J R Coll Physicians Edinb 2020; 50: 80–6 | doi: 10.4997/JRCPE.2020.121 **PAPER**

Three poisonous plants (*Oenanthe*, *Cicuta* and *Anamirta*) that antagonise the effect of γ-aminobutyric acid in human brain

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Abstract

Although we are familiar with common British plants that are poisonous, such as *Atropa belladonna* (deadly nightshade) and *Aconitum napellus* (monkshood), the two most poisonous plants in the British Flora are *Oenanthe crocata* (dead man's fingers) and *Cicuta virosa* (cowbane). In recent years their poisons have been shown to be polyacetylenes (n-C2H2). The plants closely resemble two of the most common plants in the family *Apiaceae* (*Umbelliferae*), celery and parsley. Unwittingly, they are ingested by naive foragers and death occurs very rapidly. The third plant *Anamirta* derives from South-East Asia and contains a powerful convulsant, picrotoxin, which has been used from time immemorial to catch fish, and more recently to poison Birds of Paradise. All three poisons have been shown to block the γ-aminobutyric acid (GABA) system in the human brain that normally has a powerful inhibitory neuronal action. It has also been established that two groups of sedative drugs, barbiturates and benzodiazepines, exert their inhibitory action by stimulating the GABA system. These drugs are the treatments of choice for poisoning by the three vicious plants.

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The Sardinian poison and the Sardinian smile (risus sardonicus)

The Mediterranean island of Sardinia has a climate favourable to the cultivation of many sorts of cereals, such as corn, wheat and barley. As a result, it became known as 'the granary of the Mediterranean'. Initially part of the Carthaginian Empire, the natives of the island rebelled during the first Punic war and ejected their North African oppressors.[1] Seizing the opportunity, the Romans then took the short sea journey from Italy and occupied the island in 238 BC. When they arrived there, they were shocked to find that the Sardinians carried out a form of ritual murder in which they administered a poisonous plant (at the time ill defined) to criminals and elderly people. They then killed them by hitting them over the head or throwing them over steep cliffs. The Romans also noticed that the corpses all had a grimace on their faces (the sardonic smile). The Sardinians believed that as Heaven was a 'happy place' those souls would be welcomed if they had a smile on their faces.

Oenanthe crocata

For a long period, the nature of this poisonous plant and that of its poisonous chemical were undefined. When cut, its tuber exudes a yellow juice, hence Carl Linnaeus in 1753 gave the species the Greek name *Oenanthe crocata* (oenos – wine and crocata – yellow) (Figure 1). It is a member of the *Apiaceae* family (previously the *Umbelliferae*; the parasols).[2,3] At first it was thought that the plant was confined to Sardinia but later it was recognised as being widely distributed in temperate North Europe. The plant is a perennial, closely related to cowbane, *Cicuta virosa*, but somewhat more poisonous. *O. crocata* prefers marshy and wet areas and grows to a height of three to five feet. The poisonous tubers can be exposed by flooding (Figure 2). Many deaths occur in children who are foraging (or digging) on the banks of water courses.[4] The roots (tubers), which are the most poisonous part of the plant, resemble those of dahlias and the leaves those of parsnip and celery. The leaves have a fragrant smell and the roots taste sweet, two properties that encourage their consumption.

Clinical features

Virtually all patients develop convulsions[5] usually between 30 min and 1 hour after ingestion. They take the form of tonic/clonic muscle spasm accompanied by trismus.[4–7] The contraction of the muscles may be so severe as to produce arching of the back (opisthotonus)[5] akin to that seen in

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Figure 1 *Oenanthe crocata*; dead man's fingers; hemlock water dropwort

tetanus and strychnine poisoning. Contraction of the levator anguli oris muscles produces the classical sign, the sardonic smile (risus sardonicus) (Figure 3). The convulsions may also lead to biting the tongue, and this, together with the accompanying hypersalivation may produce blood-stained oral froth. Occasionally, nausea, vomiting (which may be profuse) and abdominal pain supervene first.[5] If vomiting and convulsions occur simultaneously, aspiration pneumonia may result. Dilation of the pupils may also be observed together with tenderness of the muscles due to rhabdomyolysis, which has resulted in renal failure.[5] Death usually occurs between 1–8 hours after ingestion and is due to progressive respiratory failure, secondary to refractory status epilepticus and ventricular fibrillation.[5]

