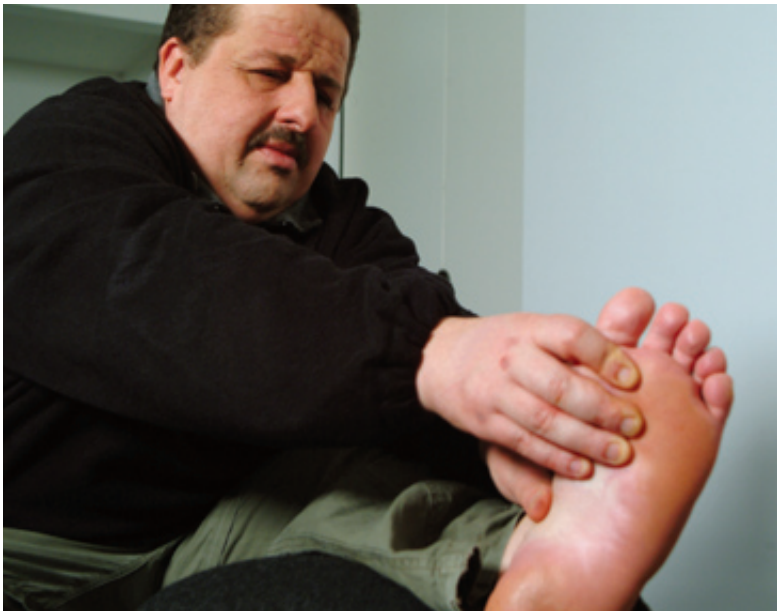
Gout

Gout causes extreme pain in those affected. It is caused by crystals of uric acid settling in the joints. Its treatment is a pharmaceutical success story. Nowadays, medicines treat it so effectively that patients can have an undisturbed quality of life.

What is gout?

Gout is the clinical manifestation of hyperuricaemia with acute arthritis and/or gouty *tophi* (deposits of salts of uric acid under the skin and around a joint). In nearly all patients affected, the disease is caused by an isolated defect in excretion from the kidneys of uric acid. Uric acid, a member of the purine family of metabolites, is only sparingly soluble in body fluids.

Reduced clearance combined with purine-rich food raises blood levels of uric acid to the limit of solubility of monosodium urate, so that the compound finally precipitates in joints and the kidneys, leading to arthritis and kidney stones. Nerve ends in the inflamed area become irritated, causing extreme pain. Deposition of monosodium urate favours the cooler parts of the body such as the joints of fingers and big toe, and the helix of the ear.



The kidneys are responsible for most of the excretion of uric acid. Most mammals have an enzyme to break down uric acid called uricase and so they have much lower blood levels but this enzyme is not found in humans.

Who does gout affect?

Gout and an inherited predisposition to the disease have been recognised for centuries. Such famous people as Alexander the Great, Charlemagne, Leonardo da Vinci, Isaac Newton, Voltaire and Charles Darwin suffered from the disease.

The description of signs and symptoms of gout by the English physician Thomas Sydenham holds as true today as it did in the 17th century: *"The victim goes to bed and sleeps in good health. About two o' clock in the morning he is awakened by a severe pain in the great toe; more rarely in the heel, ankle or instep. This pain is like that of dislocation.... Then follow chills and shivers and a little fever. The pain, which was at first moderate, becomes more intense.... So exquisite and lively meanwhile is the feeling of the part affected, that it cannot bear the weight of bedclothes nor the jar of a person walking in the room"....*

In central Europe, about 30 per cent of men and three per cent of women suffer from hyperuricemia. Gout rarely occurs in premenopausal women. Patients may go without clinical symptoms for many years. Depending on the duration and extent of the disorder, ten per cent of affected people will develop gout in the joints and arthritis.

Acute attacks mostly occur as pain in the big toe, but they can happen at every joint. Patients suffer from chronic gout if they exhibit hyperuricemia and recurrent attacks of gout leading to joint damage, deposits of monosodium urate, kidney stones, or kidney damage.

Accelerated cell death or massive turnover of cells has also been shown to be a cause of temporary hyperuricemia, since upon death the cells´ nucleic acid and soluble purines are converted to uric acid. This is seen, for example, following cancer chem-

otherapy or radiation, or in psoriasis or haemolytic anaemia. In acute states, these patients are treated with uricase and rarely develop gout.

Present treatments:

The goals of treatment are to: (i) abort acute attacks; (ii) prevent future attacks; (iii) treat chronic hyperuricemia. For therapy of acute gout, colchicine (an alkaloid derived from the plant *meadow saffron* or *colchicum autumnale*), steroids or non-steroidal anti-inflammatory medicines are used.

Chronic gout can be avoided with consequent uric acid lowering treatment, e.g. with uricostatic compounds (which belong to the class of xanthin oxidase inhibitors) that block the synthesis of uric acid or with uricosuric molecules which increase the excretion of uric acid via the kidney. Good compliance can be achieved with a combination in low dosage.

