HEBERDEN ORATION, 1957*

GOUT

BY

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Gout is one of the classics of medicine, first described more than 2,500 years ago; yet, although our knowledge about the disease is increasing, it still presents so many open questions that it remains a challenge to medical science.

Indeed, I hesitate to talk about gout in the country in which Sydenham (1683) gave his classic description of the clinical picture, Wollaston (1797) found uric acid in gouty deposits, Garrod (1848) demonstrated hyperuricaemia in patients with gout, and so many other important contributions to our present knowledge and understanding have been made.

Moreover, in a short lecture, it is not possible to cover more than a small section of the topic, but I will try to tell you a little about our experiences in Denmark in recent years.

Incidence.—This varies considerably from country to country, even within a small area such as Scandinavia.

Gout is very common in Denmark and southern Sweden, rare in northern Sweden and Norway, and apparently almost non-existent in Finland. Great Britain has long been considered the kingdom of gout and London its capital.

Some doctors in many countries feel that gout is disappearing, but more likely it is a forgotten disease—forgotten perhaps by the doctors, but certainly not by the patients.

In Denmark we have fairly good evidence that the incidence of gout was decreasing during the two world wars, but it has now again become fairly

common. It is very difficult to obtain exact information of the total number of cases, since only a few patients are hospitalized, but I would estimate that about 5-10 per cent. of male arthritis is gouty.

Everyone agrees that gout may be found—though rarely—in women, but most of the cases diagnosed in women are rather doubtful. I have seen tophaceous gout in three females, but I find that at least 95 per cent. and probably 98-99 per cent. occurs in male patients.

Age at Onset.—I have never observed an attack below the age of 20, but two of my patients claim that their first attack occurred at the age of 15.

In almost all cases gout first appears in the age group 25 to 60, but I have seen a first attack of primary gout in a man of 71 (Table I, overleaf).

Weight and Drinking Habits.—Table II (overleaf) shows that most of my patients are overweight (Brøchner-Mortensen, 1941).

Gout was formerly called the arthritis of the rich, but this is no longer so, at least not in Denmark, though certain professions (including bartenders, brewery-workers, and some salesmen) predominate among the patients.

It is difficult to obtain reliable information on drinking habits of patients, some being over modest in their statements, and some liking to boast a little.

Out of 93 of my patients thirteen said that they were teetotallers, 21 took one or two bottles of beer a day, 31 had five to ten bottles, and 17 more than ten bottles. A bottle of Danish beer contains 15-50 mg. of oxypurines. I should like to emphasize that this does not reflect the drinking habits of the average Dane.

* The Heberden Oration was delivered before the Heberden Society at the Wellcome Foundation, London, on December 13, 1957.

ANNALS OF THE RHEUMATIC DISEASES

TABLE I
AGE AT FIRST ATTACK OF GOUT
(PERCENTAGE DISTRIBUTION)

Age (yrs)	Scudamore (1866)	Williamson (1920)	Brøchner-Mortensen (1940)	Villa, Robecchi, and Ballabio, with de Sèze, Ryckewaert, Levernieux, and Marteau (1958)
0-10	0	0	0	0
11-20	2	0	2	1
21-30	27	15	4	23
31-40	37	37	26	36
41-50	23	29	27	27
51-60	8	18	24	13
61-70	2	1	16	0
71-80	0	0	1	0

TABLE II
WEIGHT OF PATIENTS WITH GOUT

Deviation from Standard Weight (per cent.)	Number of Patients
± 10	17
+ 11-20	17
+ 21-30	15
+ 31-40	13
+ 41-50	10
+ 51 and more	7

Heredity.—It has long been believed that gout was a hereditary disease. Various recent investigations show that hyperuricaemia without attacks is fairly common among the relatives of gouty patients, and the theory has been advanced that hyperuricaemia is the genetic factor in gout. Some authors conclude that hyperuricaemia is inherited as a dominant characteristic, but does not always lead to gouty manifestations.

In Denmark, Hauge and Harvald (1955) recently made a study of the relatives of 32 male probands with classic primary gout and a comparable control group. Table III shows that clinical signs of gout were found in sixteen of the relatives of the 32 probands—and none in the control series. Urinary calculi were found in twenty relatives and four controls.