Treatment

Airway care and seizure control are the two most important aspects of present-day management. Endotracheal intubation is vital but may present serious difficulties due to the spasm of the masseter muscles (trismus; lockjaw). Diazepam 10–20 mg intravenously in an adult (child 300–400 µg/kg) or intravenous lorazepam 4 mg in an adult (100 µg/kg in a child) may be effective if convulsions are only short lived.[7] However, thiopental sodium is often needed to control repeated and sometimes refractory convulsions. One patient required it in a dose of 2–6 mg/kg/hour for 24 hours to control convulsions after diazepam and phenytoin had failed.[6]

Figure 2 The tubers of *Oenanthe crocata* (dead man's fingers)

Cicuta virosa

C. virosa does occur in the UK but is sparse. Most of the severe cases of poisoning have occurred in the USA. This plant is known variously as water hemlock, beaver poison, wild carrot, wild parsley and false parsley (Figure 4).[2] Water hemlock (*Cicuta douglasii*) is a member of the *Apiaceae* and can be confused with parsnip, celery, artichoke and also sweet anise. The flowers are typically of the umbel type – compact masses of heads.[8] The plant has hollow stems and cavities in the root to keep afloat when flooded (Figure 5).

Clinical features

Even chewing small thumbnail-size pieces can cause severe poisoning. The features are similar to those reported for *O. crocata*.[5,9–12] Occasionally, poisoning has occurred under unexpected circumstances, such as white water rafting, the holiday experience that has developed in recent years with as many as 250,000 people taking part annually. Some of the participants, 'living off the land' as they make their way downstream, have unwittingly ingested poisonous plants, such as in 1985 when six out of eight men who floated down the Owyhee River were poisoned after eating what they thought was wild parsnip but was later identified as *C. douglasii*.[11] One suffered his first convulsion about 45 min after ingesting the root and had a further four seizures before making a full recovery. A second was not so fortunate. He suffered six seizures before going into cardiopulmonary arrest about 1.5 hours after eating the root and could not be resuscitated.[11]

Treatment

Thiopental sodium was required in one patient after the failure of diazepam and phenytoin to control repeated and

Figure 3 Death mask of a victim of poisoning with *Oenanthe crocata* (the sardonic smile)

Figure 4 *Cicuta virosa* (cowbane)

'extreme' muscle spasms, opisthotonos and convulsions.[12] In addition to an initial bolus of thiopental sodium 350 mg, the patient also received an infusion of thiopental sodium 1,850 mg (a total of 2,200 mg over 8 hours).[12] Although Starreveld[12] suggested that an anticholinergic drug, such as atropine, might be of value in mitigating the convulsive effects of this plant, there is no experimental data to support such treatment.[13]

Picrotoxin and poisoning of fish and Birds of Paradise[14,15]

Anamirta cocculus

Anamirta cocculus is common in South-East Asia, including Papua New Guinea and India (Figure 6). Anamirta had been known to the natives of Papua New Guinea for many centuries. When western explorers reached these remote areas in the nineteenth century, they found that the natives were throwing an Anamirta extract onto the water where it killed many fish. These floated to the surface and were easily harvested. The seeds of *A. cocculus* are still being used as a potent aquaculture management tool to eradicate unwanted wild fish from culture ponds before stocking.[16] The natives also trapped Birds of Paradise for feathers to decorate their headdresses. Some feathers were then transported to Europe to embellish the hats of ladies of the higher classes and often worn at Ascot races or Henley Regatta (highlights of 'the season') (Figure 7). Soon a feather 'craze' developed and every genteel woman wanted to wear them. The demand for feathers grew exponentially and many factories were opened in the East End of London and millinery shops multiplied.[17]

The Papuan natives then realised that there was money in this trade and started to slaughter thousands of Birds of Paradise. They also realised that trapping (or shooting) might damage the feathers; therefore, they resorted to doctoring the waterholes with *A. cocculus* berries. The birds dropped to the ground and their feathers were recovered in prime condition.

