

## COLCHICUM AUTUMNALE AND THE GOUT. NAKED LADIES AND PORTLY GENTLEMEN

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Gout has a long and venerable history. It was recognised by Hippocrates who regarded the disorder as an excessive accumulation of one of the body humours; this substance, 'phlegm', flowed into the affected joints producing a painful inflammation, and it was considered that such accumulations of the humour could result from sexual excess or too rich a diet combined with a sedentary life. In one of his aphorisms Hippocrates also says 'a young man does not take the gout until he indulges in coitus'. As a result, castration was a serious proposal for the treatment of chronic sufferers from gout up until the eighteenth century! The name gout was derived from the Latin 'gutta', a drop to symbolise the flow of drops of phlegm into the joint or joints.

Initially, treatment was directed to removing the evil humour from the body by various means which included bleeding, emesis, diuresis, and in particular, purgation. Two of the common cathartics employed in ancient times were scammony and white hellebore. It is likely that colchicum was used, at first, as yet another purgative but then proved to have a more specific and salutary effect.

The fascination for the clinical investigator of today is that, although known for centuries, colchicum – the autumn crocus – was the first drug to be shown to have an anti-mitotic effect when Pernice made this observation in the late 1800s.<sup>1</sup> The elucidation of this anti-mitotic action expanded our knowledge of cell division and, in time, led to the development of other medicinal compounds that could be used in the treatment of malignancy.

### THE PLANT

The plant is a member of the Lily family. Known in Latin as *Colchicum autumnale* (autumn crocus, Figure 1) it also goes by other names e.g. meadow saffron, 'naked ladies' and 'naked boys'. The species is a herbaceous perennial of the meadows of Europe which is thought to have originated in Colchide on the eastern bank of the Black Sea (a part of modern-day Georgia). The plant has an unusual vegetative cycle. The flowers appear from the corm in September and October without leaves (hence naked ladies or naked boys). Following a winter resting period, the leaves appear, together with the fertilized ovum. The latter structure resembles a nut, and children have confused it with a walnut resulting in poisoning after ingestion. Each year a replacement corm develops at the expense of the parent.

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FIGURE 1

*Colchicum autumnale* - the 'autumn crocus'.

### HISTORY

The plant has been recognised for several thousand years. The Greeks knew of it as a powerful poison but not in the treatment of gout. Dioscorides described it as a deadly poison used by slaves to end their unhappy lives.

When Rome fell to the barbarians and Constantinople became the capital of the ancient world, the arts and sciences flourished there, and Byzantine physicians began to introduce some empirical Eastern remedies. The first definite description of colchicum was given by Alexander of Tralles.<sup>2</sup> He recognised the selective and specific action of colchicum (or hermodactyl, as it was also known) on gout but suggested, from his own observations, that it might not be effective in every form of arthritis. He probably made use of *Colchicum variegatum* rather than *autumnale*, and his formula was 'four scruples of the dried corm of Colchicum; two scruples of scammony, suspend in warm water'. He then describes the immense and rapid relief of pain and of swelling of the joint (or joints). Another Byzantine physician, Aetius,<sup>3</sup> while also advocating the use of the corm of Colchicum pointed out that if the dose given was too great, it produced anorexia, nausea, vomiting and diarrhoea. He confirmed that with proper use the

disease could be removed within two days and that as a result some physicians called the plant *anima articularum* – the ‘soul of the joints’.

Later when the Moslems invaded and annexed Constantinople, their physicians continued to investigate colchicum, both for the effect on gout and for the claim that it possessed aphrodisiac properties. The Muslim empire then spread into Spain and Italy taking this knowledge with it. The Salerno pharmacopoeia of the twelfth century contains a description of the *Bulbus rusticus* (the Latin name for colchicum); its authors stated ‘we know that it helpeth the arthritic gout and the pellagra’.

In Europe, colchicum then passed into its own Dark Age. There were a number of problems: obtaining the correct corms, drying and preparing them in an appropriate way, and avoiding overdosing the patient. Moreover the work of the Moslem physicians was despised as heretical in a time of vicious religious warfare. Abbess Hildegard of Bingen in Germany condemned Colchicum saying that ‘it is a deadly poison and not a health-giving drug’. As she was a noted authority on medicines, her views carried a great deal of weight.

