THE SNOWDROP (*GALANTHUS NIVALIS*): FROM ODYSSEUS TO ALZHEIMER

*M.R. Lee**

INTRODUCTION

The author Robert Graves, in his work on Greek mythology published some years ago, suggested that such myths embodied folk memories of ancient knowledge.[1] For this reason, if no other, they deserve our serious consideration. In this article, I hope to develop that proposal in relation to the snowdrop and Odysseus' encounter with the enchantress Circe.

Since early Greek times there has been a desultory interest in the snowdrop (*Galanthus nivalis*) for the treatment of pain and other neurological disorders. About 30 years ago, an active principle galanthamine was extracted from the plant and subsequently synthesised. This development quickened interest markedly and has led to studies with the compound in Alzheimer's disease.

THE PLANT (*GALANTHUS NIVALIS*)

The common name for *Galanthus nivalis*, the snowdrop, appears to be derived from Germany in the sixteenth century where the flower was thought to resemble an earring or pendant (*Schneetropf*). The generic name Galanthus comes from the Greek *gala* (milk) and *anthos* (flower) and refers to the milk-white flower (Figure 1). The genus comprises some 12 species of small perennial bulbous herbs.[2] The leaves are linear (or elliptical) and the flowers solitary and nodding.

Originating in Turkey, Iran and the Caucasus, the plant was probably introduced into Great Britain in the early medieval period by religious communities and has naturalised widely (see below).[3] One species is named after the British naturalist Elwes and another after the distinguished physiologist Sir Michael Foster.[2]

The common snowdrop *Galanthus nivalis* has narrow linear leaves (Figure 1) and exists in many cultivars and varieties. The outer three tepals are long and conceal the inner three, which are usually marked in green. In many parts of Europe snowdrops grow in damp deciduous woodland, often beside rivers and streams.

A SYMBOL OF SPRING

The snowdrop flowers in early February (or in late January if the winter has been mild). For this reason it has been associated with 2 February (or Candlemas) which is the feast of the Purification of the Blessed Virgin Mary. Not surprisingly it has often been called the Candlemas bell or Mary's taper. Other names for the plant have included the Snow-piercer; February fairmaids and Dingle-dangle.[3]

The plant may have been introduced initially to Great Britain by monks. Notable colonies exist at many ancient monastic sites including Maltby in Yorkshire (the Cistercians);

*(Emeritus Professor, University of Edinburgh)
112 Polwarth Terrace, Edinburgh EH11 1NN

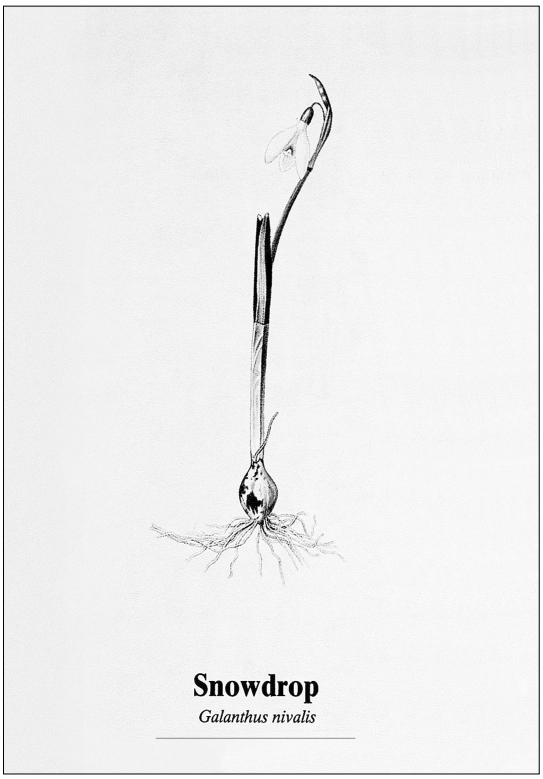

FIGURE 1
The snowdrop (*Galanthus nivalis*).

Dunwich in Suffolk (the Greyfriars) and Brinkburn Priory at Rothbury in Northumberland. One of the most northerly sites is an old graveyard outside Cromarty on the Black Isle. The plant appears to have escaped from these monastic colonies by direct transport of the bulbs or by being carried downstream in local flooding.

