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Duboisia myoporoides: The Medical Career of a Native Australian Plant

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Alkaloids derived from solanaceous plants were the subject of intense investigations by European chemists, pharmacologists and clinicians in the second half of the nineteenth century. Some surprise was expressed when it was discovered in the 1870s that an Australian bush, *Duboisia myoporoides*, contained an atropine-like alkaloid, 'duboisine'. A complicated and colourful history followed. Duboisine was adopted in Australia, Europe and the United States as an alternative to atropine as an ophthalmologic agent; shortly afterwards, it was also esteemed as a potent sedative in the management of psychiatric patients, and as an alternative to other solanaceous alkaloids in the treatment of parkinsonism. The Second World War led to renewed interest in *Duboisia* species as sources of scopolamine, required for surgical anaesthesia and to manage sea-sickness, a major problem in the naval part of the war. As a consequence of the efforts of the CSIR and of Wilfrid Russell Grimwade (1879–1955), this led to the establishment of plantations in Queensland that today still supply the bulk of the world's raw scopolamine. Following the War, however, government support for commercial alkaloid extraction waned, and it was the interest of the German firm Boehringer Ingelheim and its investment in the industry that rescued the *Duboisia* industry in the mid-1950s, and that continues to maintain it at a relatively low but stable level today.

> 'It is to be regretted that scientific men in this colony have paid so little attention to the subject of Medicinal Botany. Surrounded, as we are, by shrubs and plants possessing medicinal properties, there is a wide field for investigation; and, no doubt, it will be found in time to come, that we have been sending to distant countries for expensive medicines, whilst remedies equally efficacious might be provided close at hand in all their native freshness.'
> William Woolls, *A Contribution to the Flora of Australia* (1867), p. 94.

Introduction: Solanaceous Plants

The *Solanaceae* family includes a fascinating variety of plants. Some members — including the mandrake (*Atropa mandragora*), Russian henbane (*Hyoscyamus albus*) and scopola (*Scopolia carniolica*) — have been employed for centuries to induce hallucinations and in 'witches' salves', in religious contexts and as instruments of crime, while others — including the tomato (*Lycopersicum esculentum*), potato (*Solanum tuberosum*) and capsicum (*Capsicum frutescens*) — have found favour in the kitchen.

A number of solanaceous (*solamen* = 'comfort-giving') plants have also long played significant roles in European medicine, both in folk traditions and in so-called 'school medicine'. Certain of these achieved particular prominence and remained in standard pharmacopoeias until the mid-twentieth century: deadly nightshade (*Atropa belladonna*), henbane (*Hyoscyamus niger*) and the thorn-apple (*Datura stramonium*). The isolation of the active components of these plants attracted a great deal of attention at the end of the eighteenth century, but it was only in the middle of the nineteenth that what might be termed the first golden age of alkaloid isolation unfolded.[1] Within a short time, a range of alkaloids had been isolated from various *Solanaceae*, each named for the plant from which it was derived: 'solanine' from *Solanum nigrum* was the first in 1820, followed by 'atropine' from *Atropa belladonna* in 1831, 'hyoscyamine' from *Hyoscyamus niger*, and so on.[2] Analytical techniques available at this time did not

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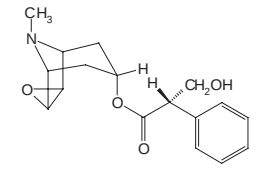
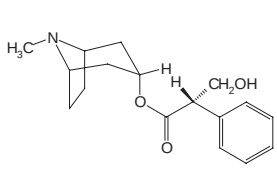
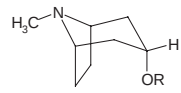
permit determination of their structures, so that these alkaloids were defined according to estimated absolute chemical composition and the physical characteristics of their salts. By the close of the nineteenth century, however, it was generally recognized that many of the solanaceous alkaloids were, in fact, identical with one or other of the two major tropane alkaloids, *atropine* (= racemic *hyoscyamine*) and *scopolamine* (= *hyoscine*; Fig. 1). These alkaloids were widely employed in the



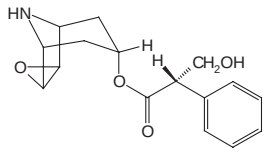
1a (–)-scopolamine (hyoscine)
1b atroscine ((±) -hyoscine)*