In the United Kingdom hermodactyl appears in the list of simples given in the first edition of the *Pharmacopoeia Londinensis* in 1618 but was then omitted in subsequent editions, until that of 1788. A major influence here was the great physician Sydenham who, himself a sufferer from the gout, declared ‘that all purgative treatments are bad because they bring on what they were meant to keep off’. Purgatives were abandoned and colchicum once again condemned to oblivion. In the second half of the eighteenth century, matters began to change and colchicum was resurrected. Von Stoerk in Vienna in 1763 suggested that colchicum could be given safely in small quantities without risk of sudden death. This new advocacy did not generate any marked degree of excitement as van Stoerk used colchicum principally in dropsy where, as we know now, it lacks efficacy.

The situation changed radically in 1780. Husson, an officer in the French army, marketed a patent medicine which came to be known as *l'eau de Husson* (Husson's water).<sup>4</sup> This, he claimed, had specific effects in gout and many other diseases and disorders. The medical profession opposed its use and its sale was banned for a time. The active constituents of this panacea were a secret. However, it soon became very clear that it was extremely active in gout and the ban was lifted. Dr Edwin Godden Jones introduced the remedy to England in 1808 and subsequently in 1810 produced a small treatise on its use entitled *An Account of the Remarkable Effects of the Eau Medicinale d'Husson in the Gout*.<sup>5</sup> Thereafter, matters moved quickly. In 1814, Dr James Want discovered that the active principle of the water was colchicum. Several distinguished individuals attested to its efficacy including Sir Joseph Banks (then President of the Royal Society of London) and the Prince Regent, later to be George IV.

The Regent seems to have had his first attack of gout in 1811.<sup>6</sup> This was followed by further attacks at regular intervals from 1816 to 1828. In 1817 he is said to have been taking 1,200 drops of laudanum a day without any definite effect on his gout. He therefore informed his physicians ‘Gentlemen, I have taken your half measures long enough to please you...from now on I shall take

colchicum to please myself’. George was the very essence of a portly gentleman of the times. He ate and drank a great deal even for that indulgent period. With one or two cronies, he is said to have consumed six bottles of port regularly after dinner, which ‘barely changed his countenance’. Port wine was relatively cheap at this period (about three shillings a bottle). In 1825 some 40,277 tuns were imported. Halford, the King's physician, estimated that this would be equivalent to 40,000 attacks of gout! George became so obese (Figure 2) that, at times, as a result of both this and gout, he had to be carried by bearers, or, when riding for exercise, hoisted onto his horse by a crane. In 1828 he had such severe gout in his right hand that he could hardly hold a pen to sign official papers.<sup>6</sup>

At about the same time (1828) he began to develop dropsy. Halford diagnosed heart disease which progressed, and he died aged 68 on 26 June 1830. Sir Astley Cooper carried out a post-mortem at which the findings were a ruptured blood vessel in the stomach (probably a varix), cirrhosis of the liver, cardiomegaly, aortic stenosis and a large urinary calculus. Gout was not mentioned.

George's decision to take colchicum, initially against the wishes of his physicians, helped to make Husson's water respectable in the upper strata of society. Indeed he is said to have recommended colchicum to the Bourbon Prince Louis with such good effect that Louis was able to leave Richmond, Surrey, to assume the throne of France as Louis XVIII, following the defeat of Napoleon at Waterloo.