Table IV shows that the mean value of serum uric acid was definitely higher in the siblings than in the controls even after deducting those in whom the diagnosis of gout was made.

The brothers as well as the sisters presented mean values 0.8 mg. per cent. above normal.

Our genetic experts, however, felt that there was insufficient evidence to support the assumption of a monomeric dominant or recessive inheritance,

TABLE III
GOUT, URINARY CALCULI, CHOLELITHIASIS, AND DIABETES MELLITUS IN RELATIVES OF GOUTY PATIENTS AND A SERIES OF CONTROLS

Series		Propositi	Control
Total Number of Near Relatives (parents, siblings, children) ..		261	266
Gout	Typical	16	0
	Atypical	2	1
Urinary Calculi		20	4
Cholelithiasis		16	18
Diabetes Mellitus		5	4

TABLE IV
SERUM URIC ACID IN SIBLINGS OF PATIENTS WITH GOUT

Siblings	Brothers		Sisters	
	No.	Uric Acid (mg. per cent.)	No.	Uric Acid (mg. per cent.)
Total Material ..	47	6.1	57	5.4
Siblings without Arthritis ..	39	5.9	57	5.4
Normal Values ..		5.1		4.2

the serum urate level in each individual being probably influenced by a number of different genes.

Uric Acid.—Since the days of Wollaston and Garrod it has been thought that a disturbance of purine metabolism plays a decisive role in gout.

The important observations made in former days were hampered by unsatisfactory analytical methods. In the mid-19th century Garrod developed his thread method, which was ingenious but impracticable.

For many years Folin's phosphotungstic acid method and its numerous modifications was followed. The technique was easy but the method was neither specific nor quantitative, and the results obtained by the various modifications varied enormously. This fact was stressed again and again by Folin even in his last paper (Folin, 1934), but it was forgotten by most other workers using this so-called standardized method.

In 1935 I developed my ferricyanide method (Brøchner-Mortensen, 1937). This was also very easy; it was quantitative but not quite specific, and consequently gave too high values in most cases.

The modern spectrophotometric enzymatic method (Table V) developed by Kalckar (1947), Praetorius (1947), and Praetorius and Poulsen (1953), and modified by others, is a little time-consuming and difficult except for well trained technicians, but it is apparently both specific and quantitative (Gjørup, Poulsen, and Praetorius, 1955). Research work of to-day ought to be carried out with methods based on this principle.

Hyperuricaemia is found in about 75 per cent. of early cases of gout (Brøchner-Mortensen, 1940). It was previously believed that the level was higher before and during the acute attack than in the intervals, but I have not been able to confirm this. After 5 years' duration hyperuricaemia is found in most patients, but normal or only slightly elevated values may sometimes be found even in cases of severe tophaceous gout.

The determination of uric acid in serum for diagnostic purposes should never be performed in patients who have been given uricolytic agents within the last few days.

The total uric acid in the normal human body is about 1.1-2 g.; this was found by Gudzent (1928), and has been confirmed by modern experiments with labelled uric acid.

In gouty patients the total uric acid is increased to 5, 10, or 30 g. or even higher values.

The increased uric acid in patients with gout may

be caused by increased production, decreased destruction, decreased excretion.

(a) *Increased Production.*—Only a part, and probably a minor part, of the uric acid in the body is derived from preformed purine ingested, most being synthesized from non-purine precursors either directly or by way of nucleic acid.

The problem is whether the biosynthesis is higher in gout than in normal physiological conditions.

Studies by Benedict, Roche, Yü, Bien, Gutman, and Stetten (1952) with ingestion of N¹⁵ labelled glycine seem to support the theory that the biosynthesis of uric acid is greater in patients with primary gout than in normal individuals.

(b) *Decreased Destruction.*—The destruction of uric acid in man is still a matter of discussion. In man the presence of uricase has never been established.

Balance studies after the ingestion of uric acid or purine gave very conflicting results, but after the intravenous injection of labelled uric acid about 75 to 80 per cent. appeared as uric acid in the urine. This has been taken as evidence for the destruction of uric acid in man.