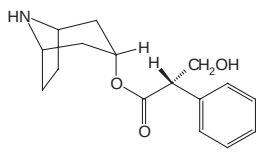
2a (–)-hyoscyamine
2b atropine ((±)-hyoscyamine)



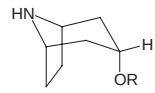
3a tropine, R = H
3b acetyltropine, R = $COCH_3$
3c butropine, R = $COCH(CH_3)_2$
3d valtropine, R = $COCH(CH_3)CH_2CH_3$
3e tropine nonanoate, R = $CO(CH_2)_7CH_3$



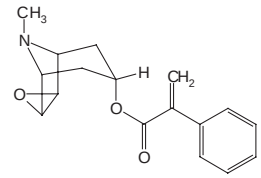
4 norscopolamine (norhyoscine)



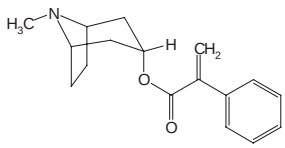
5 noratropine



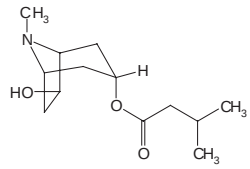
6a poroidine, R = $COCH_2CH(CH_3)_2$
6b isoporoidine, R = $COCH(CH_3)CH_2CH_3$



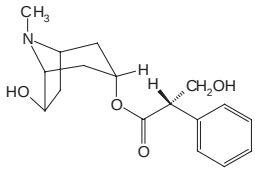
7 aposcopolamine (apohyoscine)



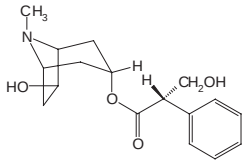
8 apoatropine



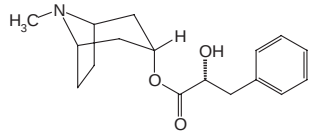
9 valeroidine



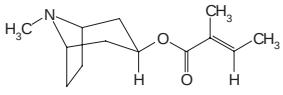
10 6β-hydroxyhyoscyamine



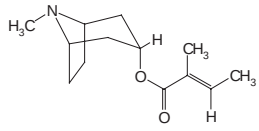
11 7β-hydroxyhyoscyamine



12 littorine



13 tigloidine



14 tigloyltrop(e)ine

Figure 1. Tropane alkaloids identified in *Duboisia myoporoides*. *Included for completeness, but not identified in *D. myoporoides*.

second half of the nineteenth century as sedatives and hypnotics (especially in psychiatric patients), for which reason they were also used as antiparkinsonian agents, and atropine was also utilized in ophthalmology for its mydriatic (pupil-dilating) properties.[3]

Alkaloid nomenclature was often the subject of heated and confusing debate, and a particular instance is relevant to the present discussion. 'Hyoscine' — first prepared by Albert Ladenburg in 1880[4] — and 'scopolamine' — first isolated by Ernst Schmidt from *Scopola* species in 1888[5] and subsequently also from *Duboisia myoporoides* leaf procured in the eastern German city of Görlitz[6] — are synonyms, but a colourful controversy regarding their identity raged, especially in Germany, from their discovery until the early twentieth century. Both names continued to be used for many decades, the choice often seemingly dependent on the nationality of the writer,[7] and by the mid-1920s, the name 'hyoscine' had largely been abandoned except in England and associated countries.[8] For the sake of clarity, I shall generally employ 'scopolamine' in this paper, except where 'hyoscine' appears in a directly cited text.