Scientific advance now assumed a more rapid pace as the Age of Chemistry dawned. In 1820 Pellétier and Caventou<sup>7</sup> isolated the active alkaloid colchicine from colchicum. Subsequently, in 1884, Houdé crystallised the alkaloid from extracts and tinctures of the corm.<sup>8</sup> Soon all the tinctures and Galenical preparations could be replaced by stable and reliable materials and accurate dosage schedules established. The margin between therapy and toxicity (the therapeutic index for this drug) was found towards the end of the nineteenth century. Sir Alfred Garrod devised the ‘string’ test for urate in blood and published his results in 1848 – one of the earliest biochemical tests for a disease.<sup>9</sup>

The work of Pernice, a Sicilian pathologist the centenary of whose observation has just been celebrated, should not go unrecognised.<sup>1</sup> Working in Palermo between 1884 and 1906, he deliberately poisoned dogs with colchicine (which was then available for the first time as the pure crystalline compound). Pernice found, on microscopy of postmortem specimens, that there was a considerable increase in mitotic figures in the cells of the gastric and intestinal mucosa. He remarked further that anatelophase was absent in the mitotic cell cycle and suggested that colchicine was a mitotic spindle poison. These prescient observations remained in limbo for 50 years until the end of the Second World War when the antimitotic effect of colchicine was rediscovered. In turn this stimulated work on mitosis (and cancer) and led to the discovery of the vinca alkaloids<sup>10</sup> in the periwinkle and the taxel alkaloids in the yew.<sup>11</sup>

#### PHARMACOLOGY AND TOXICOLOGY

##### *Pharmacology*

Colchicine is an alkaloid of the phenylethylisoquinoline family of molecular weight 399.4 (structure shown in Figure 3). It binds to microtubular proteins resulting in

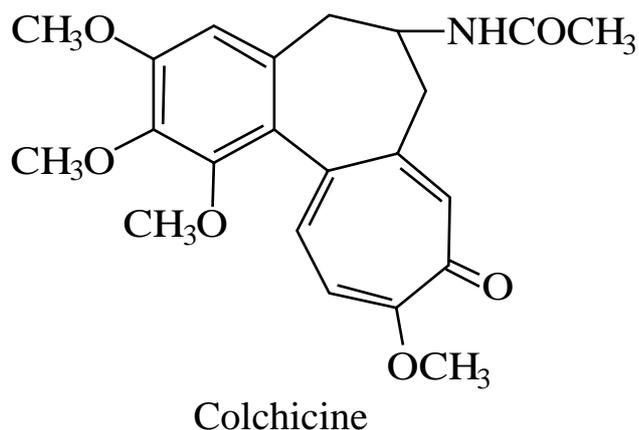


FIGURE 2  
The Prince Regent: The Brightest Star in the State, November 1820. ©The British Museum.

depolymerisation and the disappearance of microtubules in granulocytes and other cells (see Figure 4). This results both in the inhibition of mitosis and interference with cellular migration. It would appear that a higher concentration of colchicine is needed to stop mitosis than is required to inhibit cellular migration. In subjects with gout, colchicine does not affect either the production of uric acid or its further metabolism. The specific effect appears to be mediated by preventing the neutrophil polymorph producing glycoproteins and other cytokines which mediate the acute inflammatory reaction in acute gouty arthritis. The polymorphs continue to ingest crystals of uric acid, but they no longer initiate the appropriate

inflammatory cascade.

Colchicine is rapidly but poorly absorbed from the gastrointestinal tract. The drug and its metabolites undergo extensive change during enterohepatic circulation, and it is thought that this recirculation could contribute materially to the serious damage to the gut which occurs after an overdose. Colchicine is concentrated in white blood cells and also widely distributed in the kidney, liver, spleen and gastrointestinal tract. In patients with chronic renal failure or hepatic insufficiency the dose should be reduced.



**Colchicine**

FIGURE 3  
The chemical structure of colchicine.

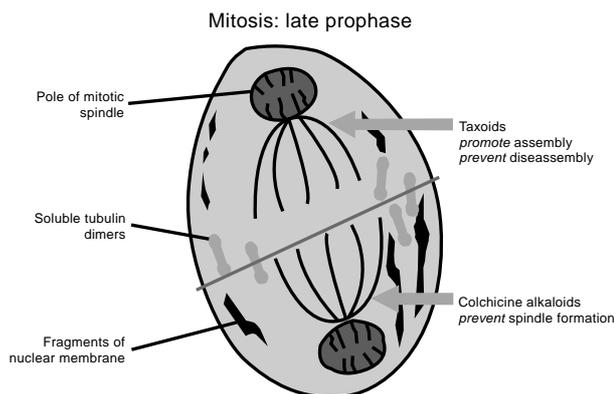


FIGURE 4  
The effect of colchicine and taxoids on the mitotic process.