The flower had various symbolic associations. It was brought into churches on Candlemas as a symbol of virginity and purity. Another name for the plant is the Purification flower. Village maidens also used to wear them in garlands on 2 February, again as a symbol of purity.[3]

Strangely the flowers were regarded also as a symbol of death because a single bloom looked like a corpse with its head in a shroud. As a result it was held to be unlucky to bring a flower into the house. In contrast, Saint Francis of Assisi called the flower an emblem of hope as it bloomed at the end of winter. By the sixteenth and seventeenth centuries, the plant was widely known. It was described by both John Evelyn and Robert Boyle. The poet Thomas Tickell referred to it as 'vegetable snow' and in the nineteenth century the Laureate Tennyson mentions it in the stanza 'the first snowdrop of the year in my bosom lies'.

On a more mundane level one authority notes that

they were planted in parallel lines to guide cottage dwellers to their outside privies on winter nights!

ODYSSEUS AND CIRCE

Odysseus, in his wanderings (as they were described by Homer) arrives at the island of Aeaea on which the enchantress Circe lives.[4] Circe then gives food to the sailors in Odysseus' crew. Unhappily for them, the enchantress has mixed 'malignant' drugs with the food so that they might 'forget totally the land from which they had come'. Circe then waved her wand and changed them into pigs.

Odysseus sets out to rescue his men. As he walks up through the forest, he encounters the god Hermes in the form of a young man. Hermes warns him of the risk of meeting Circe and that he will need an antidote to her poison. So saying Hermes supplies him with the antidote 'by drawing it up from the earth. It had a black root but a milk-like flower. The gods call it moly and it is difficult for mortal man to dig it up.'[4]

Circe then gives Odysseus the deadly charm (Figure 2) but he is not bewitched. He rushes upon Circe threatening to run her through with his sword. Circe pleads for mercy saying 'I marvel that thou couldst drink of this potion that I have charmed and yet take no hurt'. After a great feast Circe releases the men and they are transformed from pigs back to human beings.[4]

FIGURE 2
Odysseus at the Court of Circe (after Flashman).

THE NATURE OF CIRCE'S POISON

Over the centuries two candidates have emerged for Circe's poison: either a member of the family Solanacae or Enchanter's nightshade (*Circaea lutetiana*).

In respect of the Solanaceae two possibilities have been considered: the woody nightshade or bittersweet (*Solanum dulcomara*) and the thornapple or Jimson weed (*Datura stramonium*).[5] The most compelling candidate is woody nightshade as it is widely distributed in Europe. The Flemish botanist Mathias de l'Obel (of Lobelia fame) reported that the learned botanists of Montpellier favoured bittersweet, whereas those of Paris supported enchanter's nightshade (*Circaea lutetiana*).[6] Interestingly the Lutetiani means Parisians (or mud dwellers as they were described by Julius Caesar).

Certainly the balance of the argument favours bittersweet as it contains tropane alkaloids such as atropine and hyoscine. The ancient Greeks knew that this plant produces poisons. After ingestion common symptoms include impairment of memory, delusions and hallucinations. The sailors in Odysseus' crew believed that they had been turned into pigs and behaved appropriately.

ODYSSEUS' ANTIDOTE

The question now arises, What was the nature of moly? How could it antagonise a tropane alkaloid?

In 1981 Plaitakis and Duvoisin put forward a convincing argument that the plant moly is in fact *Galanthus nivalis* the common snowdrop.[7] First, Homer's description of where it was found, the colour of its flower and the black root fit the snowdrop well (or a related Galanthus species). Second, one of the chemicals in the bulb, galanthamine, acting as an anticholinesterase, would reverse the central actions of a tropane alkaloid such as hyoscine or atropine.

Other authorities have put forward alternative suggestions for the nature of moly. Theophrastus, in the third century BC identified it as a variety of Scilla. Goodyer in 1655 suggested that Homer's plant was *Allium nigrum* but this seems unlikely as this plant has a purple flower. Dioscorides had suggested earlier *Leucojum bulbosum* (the Snowflake or white violet) and this is eminently possible as many members of the Amaryllidaceae and Narcissi may contain the active principle galanthamine.

At all events Homer's description of the effect of moly on Odysseus may be the first suggested example of the use of an anticholinesterase drug to prevent (or reverse) poisoning with a tropane alkaloid.