The trade grew to be a scandal and led to the formation of the Society for the Protection of Birds, which was started in Manchester in the 1860s. This society expanded rapidly and the feather trade was one of its first targets. The final nail in the coffin came when Queen Alexandra, the wife of King Edward VII, announced that she was a supporter of the Bird Protection Society and banned bird feathers from her hats. Finally, in 1921 an Act of Parliament came into force that stopped the importation of bird feathers. In recent times, a final, ironic twist has occurred. The Birds of Paradise are now protected species and it is a criminal offence to kill, or interfere, with them. The Papuan natives are paid to protect them! They also lead small groups of tourists to witness the magnificent mating displays by the multicoloured male birds.

The chemical structure of the poisons

Over 30 related C15 or C17 polyacetylenes have been isolated from the roots of *O. crocata*, with the C17 polyacetylenes, oenanthotoxin and 2,3-dihydro-oenanthotoxin, being obtained in greatest yield.[18] Cicutoxin produced by *C. virosa* is also a C17 polyacetylene (Figure 8).[19] The berries

Figure 5 *Cicuta virosa* roots with their flotation chambers

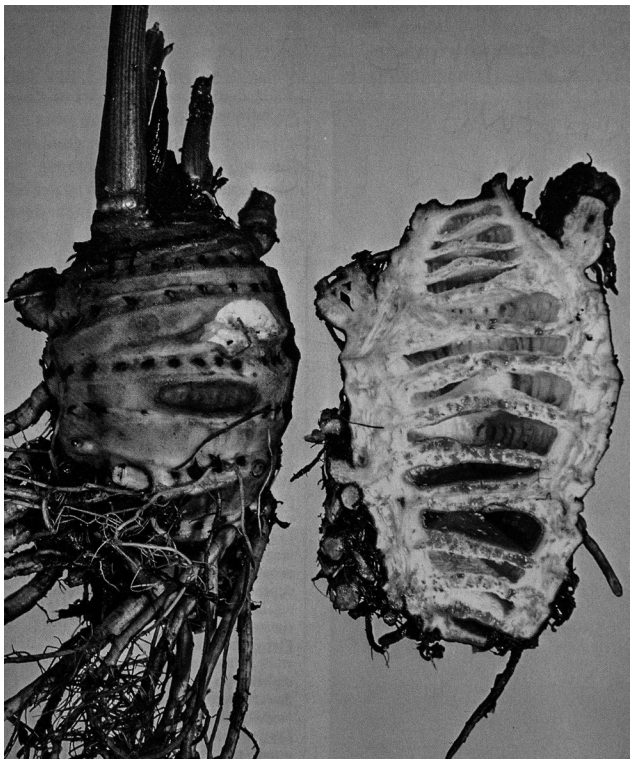
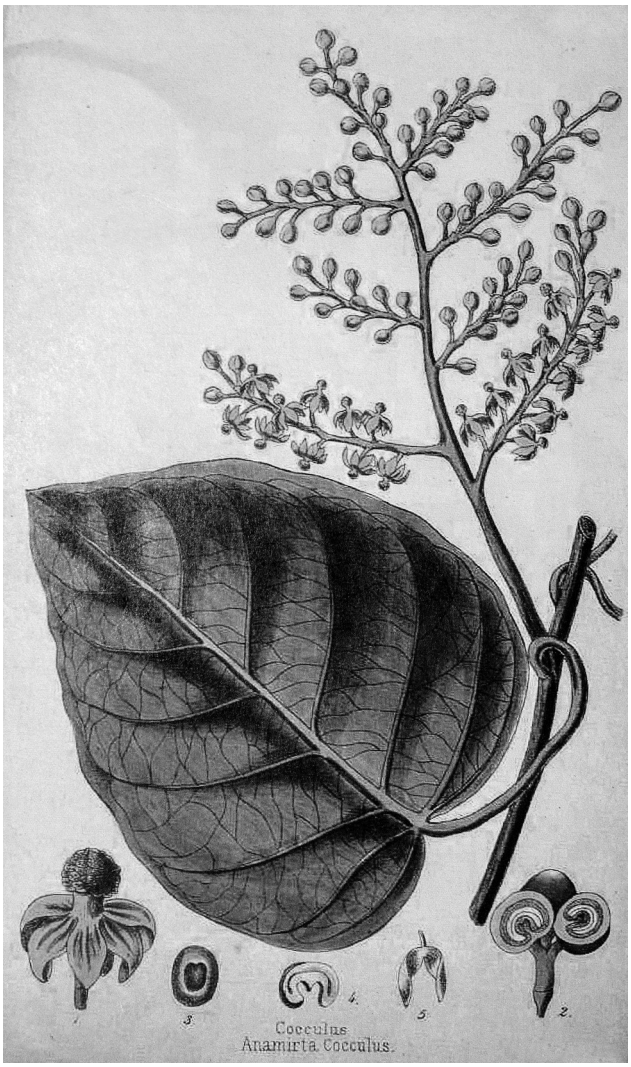