Duboisia

Late additions to the *Solanaceae* family were identified in the mid-nineteenth century in a corner of the world then regarded as both exotic and remote: Australia. Joseph Bancroft (1836–1894), medical practitioner and the first of a family line of medical naturalists,[9] had become intrigued by the properties of *pituri*, or 'native tobacco', a drug traditionally employed by Aborigines as a chewed intoxicant allowing long periods of work without food or rest, similar to the chewing of coca in central America. Pituri was first placed at the disposal of European investigators by John King (1841–1872), sole survivor of the unfortunate Burke and Wills expedition to Australia's interior,[10] who supplied material to W. Johnston in Tasmania and a powdered sample to the Rostock-born botanist Ferdinand Mueller (1825–1896) in Melbourne.[11] Bancroft independently obtained material from the vicinity of Cooper's Creek (north-eastern South Australia), and reported his preliminary investigation of its physiological properties to the Queensland Philosophical Society in 1872.[12] A few years later, Bancroft serendipitously obtained samples of the source plant, which Mueller identified a short time later as the Central Desert tree *Duboisia hopwoodii*, recently (re)named by Mueller himself.[13] An alkaloid isolated from *D. hopwoodii*, 'piturine', was initially identified by the French chemist A[rthur-Léon?] Petit with nicotine,[14] but *D. hopwoodii* was later found also to contain the more potent *d*-nornicotine.[15] More recently it has been recognized that 'pituri' in most parts of Australia is not, in fact, derived from *D. hopwoodii*, but rather from local *Nicotiana* species (also members of the *Solanaceae* family).[16]

In a letter to Bancroft read to the Queensland Philosophical Society in 1877, Mueller commented:

> Now an interesting field opens to Dr. Bancroft for further research. Let the Doctor try the foliage of Duboisia myoporoides, as he could easily, for a little payment, get a blackfellow to administer small doses of that plant to. There could be no danger in the experiment if the quantity is given cautiously. I fancy that the properties of the Duboisias will prove similar to those of stramonium.[17]

The recommended species, *D. myoporoides* (Figs 2, 3), had been first described in 1810 by the distinguished Scottish naturalist Robert Brown (1773–1858) in his report on the botany of New Holland (1802–1805), conducted in conjunction with Flinders' circumnavigation of the continent. Brown had collected his sample in the Sydney-

Hunter region; the species designation *myoporoides* derived from its resemblance to an unrelated east coast plant, *Myoporum acuminatum*, but Brown did not explain his christening the genus *Duboisia*.[18] It may honour the French botanist François Nöel Alexandre Dubois (1752–1824), consistent with a comment made in 1893 by the New South Wales botanist Joseph Maiden,[19] but it could also refer to Charles Du Bois (1656–1740), treasurer of the East India Company (1702–1737), who had a botanical garden at Mitcham in Surrey.[20] An alternative designation, *Noteleae ligustrina* Sieber ex Bentham,[21] was never broadly accepted, and the new species *D. myopo-*