GALANTHAMINE

After much chemical work in Russia and elsewhere, the structure of the active alkaloid of the Amaryllidaceae was established as galanthamine (Figure 3). Confusingly, it has also been known as galantamine, galanthine, lycorimine and lycorenine. It is widely distributed in the plant kingdom occurring in the following families: Crinum, Galanthus, Hippeastrum, Hemerocallis, Leucojum, Lycoris, Narcissus and Ungeria.[8] It is often accompanied in these plants by lycorine which is more toxic causing profuse vomiting. This latter compound may account for the poisonous effect of the bulbs of narcissi such as daffodils.[9]

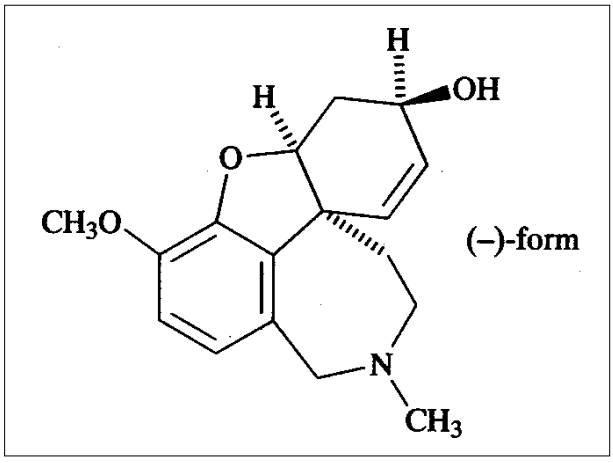

FIGURE 3
The chemical structure of Galanthamine.

Galanthamine is a phenanthrene alkaloid similar to codeine but also contains a tertiary nitrogen (Figure 3). It was isolated from the Caucasian snowdrop in 1952 and from the common snowdrop in 1954.[10] Most of the original work on galanthamine was carried out in the Eastern Bloc countries between 1950 and 1960. Only in the last 10-20 years has it attracted any attention in the West.

THE PHARMACOLOGY OF GALANTHAMINE

Galanthamine inhibits acetylcholinesterase *in vitro* and *in vivo*.[10] This competition is competitive whereas that of Tacrine, another drug used therapeutically, is non-competitive. Galanthamine is 50 times more active against human acetylcholinesterase (from red blood cells) than against the butyrylcholinesterase present in human plasma. The compound penetrates the blood brain barrier readily and inhibits central cholinesterase.[10]

As a result of this pharmacological activity, galanthamine has been used for some years to reverse non-depolarising muscle relaxants (as an alternative to neostigmine). Most of these reports were anecdotal and difficult to evaluate until 1971 when Cozanitis in Finland reported on 40 patients undergoing surgery. Using intravenous doses of galanthamine ranging from 5 mgm to 20 mgm he was able to reverse the effect of alcuronium, pancuronium, gallamine and tubocurarine. The rate of recovery of muscular activity was slower than with neostigmine. Side-effects of the drug included nausea, vomiting, salivation and blurred vision (characteristic parasympathetic effects).

In rabbits galanthamine eye drops lowered the intraocular pressure and the duration of the effect was much longer than that seen with physostigmine. The compound has the potential therefore to be of use as a treatment for glaucoma.[12] Galanthamine also has positive effects on memory in rats in various experimental models[10] which led to its evaluation as a potential therapy in Alzheimer's disease (see below).

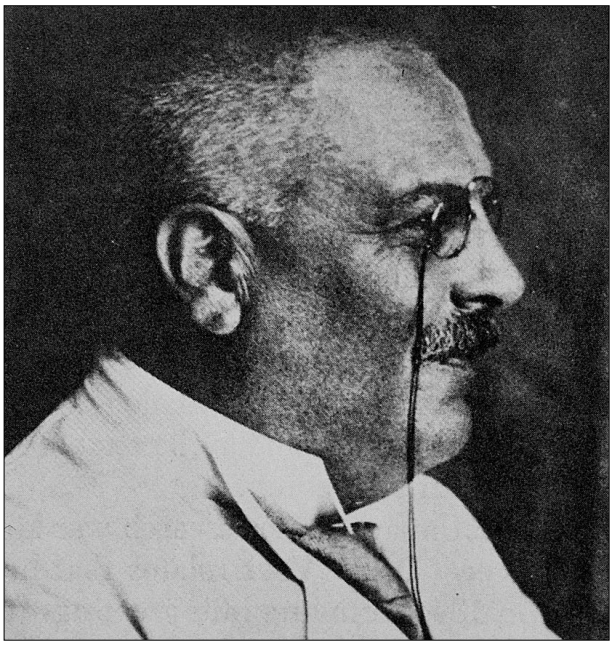

FIGURE 4
Alois Alzheimer (1864-1915).