Figure 6 *Anamirta cocculus* (fish and bird poison)



of *A. cocculus* contain picrotoxin, a sesquiterpene mixture of picrotoxinin, picrotin, (predominantly) methyl picrotoxate, dihydroxypicrotoxinin and picrotoxic acid.[20]

Picrotoxin is unrelated chemically to the polyacetylenes (Figure 9). It is derived from the heterocyclic compound, azulene. The evolutionary process, by convergence, has produced two distinct types of chemical structure that act on the same neurotransmitter.

Potential antidotes

Barbiturates were developed in Europe for sedation and to treat (and prevent) epileptic fits. Patients then began to take barbiturates in excessive doses deliberately. On an empirical basis picrotoxin was given to rouse these patients from coma. In some cases this appeared successful, but care had to be taken to avoid an overdose resulting in fits and death. Conversely, when an animal was poisoned by picrotoxin, barbiturates were given to control fitting. These observations remained mysterious until a common mechanism was discovered.

The barbiturates

Barbiturates were first synthesised in the 1880s (Figure 10). It had been observed for some time that the simple organic compound urea had a mild sedative action and the derived compound malonylurea was even more active. Eventually barbital, the first barbiturate, was synthesised from malonylurea by reaction with sodium ethoxide. This started a 'gold rush' of compounds as they were found to be powerful sedatives and effective anticonvulsants. They were classified by their length of action: short, medium and long. The short-acting compounds (such as amylobarbital) were used mainly in sedation and the long acting (such as phenobarbital) to prevent convulsions. They reigned supreme between 1890 and 1970, when they were banned. This proscription resulted from the fact they proved to be highly addictive and produced marked withdrawal reactions. Moreover, they became a common method of self-harm. As has been pointed out earlier, it was found on an empirical basis that picrotoxinin (picrotoxin) antagonised barbiturate intoxication and vice versa. The question remained: what was the mechanism? It would be as late as the 1960s before this problem could be resolved.

The benzodiazepines

As the barbiturates declined, another group of sedatives replaced them, the benzodiazepines. They proved to be effective at inducing sleep, calming anxiety and in the treatment of epileptic seizures. They could be administered orally, intravenously or per rectum as suppositories (this last route being very effective in children). Unfortunately, within 10 years, as with the barbiturates, problems appeared, particularly physical and psychological addiction, together with difficulties in withdrawal. They were less

Figure 7 A lavishly decorated hat of the 1880s bearing bird of paradise feathers derived from poisoned birds

liable to be used in self-harm attempts because a large dose was required to prove fatal. The benzodiazepines are still used extensively, but with caution. In mild cases of poisoning with cicutoxin or oenanthotoxin poisoning, they were effective, but when they failed to control the convulsions, it was found that the barbiturates were more active (particularly thiopental sodium when given intravenously). The same question arose, as it had with the barbiturates: was diazepam acting on a common mechanism in the brain as yet undiscovered?

γ-aminobutyric acid – the elusive neurotransmitter

Early in the 1950s, a new neurotransmitter was discovered, γ-aminobutyric acid, now commonly referred to as GABA.[21] The compound was virtually confined to the brain and was in substantial concentrations (10 μmol/g) in the nigrostriatal system but occurs at lower concentrations (2–5 μmol/g) throughout the grey matter. It is also widespread in some plant seeds, including those of the genera *Pisum*, *Vicia*

Figure 8 Two poisonous polyenes: oenanthotoxin (top) and cicutoxin (bottom)

