Poppies: Pleasures, Pains and Problems

A Dayan podcast

Poppies belong to the Papaveraceae (subfamily Papaveroideae) of herbaceous plants. The best known genus is *Papaver* which includes the Opium or Breadseed Poppy *Papaver somniferum*; the Field, Corn or Flanders’ Poppy, *Papaver rhoeas*, and the Oriental Poppy *Papaver orientale*. There are 41 other genera in Papaveraceae including *Eschscholtzia* (eg Californian poppy), and *Meconopsis* (eg the yellow Welsh and the blue Himalayan Poppies).

In this and the subsequent podcast by Anthony Dayan from the Medicinal Plant Garden of the Royal College of Physicians of London the history of the group and the varied uses of particular species of poppy are related to the principal alkaloids they contain. Part I concentrates on *Papaver somniferum* as the only viable source of opium and the nature and medicinal uses of the morphine it contains. Part II discusses the other alkaloids found in opium and the histories and properties of certain other species from *Papaver* and related genera.

The Opium Poppy, *Papaver somniferum*, has long attracted attention as the source of opium, one of the oldest pain relieving drugs, and as a cultivable plant with beautiful flowers. The ‘Poppy Seeds’ used in cooking come from the same plant. Early studies of the composition of opium and subsequent research into its biological actions led to major discoveries in chemistry and in how the nervous system works.

The Opium Poppy is a hardy annual, with mauve, red or white flowers showing a darker, purple patch at the base of the petals. It probably arose in Asia Minor and has now become naturalised throughout the world. In addition to its popularity with ordinary gardeners it is a major commercial crop with cultivars selected for their vigour and high or low content of morphine and other alkaloids. The immature seed capsule is a smooth green sphere which expands and then turns brown as it ages. Cuts in the green capsule exude a creamy latex, which dries to a brown gum - crude opium. Opium may be collected in that form, used in an alcoholic tincture, such as laudanum devised in the 1660s by the great English physician Thomas Sydenham, and in other popular medicines. It may be smoked or swallowed for its mind-altering actions, or refined to separate morphine and the other principal alkaloids codeine, papaverine, thebaine and noscapine. They, too, can be used as medicines or converted to other pharmaceuticals. Worldwide about 4770 tons of morphine were believed to have been produced in 2015, including 1360 tons consumed as opium and 327 tons as heroin, a simple but more potent derivative of morphine. Almost 100000 tons of poppy seeds were produced in the same year, of which 25000 tons came from the Czech Republic.

The seeds for cooking are harvested from the ripe brown capsule of cultivars selected for their low alkaloid level. Morphine and the other alkaloids are present in lower concentrations in the seeds than in opium sap. Although the concentration of morphine in seeds supplied for cooking is very low the sensitivity of modern forensic analyses may lead to positive drug test results after eating such foods. Poppy seeds are prominent in European and Near Eastern cuisines and immigrants have popularised them in the Americas and elsewhere. They were used to flavour foods by the early Egyptians about 1500BCE and probably even by their predecessors the Sumerians as far back as 5000-3500 BCE.

The power of opium to relieve pain and produce sleepiness has been exploited since at least the Sumerians and ancient Egyptians, about 5000-3500 BCE. Those uses were probably described by Bian Que, a Chinese surgeon in 300BCE, and in Indian Ayuverdic medicine about 1000BCE but in mixtures containing other plant extracts that affect the brain, including Cannabis, Henbane, Mandragora and Deadly Nightshade.

In the European tradition opium is mentioned by Theophrastus (c.300 BC) but with no medicinal usage. Pliny and Dioscorides (70 AD) give extensive accounts of it as a food and medicine, noting its sedative powers and dangers. Dioscorides (70AD) described it as a treatment for diarrhoea and coughs, and almost in passing mentions its analgesic activity and that overdosage could cause death. Pliny mentions its value in palliative care in the terminally ill with great pain, and that it was used, too, by poisoners. Celsus (200 AD), Galen (200AD), Paulus Aeginetus (600 AD), Mesue (c. 850AD) through to the School of Salerno (1000AD) and later writers in the early modern era continued the same uses. Manuscript herbals of the 1300s note its ability to induce sleep, and to bring on death. Most writers before Culpeper (1649) mention its sedative effect and topical use, but he notes it as good for violent pains and warns of death from its use. Galen recommended castoreum (a secretion from beaver glands) as an antidote for its toxicity. It was included in the laudanum tablets in the College’s Pharmacopoea of 1618.

There is much overlap between the early European accounts of opium and descriptions of its use as a sedative and analgesic. In the Golden Age of Islamic medicine in the 9th-10th centuries AD it was one of several plant ingredients in sleep inducing and analgesic mixtures swallowed, sniffed or absorbed through the nasal mucosa, in the Anaesthetic Sponge described by Al Rhazes about 900AD

Opium in various forms came into extremely wide use mainly as a sedative, sleeping aid, cough suppressant and recreational drug in Europe from the end of the 17th century. Its addictive potential appears to have been realised about this time, particularly when it became freely available as an alcoholic tincture of opium, which acquired the name ‘Laudanum’, although earlier mixtures with this name did not contain opium. In the College’s Pharmacopoea of 1618 laudanum was a tablet of 19 different ingredients, and in the continental Pharmacopoeia Augustana, of 1672, tablets of laudanum ‘without opium’ were also described. Usage was similar in China and India until the late 1800s when production in India was greatly increased to supply the growing number of addicts in China. Forced importation of opium into China by British traders encouraged millions of addicts and finally led to the Opium Wars of the 1840s - 1860s. It is only in the last decades that popular opium-containing medicines, which have sometimes caused addiction, such as Dr Collis Brown’s Chlorodyne, originally invented to treat cholera; ‘Kaolin and Morphine mixture’ for diarrhoea; laudanum as a general soothing agent and paregoric for anxiety and cough ceased to be available as over-the-counter drugs in the UK. Addiction, morbidity and fatalities from opium and prescribed and illegally sourced opiates, including synthetic opioids have reached epidemic proportions, with 50,000 deaths annually in the USA alone.