ALOIS ALZHEIMER AND HIS DISEASE

Alzheimer (1864-1915; Figure 4) was one of the giants of German neuropathology.[13] Together with his lifelong friend and collaborator Nissl he published a six-volume treatise entitled *Histologic and Histopathologic Studies of the Cerebral Cortex*. At various times he worked with Kraepelin, the Linnaeus of Psychiatry, in the Universities of Heidelberg and Munich. In 1912 he was appointed to the Chair of Psychiatry in Breslau. Whilst in the train travelling to take up this position he suffered a serious heart attack and died some three years later at the early age of 51 years. Alzheimer had married the rich widow of a banker and he was in the happy position of being able to fund his own research and, in particular, the expensive illustrations of neuropathology specimens in his papers and books. A devoted teacher he was also known for his pince-nez and ever-present cigar.[13]

In 1906 Alzheimer described the clinical and neuropathological features of a woman aged 51 who had died after a progressive illness that had lasted for five years and had been characterised by depression and hallucinations. Progressive dementia then ensued. At post-mortem there was generalised brain atrophy. Silver staining demonstrated characteristic neurofibrillary tangles and senile plaques which have since been recognised as the pathological hallmarks for the disease.[14] We now know, almost 100 years later, that there is widespread deposition of amyloid in the brain and this is accompanied by a serious reduction in brain transmitters, in particular in the amount of acetylcholine at the cholinergic synapses.[15]

By analogy with Parkinson's disease (and L-dopa), it was decided in the 1980s to try the effect of cholinergic agonists and other agents acting on the cholinergic system as therapy for Alzheimer's disease. It was realised from the outset that not all Alzheimer sufferers would benefit because the condition varies widely on a clinical and genetic basis. The most common strategy to be adopted has been an attempt to inhibit the catabolic enzyme acetylcholinesterase in cortical synapses. This would allow the concentration of acetylcholine to rise and restore cholinergic transmission to some degree.

The classic drug physostigmine was tried initially but was too toxic and too short acting. The first success was with tetrahydroaminoacridine (Tacrine) but it proved to be hepatotoxic and is not widely used.[16] In the last year or two, 'second' generation drugs have started to appear including donezepil[17] (Aricept). This is said to slow the progression of Alzheimer's in up to 40% of patients. It has however a number of potentially dangerous side-effects including atrioventricular block, bladder neck obstruction and convulsions.[17] Several other drugs are under active development.

GALANTHAMINE AND ALZHEIMER'S DISEASE

Galanthamine possesses several positive features as a candidate drug for Alzheimer's disease. It has been used in anaesthetic practice for a number of years as pointed out earlier. Moreover it is relatively easy to achieve 40-70% inhibition of cholinesterase (the therapeutic window) and it appears to be free of toxic effects on the liver.

Pilot studies on its use in dementia were carried out in Vienna and Berlin and were published in 1989.[18] In a relatively small number of patients there appeared to be a positive effect and this encouraged randomised trials with greater numbers of patients. Most of these have proved

positive. Some patients who have received galanthamine for periods up to three years have shown a lower rate of cognitive decline when compared with the control group of patients receiving treatments other than galanthamine.[15]

The side-effects of galanthamine were dose-dependent, mild and tended to disappear on prolonged treatment. They included nausea and vomiting (10-20% in different trials), diarrhoea and abdominal cramps (2-5%), anorexia (33%) and weight loss (1-2%). The nausea and vomiting were abolished by domperidone. There was no deleterious effect on hepatic or renal function. It would appear that galanthamine compares favourably with other second generation drugs such as donezepil and metrifonate.[19]

THE ROLE OF DRUGS IN ALZHEIMER'S DEMENTIA.

There has been much discussion recently regarding the role of these drugs in Alzheimer's disease. Should they be prescribed at all in the light of their variable efficacy and considerable expense?