### Poisoning

The toxic dose in human beings is about 10 mgm. The ingestion of 40 mgm of the pure alkaloid is always fatal within three days.<sup>12</sup> The poisoning is usually deliberate and suicidal. Occasionally the plant or its parts are ingested accidentally, for example when the leaves of *Colchicum* are mistaken for the herb ransoms (*Allium ursinum*, garlic-like flavouring), or the corm is confused with a walnut by children. Poisoning with colchicine has also been reported after eating the Tiger Lily (*Gloriosa superba* L.), another member of the lily family which contains the alkaloid.

Acute overdose with the alkaloid first produces nausea, vomiting and diarrhoea; liver and kidney failure may follow. All the haemopoietic elements of the bone marrow may be depressed. Pancytopenia may result and sepsis follow. Muscular weakness and ascending paralysis can occur. Death usually results from a combination of respiratory and cardiac failure. In view of the antimetabolic effects of colchicine, it is interesting to note that delayed alopecia (of the scalp and body) and azoospermia have been described.<sup>13</sup>

Until very recently, there was no specific treatment for severe overdose with colchicine but in 1995 Baud and his colleagues<sup>14</sup> described the use of Fab fragments colchicine-specific antibody. The patient treated with this therapy was a woman of 25 who had taken 60 mgm of colchicine together with 900 mgm of phenobarbitone and 750 mgm of an extract of opium. 6.4 gms of Fab antibody fragments were infused over a period of six hours. There was an immediate marked increase in cardiac output and pulmonary oedema cleared. The patient was discharged well at 15 days. Unfortunately Fab fragments specific for colchicine are not available commercially at the present time.

The patient described by Baud *et al* also developed transient bone marrow depression. Sometimes this can be a very serious problem as in the patient described by Critchley and colleagues.<sup>15</sup> A previously healthy 43-year-

old woman took 25-30 mgm of colchicine. Initially she had severe gastrointestinal symptoms, but on the fifth day developed marked pancytopenia and signs of incipient sepsis. She was treated with granulocyte recombinate colony stimulating factor (G-CSF) and made a full recovery associated with a marked increase in bone marrow activity. The authors make the point that individuals who have taken a large dose of colchicine should have daily blood counts for seven to ten days following the poisoning. The depression of haemopoietic cellular elements, if and when it occurs, should be dealt with appropriately.

### THERAPEUTIC AND OTHER USES OF COLCHICINE

Two hundred years after Husson, what is the place of colchicine in modern medicine and science?

#### Gout

The treatment of gout today depends largely on the use of non-steroidal anti-inflammatory drugs (such as indomethacin and ibuprofen) for the acute attack and allopurinol for the prevention of further attacks. However, in patients who are intolerant of non-steroidal anti-inflammatory drugs or xanthine oxidase inhibitors, colchicine still has a limited but definite place.<sup>16</sup>

For the acute attack the dose ranges usually between 4.0 and 8.0 milligrams. In prevention a dose of 0.6 mgm is usually employed at intervals ranging from once a week to once a day. As is well known, even minor surgery may provoke an attack and in this situation 0.6 mgm of colchicine has been given three times a day for three days both before and after the operation.

#### Calcium gout (pyrophosphate arthritis)<sup>17</sup>

For patients with recurrent attacks of calcium gout (pseudogout) daily prophylaxis with colchicine may be helpful. The release of calcium pyrophosphate dihydrate crystals into the joint causes the neutrophils to release a glycopeptide which is chemotactic for other neutrophils.

Production of this glycopeptide can be suppressed by colchicine.