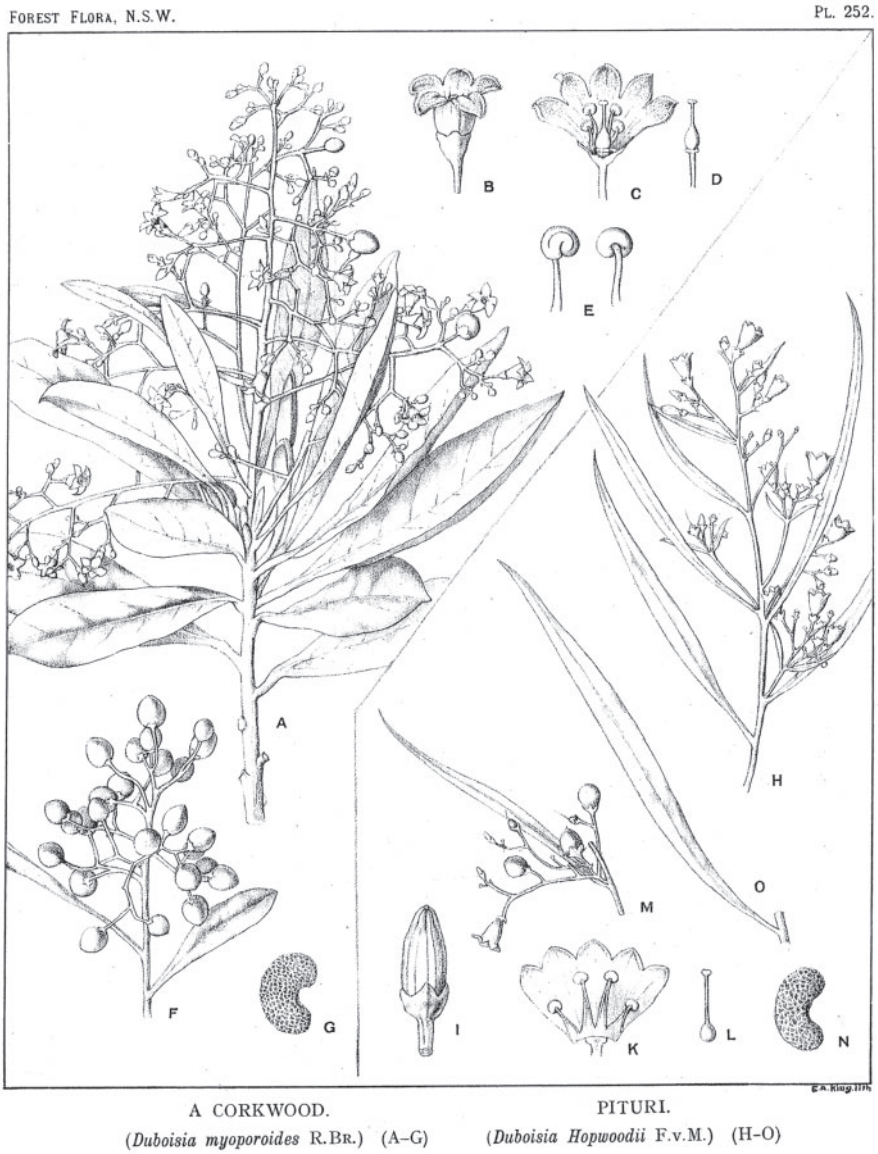


Figure 2. (*A–G*) *Duboisia myoporoides* and (*H–O*) *Duboisia hopwoodii*. Source: plate 252 from Maiden, *Forest Flora of New South Wales* (n. 32); lithograph by E.A. King.

roides was quickly accepted into standard plant catalogues.[22]

A third *Duboisia* species, *D. leichhardtii*, was named in 1867 by Mueller for the German explorer who first brought samples from central Australia.[23] Initially assigned, with some doubt, to *Anthocercis*, the receipt of a fruiting specimen prompted its transfer to *Duboisia*.[24] Its distribution is much more restricted than that of *D. myoporoides*, being limited to a few small pockets of dry vine forest in the

Figure 3. *Duboisia myoporoides*, Australian corkwood, duboisia. Source: Pabst, *Köhler's Medizinal-Pflanzen* (n. 69), nr 26. The illustration depicts a plant in the Royal Herbarium in Berlin, collected by Robert Brown on New Caledonia.

Burnett region of south-east Queensland.[25] The leaves of *D. leichhardtii* are smaller than those of *D. myoporoides*, and its flowers slightly larger. A further *Duboisia* species, *D. arenitensis*, was discovered as recently as 1995 on the sandstone plateau of Arnhem Land in northern Australia (*arenite* = sandstone),[26] but the low alkaloid content of this plant renders it comparatively uninteresting in the present context.

The genus *Duboisia* (tribe: *Anthocercideae*) thus includes only four species, all of quite restricted distribution; apart from the occurrence of *D. myoporoides* in New Caledonia, all are indigenous only to Australia. Other Australian genera in the same tribe, such as *Anthocercis*, *Symonanthus* and *Crenidium*, also include tropane alkaloid-producing species, but none has thus far proved to be of particular cultural or commercial significance.[27] Further indigenous Australian *Solanaceae* are traditionally employed as 'bush food', including bush tomatoes, bush sultanas and other equivalents of European or American species.[28]

Duboisia myoporoides itself is most common on the subtropical eastern seaboard of Australia, principally on the edges of rainforest areas;[29] Mueller described it as occurring throughout the forest between the Illawarra (35˚S) and Rockingham's Bay (18˚S), as well as in New Caledonia.[30] *D. myoporoides* was placed by Brown in the *Solanaceae*, and then transferred by the eminent English botanist George Bentham (1800–1884) to the *Scrophulariaceae*, the same family as *Digitalis*, but its regular corolla, typically solanaceous flowers and dark pulpy fruit led to its restoration to the *Solanaceae* by Mueller in the 1870s.[31] Its common name 'Australian corkwood' falsely suggests a relationship with European cork trees, but actually refers only to its soft, corky bark. *D. myoporoides* was long regarded by Australian farmers as a noxious weed, principally because of the presumed effects of tropane alkaloid intoxication on cattle and horses (but not sheep),[32] but its robust nature, including its ability to regenerate quickly after bushfire, meant that eradication attempts did not greatly hinder its profusion.