Taken together with the fact that they do not address the basic pathology of the disease which includes deposition of amyloid protein (B-AP) and hyperphosphorylation of tau proteins these considerations have been used as an argument against them. Levy has recently made the telling point that the effect of drugs is extremely variable with some patients improving greatly and some not at all.[20] He advocates the use of a particular drug for a 12-week period. The effect on the patient should be observed systematically and if a good response is obtained then, of course, treatment should be continued. The advent of less toxic and cheaper drugs (such as galanthamine) will favour this pragmatic approach. Finally the point can be made that if deterioration can be delayed the need for expensive institutional treatment may be avoided as the patient, often of an advanced age, may die of other causes in the interim period. Patient behaviour may also improve making the task of carers that much easier.

CONCLUSION

Galanthamine will probably receive a product licence for Alzheimer's disease in late 2000.[21] This will represent an end to the odyssey that stretches from Homer and the Greek gods to modern chemistry and neuropathology.

The story is an interesting example of ancient wisdom linked to modern knowledge and bears out Graves' views on the importance of the myth to ancient peoples.[1] Truly we can agree with the view expressed by Thomas Carlyle in his essay on History in 1838 when he wrote 'What is all knowledge too but recorded experience and a product of history.'

ACKNOWLEDGEMENTS

I wish to thank Mr Alex Haig of the Library of the Royal College of Physicians of Edinburgh for help with the References and Figures; Edinburgh Word Processing for typing the manuscript; and Dr D.T. Greenwood of Shire Pharmaceutical Development for his generous provision of relevant background material. Charles C. Thomas, publishers of Springfield, Illinois, allowed me to reproduce the photograph of Alois Alzheimer.

REFERENCES AND NOTES

1 Graves R. *The Greek myths* Harmondsworth:Penguin Books, 1960.
2 Hyam R, Pankhurst R. *Plants and their names: a concise dictionary* Galanthus. Oxford University Press, 1995; 202-3.
3 Mabey R. *Flora Britannica*. *Galanthus nivalis* Sinclair Stevenson, 1996; 421-5.
4 Church, Rev. AH. *The story of the Odyssey. 3rd edition* London: Seeley & Co., 1903; 128-9.
5 Cooper P. *Poisoning. 3rd edition revised and enlarged*. *Solanine and Solanin Spp* London: Alchemist Publications, 1974; 191-2.
6 See reference 3, p.238.
7 Plaitakis A, Duvoisin RC. Homer's Moly identified as *Galanthus nivalis L*: physiologic antidote to Stramonium poisoning. *Clin Neuropharmacol* 1983; **6:**1-5.
8 Harborne J, Baxter H, Moss G (eds). *Dictionary of plant toxins* Chichester: John Wiley, 1996; 167.
9 See reference 8 p.240.
10 Harvey AL. The pharmacology of galanthamine and its analogues. *Pharmac Ther* 1995; **68:**113-28.
11 Cozanitis DA. Experiences with galanthamine hydrobromide as curare antagonist. *Der Anaesthesist* 1971; **20:**226-9.
12 Agarwal HC, Gupta SE. Ocular hypotensive effect of galanthamine hydrobromide: an experimental study. *Indian J Pharmacol* 1990; **22:**117-8.
13 Beighton P, Beighton G. *Alois Alzheimer. The man behind the syndrome* Berlin and New York: Springer Verlag, 1986; 8-9.
14 Alzheimer A. Uber ein eigenartingen schweren Krankheitsprozess der einen Hirnrinde. Zentralbl. *Nervenk* 1906; **25:**1134.
15 Thomsen T, Bickel U, Fischer JP, Kewitz H. Galanthamine hydrobromide in a long term treatment of Alzheimer's disease. *Dementia 1*, 1990; 46-51.
16 Summers WK, Majovski V, Marsh GM *et al*. Oral tetrahydroacridine in long term treatment of senile dementia, Alzheimer type. *N Engl J Med* 1986; **315:**1241-5.
17 Drugs for dementia (Section 4.11) In: *British national formulary, No. 35* British Medical Association and Royal Pharmaceutical Society of Great Britain, March 1998; 232.
18 Rainer M. Clinical studies with Galanthamine. *Drugs Today* 1997; **33:**273-9.
19 Morris LC, Cyrus PA, Orazem J *et al*. Metrifonate benefits cognitive behavioural, and global function in patients with Alzheimer's disease. *Neurology* 1998; **50:**1222-30.
20 Levy R. Effect of drugs can be variable in new drug treatment for Alzheimer's disease (letter). *BMJ* 1998; **317:**924.
21 Greenwood D T. Personal Communication, 1998.