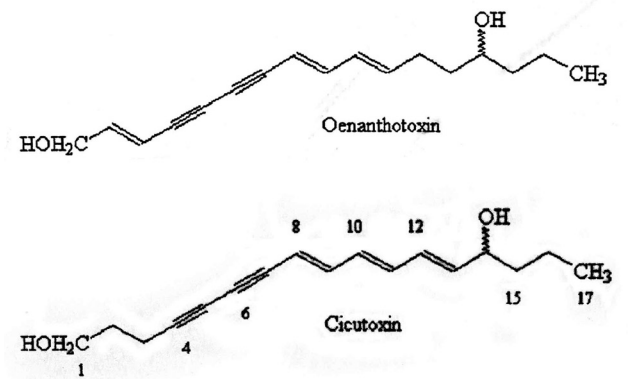
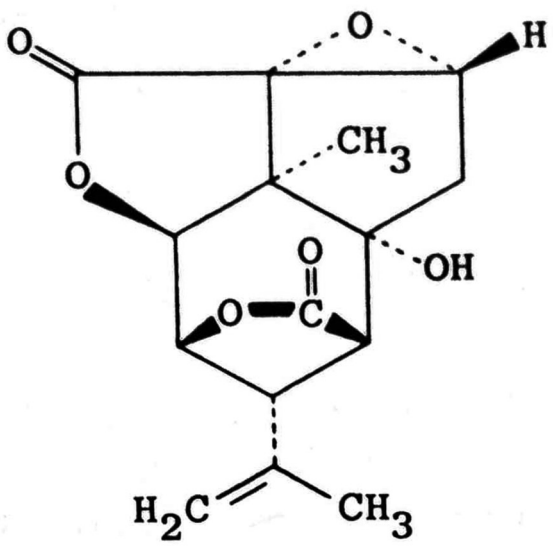


Figure 9 The poison picrotoxin derived from the plant *Anamirta cocculus*



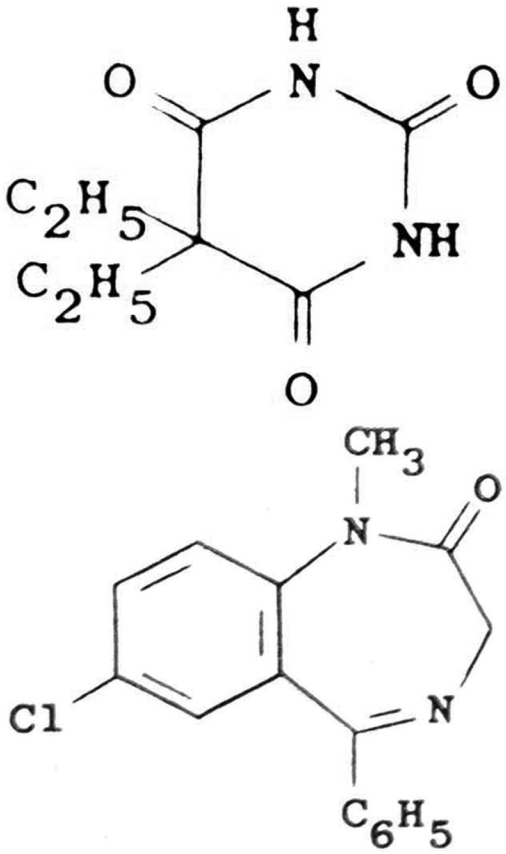
and *Phaseolus*. These seeds are toxic to birds (probably by damaging their nervous systems).

GABA is formed in the brain from glutamate by glutamic acid decarboxylase. It is destroyed as rapidly as it is formed by GABA transaminases and converted to neurologically inactive γ-oxoglutaric acid and succinaldehyde. GABA is an inhibitory transmitter in many different brain areas, including the cerebellum, hippocampus and corpus striatum. It has both presynaptic and postsynaptic inhibitory actions decreasing chloride permeability in the neural membranes.

Many different types of GABA receptor have been identified and it is on these that our plant poisons act. Oenathotoxin downregulates GABAergic currents[22] and induces open channel block and allosterically modulates $GABA_A$ receptors.[23] Cicutoxin is a noncompetitive GABA antagonist in the central nervous system. Cicutoxin inhibits the binding of [^{3}H]EBOB (ethynylbicycloorthobenzoate) to $GABA_A$-gated chloride channels in rat brain cortices, confirming that this plays an important role in its acute toxicity.[24] Picrotoxinin is also relatively nonspecific in that it is a potent antagonist at $GABA_A$ and $GABA_C$ receptors, with moderate action at glycine receptors, and weak activity at 5HT receptors.[25]

It was thought that GABA could prove to be an important new treatment for epilepsy. Disappointingly, it does not pass the blood–brain barrier. A search began, in the pharmaceutical industry, for a more lipophilic compound that would pass the barrier more readily. This was realised in 1972, when para-chlorophenyl GABA was synthesised, now known as baclofen (Figure 11).[26] This was proven to be an effective treatment for certain types of spasticity, including that seen in some forms of multiple sclerosis and also that occurring after traumatic transection of the spinal cord. This compound continues to be used successfully.