Wyngaarden and Stetten (1953) for instance, recovered 76 per cent. of the injected uric acid as uric acid in the urine, 16 to 18 per cent. of N¹⁵ was found as urea, 1 per cent. as ammonia, and a small amount was found in the faeces.

I suspect that the N¹⁵ recovered as urea and ammonia—or at least a part of it—derived from uric acid excreted in and broken down in the intestine.

So far we have no strong case for a metabolic destruction of uric acid in man and no evidence that patients with gout break down less uric acid than normal persons.

(c) *Decreased Excretion.*—The excretion of uric acid is a complicated process.

In many patients with gout, albuminuria and/or impairment of the renal function is found, and for many years it was thought that the hyperuricaemia

TABLE V
NORMAL VALUES OF SERUM URIC ACID
(SPECTROPHOTOMETRIC ENZYMATIC METHOD)

Sex	Number of Observations	Mean Value (mg. per cent.)	Normal Range (mg. per cent.)	Number of Observations within Normal Range (Mean $\pm 2 \times S$)
Male	143	5.0	2.6-7.5	138 (97 per cent.)
Female	157	3.8	2.0-5.7	152 (97 per cent.)

When examined after 3 days' purine-free diet the values are about 1 mg. per cent. lower.

of gout was of renal origin. To-day it is the general opinion that renal insufficiency in gout is due to secondary damage or disease independent of the gout.

The normal renal excretion of uric acid on a purine-free diet is 300 to 400 mg. in 24 hrs, and the amount excreted in gouty patients without renal disease is about the same or even higher.

The mechanism for the renal excretion of uric acid has long been a matter of discussion. The prevailing concept is that uric acid is freely ultrafiltrable through the glomeruli and that about 90 per cent. is reabsorbed through the tubules, so that the resulting clearance is about 10 ml. per minute. Many years ago I demonstrated an augmentation limit at about 1 ml. per minute (Brøchner-Mortensen, 1937), and examinations should always be performed at a high diuresis. Uric acid clearance is about the same in gouty and non-gouty individuals on a purine-free diet. After the intravenous injection of uric acid or the ingestion of high-purine diet

interesting observations. In normal rabbits the ratio between uric acid clearance and creatinine clearance is 0.1 : 0.7 (average 0.4). This means that about one half of the uric acid is reabsorbed in the tubules. If, however, the serum uric acid level is increased by intravenous injection, the ratio increases to an average of 1.77. These findings suggest a secretion of uric acid.

If Probenecid is given to these animals, the ratio will drop to about 0.8 : 1.0, but not to the normal level of 0.40, possibly because Probenecid inhibits both secretion and reabsorption of uric acid.

A single observation made by Praetorius and Kirk (1950) suggests the secretion of uric acid in human tubules. In a man with a very low plasma uric acid they found the uric acid clearance to be higher than the filtration rate. The analysis was made by the spectrophotometric enzymatic technique.

The mechanism of uric acid excretion probably includes several processes; ultrafiltration, passive diffusion, secretion, and reabsorption.

In Fig. 1, I have tried to put these ideas together, but there are still several hypothetical points.

The kidneys are not the sole excretory organ for uric acid, for a little is excreted in the sweat, and some in the gastro-intestinal tract.

Lucke (1932) estimated that extrarenal excretion amounted to some 40 to 70 mg. per 24 hours, but until recently no investigations with isotopes and

modern specific analytical technique have been presented.

In experiments with 2-C^{14} uric acid Sørensen (Unpublished work) has estimated that, after the intravenous injection of uric acid, up to one-third is excreted in the intestines; it is rapidly destroyed and a major part of C^{14} may be recovered from the expiration as CO_2 and a minor part from the faeces.

There is thus very suggestive evidence for an increased production of uric acid in gout, but no definite evidence for metabolic destruction of uric acid in man, and consequently none for decreased destruction in gouty men.

The old idea of a decreased excretion of uric acid in gout is not supported by recent investigations, but our knowledge is still very incomplete in many respects, as regards renal and extrarenal excretion, the latter being probably greater than previously thought.