#### *Familial Mediterranean Fever (FMF)*

Perhaps the most fascinating use of colchicine today is in the condition Familial Mediterranean Fever.<sup>18</sup> FMF is an inherited condition, prevalent among near-Eastern peoples, which is characterised by recurrent attacks of inflammation in serosal spaces including the peritoneum. The febrile episodes are accompanied sometimes by arthritis and a skin rash resembling acute erysipelas. In about 25% of cases, renal amyloidosis of the AA type develops which progresses to renal failure over a period of years. The gene for the disorder has now been cloned. It is responsible for the production of a substance called pyrin which is thought to prevent the production of a chemotactic factor inactivator. The only effective treatment for this rare and unusual disorder is colchicine, given continuously. This therapy reduces the number of attacks of fever substantially and largely prevents the deposition of AA amyloid.

#### *Primary biliary cirrhosis (PBC)*

PBC is an immunologically mediated disease in which activated T lymphocytes attack and destroy the epithelial cells in the small intralobular bile ducts of genetically susceptible patients. The process will progress over a period of five to twenty years to result eventually in obstructive jaundice, biliary cirrhosis and death.

Colchicine has been shown to improve liver function tests in three prospective trials and has improved early survival (up to four years but not up to eight years). Kaplan<sup>19</sup> has suggested recently that the way forward is combination therapy which should include colchicine, ursodeoxycholic acid and methotrexate.

#### *Experimental therapy*

Alzheimer's disease<sup>20</sup> and Behçet's syndrome<sup>21</sup> are under investigation for a possible beneficial effect of colchicine. One of the pathological features of Alzheimer's disease is the deposition of amyloid in the brain. If this deposition could be arrested, prevented (or even reversed) then mental function might be improved. Taking the example of FMF (above) where renal amyloidosis can be prevented, trials of colchicine are now in progress. This therapy would represent an attack on the basic pathology of the disease rather than the symptomatic treatment presently employed with cholinesterase inhibitors such as tacrine or donepezil.

Behçet's disease is another disorder in which neutrophils are activated in a multisystem attack on eyes, joints, gut and nervous system. Colchicine is being assessed both in the general and ocular variants of this disorder.

#### *In horticulture*

Colchicine acts on the cells of plants to inhibit the separation of daughter chromosomes at mitosis. Higher concentrations can be used than in man without killing the plant cells. The chromosomes remain attached by their centromeres. Tetraploid and polyploid strains can result, which may have advantages over the parent in terms of hardiness and pest resistance (Figure 4).

#### COLCHICINE TODAY

Although seldom used now, colchicine has a number of limited but important indications. Its effects on

inflammation, fibrosis and the deposition of amyloid deserve further investigation as they may provide useful insights into cellular pathology.

The history of the discovery and use of colchicine is a fascinating one. Unearthed by the physicians of Byzantium, developed by the Moors, it was then condemned in Europe as an heretical and dangerous medicine. Nevertheless it persisted in folk and quack medicines until it was redeveloped by Husson in the late eighteenth century.

Fortunately this coincided with the Age of Enlightenment and the development of modern Chemistry. The work of Scheele<sup>22</sup> on lithic acid (uric acid); of Wollaston<sup>23</sup> on the chemistry of the gouty tophus (uric acid), and the development of the atomic theory by John Dalton in Manchester in 1808, led on to the isolation of colchicine in 1820 by Pellétier and Caventou. The specific and salutary effect of colchicine in gout could then be established, and as Alexander of Tralles had forecast, over 1,000 years earlier, some arthritides responded to colchicine and some like rheumatoid and osteoarthritis did not. The drug, therefore, also played a part in the nosology of the rheumatic diseases.

In the eighteenth and nineteenth centuries, gout attracted a great deal of attention because it tended to affect people of high rank or high intelligence or both. The roll call is extensive, and includes George IV, the lexicographer Samuel Johnson, the poet John Milton, and the polymath Benjamin Franklin. Physicians like Harvey and Sydenham were also victims. The discovery of a new therapy, as with Husson, could make its 'inventor' a small fortune.

Oliver Wendell Holmes states:

There is a dead medical literature and there is a live literature. The dead is not all ancient and the live is not all modern.

How well this is exemplified by the compelling history of *Colchicum autumnale* and the discovery of its active principle colchicine.

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