Figure 10 Gabergic compounds: barbiturate (barbital; top) and diazepam (benzodiazepine; bottom)

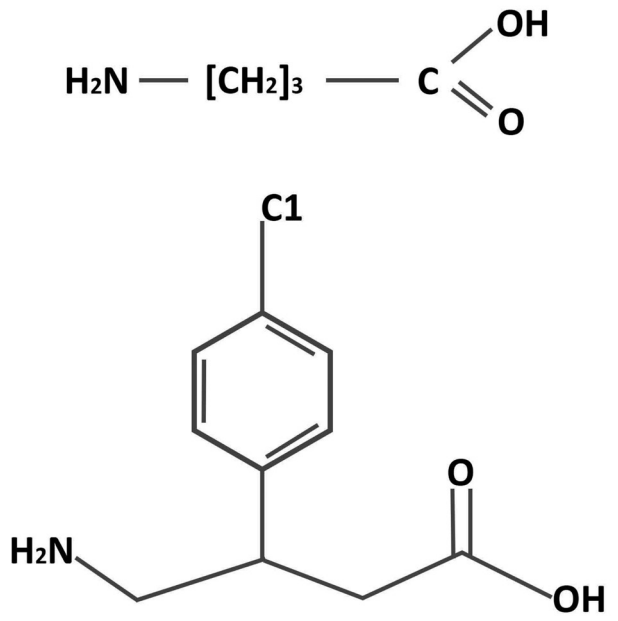


It can also be employed intrathecally in severe spastic syndromes. We have thus come full circle, from the deadly plants to the chemical structures of their poisons, to GABA and its manifold actions. We now finally have a mechanism whereby the barbiturates, and sometimes the benzodiazepines (together with mechanical ventilation) can be used with some success in the treatment of these severe forms of poisoning.

Foragers beware

Over the last 20–30 years there has developed a movement to 'live off the land'. This has led to a growing impulse to go out into the countryside and garner a harvest of plants and mushrooms. Inevitably, there have been an increasing number of poisonings, including, for example, by the mushroom *Amanita phalloides* (the death cap), by the plants: foxglove (*Digitalis*) and monkshood (*Aconitum napellus*) and also by the berries of the European yew (*Taxus baccata*). The European umbels, *Oenanthe* and *Cicuta* fall into this deadly group and result in high mortality. The only answer to this question is that those who go foraging should be accompanied by an experienced botanist or mycologist. Otherwise, dangerous (and even deadly) accidents will continue to occur. Let foragers beware.

Figure 11 Gamma aminobutric acid (an inhibitory neurotransmitter in man; top) and chlorophenyl gaba (Baclofen; trade name Lioresal® ; bottom)



Envoi

The story of these three poisonous plants is compelling. From historical poisoning in Sardinia through white water rafting to poisoning the Birds of Paradise. What was the missing link? It proved to be γ-aminobutyric acid, a powerful inhibitory neurotransmitter. Antagonism of this neurochemical messenger proved to be the common mechanism of action for the three plants. It was also shown that two sedative (and antiepileptic) drug groups, the barbiturates and benzodiazepines, acted on the GABA mechanism to reverse the effect of the polyenes. Thus was the problem solved and the ring of knowledge closed.

Acknowledgements

This is the final essay in a long series of papers on poisonous and medicinal plants in the *Journal of the Royal College of Physicians of Edinburgh* which began, in 1998, with the publication of *The European Yew (*Taxus baccata*); its place in mythology and medicine*. There are so many people and organisations that have given me assistance in this long period, too many to mention individually. However, I must single out the following: Mrs May Gibb, my first secretary from 1998 to 2014; Mr Graham Hardy of the Royal Botanic Garden Edinburgh, who provided many rare botanical illustrations; and Mr Iain Milne (together with Ms Estela Dukan) of the Sibbald Library of the Royal College of Physicians of Edinburgh, without whom the production of the later papers would not have been possible. I shall end with a long standing exhortation at functions in the College: Floreat Res Medica (Let medical knowledge flourish).

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