We know that there is an accumulation of uric acid in patients with gout, but we have no proof that this is responsible for every sign and symptom of the disease. The deposition of uric acid explains

Fig. 1.—Theoretical mechanism of renal uric acid excretion.

the uric acid clearance will increase in most normal persons, but in most gouty patients the increase is absent or less pronounced (Brøchner-Mortensen, 1940).

Berliner, Hilton, Yü, and Kennedy (1950) found that the uric acid clearance increased in most persons with increasing levels of serum uric acid, and they suggested the presence of a T_m for uric acid with a maximal reabsorption capacity of about 15 mg. per minute. The level of T_m in gout has not been examined as far as I know.

Poulsen (1955) and Poulsen and Praetorius (1954) in Denmark have recently presented some very

the tophi and some of the deformities, but we still do not know the cause of acute attacks.

It is probably too simple an explanation that the acute attack is a tissue reaction to the irritating crystals.

Some believe that the depositions are secondary to the arthritis, but I have found, during a first attack, large urate deposits in a joint which had been opened by a surgeon who thought it was due to suppurative arthritis.

Treatment

The physician has to face two main therapeutic problems: the treatment of the acute arthritis, and the prevention of new attacks and other signs and symptoms.

Colchicine

In the treatment of the acute attack colchicine was the ruling remedy for 1,500 years. It was known by the Egyptians, but apparently Psychristes, in the 6th cent. A.D., was the first to recommend it as a specific agent against gout. Its therapeutic mechanism has never been elucidated.

Colchicine may be given in many ways. I generally gave 0.5 mg. every hour for 8 to 10 hrs for 2 or sometimes 3 days. The individual dose can generally be adjusted by trial and error.

It is active in most cases, even if diarrhoea does not occur, and is well tolerated by most patients, though some were troubled with rather severe diarrhoea and nausea, and many years ago I saw an aged feeble patient die from heart failure during severe diarrhoea caused by colchicine. The intravenous administration of colchicine may be of great help but gastro-intestinal disturbances sometimes ensue.

Various related compounds have been tried, especially Colcemid, but their advantage over colchicine seems to be small.

Phenylbutazone

Since the appearance on the market of phenylbutazone this has been my treatment of choice for acute attacks, but on account of the often severe side-effects I hesitate to give it over a long period.

The administration should be individualized, but very often I give 800 mg. on the first day, 400 or 600 the next day, and sometimes 200 for another 2 or 3 days. Its action is generally prompt, and most patients who have previously had colchicine prefer phenylbutazone.

The drug is uricosuric, but the effect during the acute attacks is too quick to be explained in this way, and there must be a more direct action anti-phlogistic on the joints.

Newer compounds, such as G25671 and others, have been produced, but their value is probably not much different.

Other Measures

Cinchophen and similar compounds are no longer of interest, and their toxicity is such that we relinquish them without regret.

Treatment with adrenocortical steroids and especially corticotrophin may be of value in a few cases resistant to other forms of treatment. Their action may be very prompt, but a new attack may follow cessation of treatment. This recurrence can sometimes be prevented by giving colchicine or phenylbutazone prophylactically.

During the acute attack the affected joint should be kept at rest, but as far as possible or as soon as possible the patient should be allowed to get up.

Inactivity of the joint over longer periods should be avoided.

When phenylbutazone is given it is generally not necessary to give other analgesics, and I never prescribe hot or cold compresses.

When the acute attack is over the physician will face the much more difficult problem of preventing new attacks and other signs and symptoms.

Diet

So far, it is not possible to influence the metabolic disorder, but an effort must be made to diminish the ingestion of purines and increase the excretion of uric acid.

It has been a matter of discussion whether low-purine diet is of any value, but we know for certain that a full diet will overload the organism with some 100-200 mg. of uric acid per 24 hrs and often more; consequently I find it reasonable to diminish the ingestion of purines as far as possible without harming the patient physically and mentally.

I prescribe a diet low in purine, poor in fat and calories, and slightly limited in meat, fish, and fowl. The patient is urged to eat boiled meat and let his wife have the soup.

In most cases the patient's weight should be reduced, and his drinking habits corrected. Beer is probably most harmful. Distilled spirits on the whole are well tolerated, but some patients claim that certain alcoholic drinks provoke acute attacks, and this apparently differs from individual to individual.