The enzyme uricase tackles the excess uric acid in a different way to existing gout treatments by converting it into the molecule allantoin, which is highly soluble. It is given as a pegylated conjugate of the recombinant enzyme. Mostly, it is used in gout patients in whom conventional therapy is contraindicated or has been ineffective.

As virtually all of the purines contained in food are converted to uric acid and excreted, patients with gout should be on a low purine diet, which means for example to reduce consumption of meat, fish, beans and peas. Non-alcoholic fluid intake of more than 3 litres a day is desirable, in some cases alkalisation of urine with orally given sodium bicarbonate or trisodium citrate may be recommended.

Consumption of alcohol should be avoided. Correctly treated patients with gout will have an undisturbed quality of life, will be able to work and have a normal life expectancy.

What's in the development pipeline?

As dosage of xanthine oxidase inhibitors can be up to 600 mg daily and may be given life-long, investigations are underway with new compounds of that class to reduce daily intake of medicine.

The first new treatment in more than 40 years, a non-purine selective inhibitor of xanthine oxidase, has been shown to be an effective treatment for managing gout-associated hyperuricaemia and was filed with the authorities in 2008. Like conventional treatment, the new compound acts to stop the formation of uric acid.

But whereas older therapies inhibit a range of enzymes involved in the uric acid pathway, the new molecule only inhibits xanthine oxidase, making it a much more specific treatment. In particular, the new compound could be more suitable for patients with renal failure because the liver primarily breaks it down whereas purine-selective inhibitors are excreted by the kidneys.

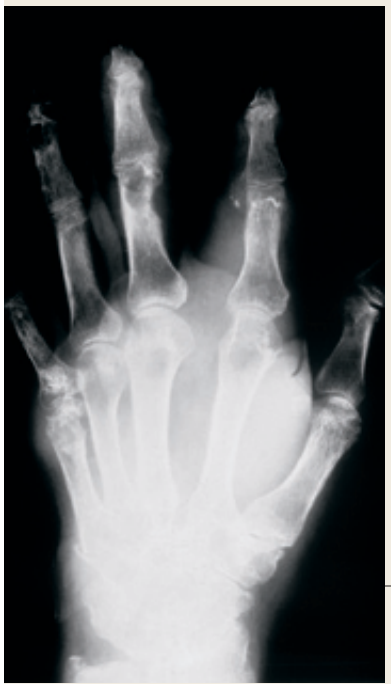
In general, research into uricosuric and uricostatic compounds has now become less intensive. Since the 1950s, medicines have been developed, the biochemical basis of purine biosynthetic systems has been elucidated, and in the past few years, some causes of gout have been defined at the molecular level. For their basic research on purine metabolism, Dr. Trudy Elion and Dr. George Hitchins were awarded the Nobel Prize for medicine.

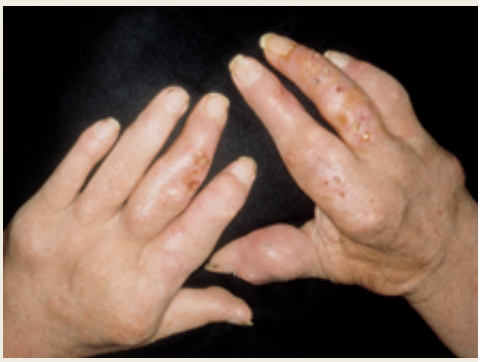
Despite these accomplishments, the metabolic and genetic basis for gout in the majority of patients remains unclear. This is due in part to the lack of animal models in which the way the kidneys handle monosodium urate is identical to that in man. Further development of these techniques and of molecular genetics will continue to improve our ability to explain these abnormalities.

The longer-term future:

In May 2008, researchers published findings which explain why some people are more susceptible to gout than others. The scientists showed that a known sugar transporter, called SLC2A9, is mainly responsible for the transport of uric acid within the body. Variations in the gene that codes for this transporter cause some people to have higher levels of uric acid in their blood than others.

The gene is associated with kidney function, in particular the capacity to remove uric acid from the body through the urine. Apparently, some people will have higher or lower risk of gout depending on which form of the gene they inherited. This discovery may allow better diagnostic tools for gout to be developed and may aid the research into molecules which could lower blood uric acid levels and prevent or treat gout.





Chronic tophaceous deposits in the tissue of both hands of a 49-year-old male patient with chronic gout.
Taken from: Deutsches Ärzteblatt, Jg. 100, 44, 2235; Courtesy of Prof. Ursula Gresser, Sauerlach/Munich.

X-ray of the left hand with typical chronic joint changes

Editing Board - Dr. Robert Geursen (Chief Editor), Bill Kirkness, Dr. Jean-Marie Muschart and Marie-Claire Pickaert (Coordinator).

Photocredits & Illustrations - ABPI, Allergan, AstraZeneca, EFPIA/Lander Loeckx, Damian Foundation, Dermatology Group Practice (Brussels), Galderma, Hilaire Pletinckx, Roche, sanofi-aventis, sanofi-pasteur

Design & Production - Megaluna

Last update: July 2009