellar.’

Brand name medicines

A market for gout treatments

The earliest brand name medicines were “cure-alls”, which claimed to treat gout alongside many other conditions.

6) Daffy's Elixir “the Health-Bringing Drink” was invented by Reverend Thomas Daffy in around 1650. Although its ingredients remained secret, it was a laxative and probably contained senna, guaiacum, elecampane root, aniseed, caraway seed, coriander seeds, liquorice root, raisins and brandy. As well as gout, it was sold to treat a wide range of conditions including dropsy, kidney stones and convulsions. 1786-1870s

Dealing with the acute pain of a gout attack was all that most medicines could try to do until recently. This didn't stop manufacturers selling hundreds of preparations, both to take internally and rub on externally.

7) Manufacturers advertised external preparations to treat many painful conditions including gout, lumbago, rheumatism, chilblains and sciatica.



Durant's Rheumatic Embrocation, C.Durant, Boston, Lincolnshire, 1879-1912

Maorix: liniment, Maorix Ltd, 1890-1920, unknown ingredients described as “containing herbal curative properties”.

Uritika Nervine Balm, J.Grimshaw and Sons, around 1900

Betul-Oil: liniment, containing menthol, betula lenta, spike lavender oil, methyl salicylate, and chloral hydrate, Anglo American Pharmaceutical Company Ltd. 1916-1931

Little Oriental's Balm: unknown ingredients, Little's Oriental Balm and Pharmaceuticals Ltd, Madras, distributed by Butler and Crispe. 1915-1941

Zox Balm, The Zox Manufacturing Company, unknown ingredients, 1923-1933

St Jacob's Liniment, with ingredients including camphor, phenol, turpentine and ether. International Chemical Company Ltd., 1940's.

8) From the 1800s, companies marketed specific brand-name medicines for gout and rheumatism in massive numbers.

Bishop's Gout Varalettes These tablets included the current gout treatments of lithium citrate and piperazine, alongside sodium bicarbonate and tartaric acid to make them fizz. Early 20th century. Alfred Bishop Ltd.

Haycock's Celebrated Gout and Rheumatic Pills included potassium iodide, guaiacum resin and powdered smallage. 1947-1952, Norman E. Taylor.

Charles Gadd's Gout and Rheumatic Pills, unknown ingredients. C.Gadd and Son, late 1800s, **Armstrong's Vegetable Gout and Rheumatic Pills** Unknown ingredients. J.M.Smith and Co, 1915-1941



Museum of the Royal Pharmaceutical Society, 2006
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New developments

Investigating other treatment types, 1895-1940s

After X-rays were invented in 1895, scientists were keen to investigate whether they would work effectively to treat gout. *Martindale: the Extra Pharmacopoeia*, recommended X-rays as a gout treatment in its 1915 and 1932 editions. Radium and radioactive waters were also suggested.

9) Scientists continued to investigate the best way to treat the pain of a gout attack. Morphine injections, liniments including chloroform, and preparations that included aspirin (acetylsalicylic acid) came into use. A high dose of a 'salicylate' drug helped the body to get rid of uric acid, but it had significant side effects.

Morphine ampoule for injection, French, around 1900

Omega Oil, Omega Chemical Company, containing methyl salicylate, chloroform and hyoscyamus.

Medical practitioners still supported the idea of purging your system in the early 20th century, even though it was no longer based on the ancient four humours theory.

A bacterial toxin is the primary factor. Adequate removal of the intestinal contents at the commencement of the attack will reduce the symptoms.

Martindale: The Extra Pharmacopoeia, 1932

Urace tablets Newbery and Phillips Ltd, 1940s. Advertised on the packaging for "diseases arising from excess Uric Acid." The ingredients were acetylsalicylic acid (aspirin), and guaiacum resin. Guaiacum is a purgative and was believed to relieve pain and inflammation during an attack of gout.

Uricure tablets contained acetylsalicylic acid (aspirin), methyl salicylate, and aloin (from aloes, as a purge). 1943. Unknown manufacturer.

10) Researchers found that **phenoquin** or **cinchophen** worked as an alternative painkiller to aspirin, and also helped the body to get rid of uric acid. Although it worked well on gout, some people experienced unpleasant after-effects, such as vomiting and severe liver poisoning.

11) At the beginning of the 20th century, medical practitioners recommended **lithium salt preparations** to treat gout. Patients took lithium citrate in water, or as tablets, to make their urine less acidic.

12) **Piperazine** was another substance that scientists discovered was more effective than lithium salts in dissolving uric acid.



Cinchopen tablets, Tabloid brand, Burroughs Wellcome and Company, mid 20th century.

Napoleon Gout and Rheumatism Powders, including phenylcinchoninic acid. Early 20th century. H.R.Napp Ltd

Lithium citrate powder, May and Baker Ltd, 1934-1945
Urodonal powder, Ingredients include hexamine, piperazine tartrate, lithium carbonate and quinnic acid. Chatelain Laboratories, early 20th century.

Pain relief Post Second World War successes

Pharmaceutical scientists have developed new drugs since the Second World War that patients suffering from acute attacks of gout can take to relieve the pain more effectively.

13) Newer Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) have replaced aspirin as the most common painkillers. Some forms of pain are registered when body tissues produce chemicals called prostaglandins. NSAIDs stop the release of prostaglandins and thereby lessen pain.

Phenylbutazone, 1950s onwards
 Phenylbutazone tablets, Charnwood Pharmaceuticals, 1980s

Indomethacin, 1960s onwards
 Indolar capsules, Lagap Pharmaceuticals Ltd, 2001

Propionic acid derivatives, 1970s onwards
 Naproxen EC tablets, Alphapharma, 2002
 Piroxicam tablets, Cox Pharmaceuticals, 2001

Diclofenac, 1980s onwards
 Slofenac sustained release tablets, Valpharma, Italy, 1996



'Prevention is better than cure'

14) After the Second World War, scientists worked on treatments that would prevent gout. **Probenecid** and **sulfinpyrazone** were two examples, which successfully worked to increase the amount of uric acid that the body got rid of in urine, rather than leaving it in the patient's system.

Anturan (sulfinpyrazone) tablets, Geigy Pharmaceuticals, 1986

15) The major breakthrough was **allopurinol**. George Hitchings and Gertrude Elion were awarded the 1988 Nobel prize in medicine for their work in developing the drug. Allopurinol is an enzyme (xanthine oxidase) inhibitor which limits the body's production of uric acid. It has since become the most frequently-used uric acid lowering drug.



Zyloric tablets, Glaxo Wellcome Operations, 1998-2002
Allopurinol tablets, CP Pharmaceuticals Ltd, 2008

In May 2008, **febuxostat** (Adenuric) was the first new type of gout medicine in four decades to receive European Union marketing authorisation. It works as a selective xanthine oxidase inhibitor, lowering the levels of uric acid in the body so that they can't form crystals.

Scientists' understanding of how to control gout has made a massive difference to sufferers today.

Effective drugs to lower the level of uric acid in the bloodstream (whether by flushing it out or limiting its production) mean that the tophi (gouty deposits of uric acid) are rarely seen.

Researchers are also able to place gout within the context of rheumatology, with the realisation that there are over 200 different rheumatic disorders with lessons that can be learnt about treating one from another.

Although doctors have recognised the importance of diet for centuries, health professionals now understand that gout sufferers should avoid too many purines, present in meat, seafood and some alcoholic drinks as they increase the build up of uric acid. Scientists also recognise that, in a few cases, inherited gout is due to a purine enzyme deficiency, so that the patient's body does not process this chemical effectively.