Morphine, heroin, codeine and their synthetic relatives are still vital medicines in the management of severe pain and care of the dying because appropriate doses both relieve suffering by removing pain and reducing anxiety without necessarily affecting wakefulness; larger doses can produce hallucinations and eventually depressed respiration and death.

The other medically important actions of morphine and so of opium include reducing the motor activity of the gut by inhibiting some of its nerve cells and the secretion of fluids by the intestinal lining cells, hence its therapeutic value in diarrhoea and the common side effect of constipation. It also leads to constricted pin point pupils, blurred vision, a dry mouth and sometimes difficulty in passing urine, all due to inhibition of local nerve cells. Sometimes morphine makes people feel sick and vomit.

There are two prominent features of repeated doses of morphine, firstly: tolerance, so that increasing doses are needed to produce the same effect and secondly: addiction, causing a severe mental craving for more of the drug accompanied by bodily disorders if it is not given.

The Part II podcast relates how these effects are due to the way in which morphine and similar drugs [opiates from natural sources and opioids if synthetic] mimic and may even surpass a major natural signalling mechanism in the body. Uses of the other alkaloids and particular features of other types of poppy are described

In 1805 the German pharmacist Sertürner first demonstrated a specific ‘soporific substance’ in opium, which he called morphium later morphine after Morpheus, the Greek god of sleep. It was the first alkaloid to be isolated; now almost 12000 such substances have been identified in plants, almost all of them with powerful biological actions. Some are probably produced as defences against insect attack and others may be metabolic waste products. Subsequent chemical analyses revealed other related alkaloids in opium – codeine, narcotine, papaverine and thebaine.

Codeine has weaker but similar actions to morphine and is widely used and abused as an approved analgesic and in cases of diarrhoea. Narcotine, also known as noscapine, is not a true narcotic although it may sometimes cause sleepiness and constipation. It is an important cough suppressant. Papaverine is a powerful relaxant of smooth muscle leading to its use dilate blood vessels and relieve painful spasm of internal ducts, such as the ureters. Overdosage risks hypotension and irregular beating o the heart. Thebaine resembles both morphine and codeine but can cause convulsions rather than depression of the brain. Industrially it is extracted from the Iranian poppy *Papaver bracteatum* for the manufacture of potent opioids, such as oxycodone and etorphine, and naloxone, the invaluable antidote for all opiates.

Morphine and the analogous drugs act principally by binding to one or more of several types of specific receptors on the surfaces of nerve and other cells and either mimicking or inhibiting their normal responses to enkephalins, small molecules produced by nerve and other cells as a fundamental signalling mechanism in the brain and other vital organs. In the brain they affect mechanisms of wakefulness and consciousness, the perception of pain, and the reward pathway, hence the possibility of addiction, and in the rest of the body control of many motor activities, secretion and cell behaviour. Differences in the overall effects of these substances come from the strength of their effects on the normal stimulatory or inhibitory actions of different receptors and the functions of the various cells that carry them.

Of the many other poppies to note one of the most familiar and appealing is the Field or Corn Poppy *Papaver rhoeas*, a once common sight in cereal fields. Its bright red flowers were notably memorialised in 1917 John McCrae’s ‘In Flanders fields the poppies blow.’ and in many other poems and paintings. It contains the alkaloids thebaine and rhoeadine. The latter is little used nowadays but formerly was considered, for example, by Dioscorides and Culpeper, as a therapy for seizures and fevers and as a poultice for local inflammations and by others as mild sedative and cough suppressant.

In different genera of the Papaveraceae the yellow-orange blooms of the Horned Poppy *Glaucum flavum* from N Africa look fine in gardens. It produces an alkaloid glaucine, which has sometimes been used as a cough suppressant but is considered by most to be dangerously toxic to the brain.

The Californian Poppy *Eschscholzia californica*, which also has golden yellow blooms, is the state flower of California. It was used by natives there to treat toothache. It contains berberine, a mild narcotic, and other alkaloids potentially useful as the sources of other drugs.

A different Poppy of considerable but unhappy medical importance is the Mexican Prickly Poppy *Argemone mexicana,* which also bears golden yellow flowers. This hardy plant grows wild in the western USA and central America, the West Indies and SE Asia and India. Its black seeds contain sanguinarine and other alkaloids that damage the kidney leading to Epidemic Dropsy, heart failure and death when eaten by humans and grazing animals. Epidemics have occurred where it has contaminated the oil produced by pressing the indistinguishable black seeds of the mustard crop to make an oil widely used in cooking and to feed animals. The only suitable precaution has been to persuade farmers to plant only yellow-seeded Mustard so that any contaminating black seeds are readily detected.

The huge family of ‘The Poppy’ can be enjoyed in many different circumstances from the sick bed to the kitchen and the studio. Their history reads almost like a tour guide to the history of chemical, biological and medical sciences and to different cultures. Unfortunately it leads straight into a growing problem of crime and society.