Diuresis

Patients should be urged to maintain a high rate of diuresis since the renal excretion is greatest when the diuresis is kept above the augmentation limit, about 1 ml. per minute.

Uricosuric Agents

For many years it has been known that a number of substances, including salicylates, cinchophen, and mercurial diuretics, will increase the renal excretion of uric acid, and during the last few years interest has centred in Probenecid.

Dioscorides (cited by Gross and Greenberg, 1948) wrote in the 1st cent. A.D., *In re materia medica*, that willow bark should be given to patients with gout, and Byasson (1877) found that salicylates had a uricosuric effect.

The mechanism of this effect is apparently fairly complicated. A transitory increase in serum uric acid was found by Crone and Lassen (1955c) when small doses of 1 to 3 g. per day were given (Fig. 2).

Fig. 2.—Uric acid in blood and urine after administration of 3 g. acetylsalicylic acid per 24 hrs.

In four out of seven experiments the excretion was unchanged, in three an increase was observed, and no decrease was seen.

After higher doses, for instance 6 g. per day (Fig. 3), there was no elevation of serum uric acid and in all cases the renal excretion was markedly increased.

The action on the kidney (Fig. 4, opposite) apparently involves an inhibition of tubular reabsorption

Fig. 3.—Uric acid in blood and urine after administration of 6 g. salicylic acid per 24 hrs.

(Crone and Lassen, 1955d). In order to obtain a marked uricosuric effect over prolonged periods, it is generally necessary to give rather large doses of salicylates, and at least on our side of the North Sea this has generally resulted in rather pronounced side-effects, and we generally prefer to give Probenecid.

Probenecid acts very quickly. After 1 hr the excretion is augmented, the maximum is reached after 2 to 5 hrs and the effect will generally last for 9 hrs (Crone and Lassen, 1955a). It should therefore be given in at least three divided doses in 24 hrs (Fig. 5, opposite).

The uricosuric effect (Fig. 6, opposite) is apparently due to inhibition of tubular reabsorption (Crone and Lassen, 1955b).

When salicylate is added to Probenecid (Fig. 7, overleaf) the excretion decreases rapidly (Lassen, unpublished work).

The action of Probenecid can be maintained over a very long period, probably indefinitely. We have closely followed about fifteen patients for 2 years or more.

We generally start with 0.5 g. per day, slowly increasing the dose to about 1.5 g. according to the serum level.

In some patients we have seen a definite reduction of tophi, and especially the drying up of fistulae from tophi.

Side-effects on the whole have been moderate; in two patients we had to discontinue the treatment

Fig. 4.—Effect of salicylic acid on creatinine and uric acid clearance. Each arrow indicates the administration of 250 mg. salicylic acid.

Fig. 6.—Effect of Probenecid on creatinine and uric acid clearance. Each arrow indicates the administration of 0.5 g. Probenecid.

Fig. 5.—Uric acid excretion before and after administration of 0.25 g. Probenecid. Arrow indicates time of administration.

on account of nausea, but we saw no exanthema and no renal calculi. We have kept the urine alkaline, and urged the patients to maintain a large diuresis.

In one patient we gave Probenecid in spite of the presence of large calculi.

The patient was a 70-year-old postmaster who had polycythaemia and secondary gout with many attacks and big fistulizing tophi. One kidney was completely blocked with calculi, and there were large stones in the other, so that the kidney function was about 20 per cent. of normal. The blood urea was about 100 mg. per cent., and the serum uric acid level 17 mg. per cent. On 0.5 to 1 g. Probenecid the serum uric acid dropped to about 10 mg. per cent., the uric acid excretion was about 1 g. per day, the tophi diminished, the fistulae dried up, and the attack rate was diminished. After about 2 years he died from a cerebral thrombosis.

Conclusion

Gout has troubled man for thousands of years, but to-day it is possible by well-planned and well-

Fig. 7.—Effect of Probenecid and salicylic acid on creatinine and uric acid clearance

conducted treatment to keep the disease under control in most cases.

From a theoretical point of view the situation is less satisfactory, since most of the problems concerning the aetiology and pathogenesis are still unsolved and gout still presents a challenge to medical science.

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