Recorded Aboriginal names for *D. myoporoides* include 'onungunabie' and 'ngmoo'.[33] Many authors have remarked that the tree sap was employed by Aborigines as a stupefacient, and even more dramatically as a hunting tool: added to a billabong (waterhole), it was said to cause eels and fish to float to the surface in a dazed condition, and also to stun emus that drank the water, all without poisoning the flesh of the animal. These references, however, appear to be ultimately based upon indirect and somewhat dubious reports recorded by William Woolls in the middle of the nineteenth century (see below).[34] On the other hand, the scopolamine content of *D. myoporoides* leaves — thin, fragile, up to 12 cm long, 3 cm broad, odourless but bitter to the taste — would lend itself to such purposes, and employment of *D. hopwoodii* as a hunting poison has been widely recorded in central Australia.[35] There is no clear evidence that Aborigines have ever employed any part of *D. myoporoides* (or *D. leichhardtii*) as food or for medical purposes, although *D. myoporoides* is employed in New Caledonia as an antidote to the toxin of the ciguatera fish.[36] Its wood was earlier used for spearthrowers on Mornington Island in north-west Queensland (specimen collected in 1916) and in an unidentified part of Australia (specimen collected 1962).[37]

It was also the timber that first attracted European attention. Samples of 'corkwood' or 'ngmoo' from the Illawarra were despatched by William Macarthur as one of 350 timbers displayed at the 1855 World Exhibition in Paris (albeit falsely labelled as *Santalum obtusifolium*) with the description: 'A low-branching small tree, with rough, cork-like bark; the wood very white, close and soft, but firm; excellent

for wood-carving, and not without beauty for inlaying and cabinet-work.'[38]

Although the colour and character of the timber were apposite for carving,[39] it was the chemistry of the leaves that would establish the international fame of *D. myoporoides*. The first report by a European of its narcotic action was that in 1867 by the Parramatta school teacher and botanist William Woolls (1814–1893), based indirectly upon local (and possibly misleading) Aboriginal reports of its being used in the Kurrajong district as a hunting poison in waterholes and as part of an intoxicating drink; he had also encountered the tree in Parramatta and along Toongabbie Creek, and noted that Europeans regarded its toxicity with consternation.[40]

Bancroft did not mention Woolls' report when, shortly after receiving the letter from Mueller cited above, he examined the effects of *D. myoporoides* leaf extracts in his house pets ('thanks to the beneficent rule of this colony [Queensland], where no law prevents professional men from experimenting'). Systemic application revealed surprising mydriatic (pupil-dilating) qualities that distinguished it from *D. hopwoodii*, much to Bancroft's surprise: 'Dogs and cats walk about in a helpless blind manner, falling over the least irregularity of surface… If let alone, they go to sleep. They seem blind, or nearly so, with a widely-dilated pupil. Surely this could not be pituri.'[41] Species differences were also recorded in these home experiments: *D. myoporoides* caused dogs, but not cats, to walk straight ahead until they found themselves in a corner, where the hound would 'struggle and cry for a long time and paw at the wall, but it appeared never to occur to him to turn around'.[42]

Bancroft also examined the direct application of the extract to the eyes of his animals and then of humans, and subsequently dispatched samples to various ophthalmologists in Australia; and within a year 'duboisia' had partly supplanted atropine as the routine mydriatic in Sydney and Brisbane.[43] The experiences of the Sydney surgeon George Fortescue (St Vincent's Hospital) with the extract were reported in Bancroft's 1877 paper before the Queensland Philosophical Society, but the doctor's own short report appeared in the *Australasian Medical Gazette* only in 1882, with the surprising editorial note that this was the previously unpublished *first* description of the extract's effects.[44] Nevertheless, Fortescue had provided a small quantity of 'duboisia' as early as December 1877 to the Harley Street ophthalmologist John Tweedy, who confirmed its mydriatic qualities.[45] His results, published in the *Lancet*, were also reported a month later in the United States, indicative of the interest that the drug had quickly aroused.[46]

In 1878, Bancroft personally conveyed samples of both pituri and *D. myoporoides* to England to be placed at the disposal of both the physiologist Sidney Ringer[47] and of a number of analytical chemists and medical botanists; he had already despatched samples in 1877 to Thomas Fraser, Professor for Materia Medica in Edinburgh.[48] Edward Morell Holmes (1843–1940), curator of the Pharmaceutical Society museum,[49] concluded the presentation on 6 March 1878 of his own findings with the remark: '…there exists a plant in tolerable abundance from which an active principle may probably be obtained more economically than from belladonna, and which may possess the same properties as atropine.'[50]

Duboisia was soon thereafter employed as a mydriatic in both America and Europe. Both the excitement generated by the drug and the confusion concerning its origins were recorded by the German author Moeller in 1883: 'Duboisia was first employed in the clinic in America and is currently almost exclusively sold by American drug suppliers, so that it seems reasonable, despite its origins in New Holland, to treat it in the category <Ameri-

can drugs>'. He further noted that its success in America had elicited the cry, premature in his opinion, that 'Atropine is dying, Atropine is Dead!'[51]

Duboisine

The first extraction of the active principle of *D. myoporoides* was performed at the behest of Bancroft in 1877 by the Queensland government analytical chemist (and custodian of the Brisbane Museum) Karl Theodore Staiger (1833–1888),[52] who had also been the first to extract 'piturine'.[53] Staiger obtained a yellow, oily extract from fresh leaf, which, despite six months' intensive effort, defied all efforts to crystallize the presumed active alkaloid.[54] The alkaloid 'duboisine' (initially also referred to as 'duboisia') was then isolated in 1878 from Bancroft's *D. myoporoides* extract by the London pharmacist Alfred William Gerrard, who did not seem aware of Staiger's efforts. (Nor, indeed, were subsequent writers on the subject.) The chemical characteristics of the sticky yellow mass that Gerrard obtained and those of atropine were so similar as to suggest the identity of the two alkaloids; the morphological differences between *Duboisia* and the European *Solanaceae* and the greater water solubility of duboisine, however, were sufficient at least to cause him doubt. Gerrard suggested that the alkaloid remain nameless until the issue was resolved; should it prove to be a distinct chemical species, he proposed the name 'duboisine'. He concluded: 'I think medical men and pharmacists in Australia may congratulate themselves that they have at their disposal … a source from whence to obtain by the simple process I have here given a therapeutic agent of great value.'[55]

In the discussion following Gerrard's presentation of his results to the Pharmaceutical Society of Great Britain, Bancroft noted that they were consistent with those of Staiger, and also further described his own animal experiments. Both he and a certain Dr Paul, who had examined the physiological effects of Gerrard's extract, did not believe that it was identical with atropine; Paul cautioned, however, that there was still much 'vagueness' about the chemical characteristics of atropine itself, so that it would be premature to decide the issue.[56] Interestingly, Gerrard's paper first attracted published notice in Australia only in 1882,[57] and was often erroneously noted as appearing in 1874,[58] somewhat consistent with the disinterest exhibited by Australian investigators following Bancroft's initial investigations.

On the same day as Gerrard's presentation, the French chemist A. Petit presented a report to the Pharmacological Society in Paris on his isolation of an alkaloid from *D. myoporoides* that he similarly named 'duboïsine', and he was soon supplying it commercially to European physiologists and ophthalmologists.[59] In the following year, Petit also isolated the alkaloid from pituri that he identified with nicotine. Subsequent authors appear to have often confused these two reports and equated 'duboisine' with 'piturine' or 'nicotine', a confusion that persisted until the end of the nineteenth century, aided by the long-standing assumption that *D. myoporoides* and *D. hopwoodii* would contain similar alkaloids. Bancroft himself commented in 1882 that it was 'very singular that *D. pituri* [Bancroft's proposed name for *D. hopwoodii*] and *D. myoporoides* should contain alkaloids so dissimilar';[60] his paper to the Queensland Philosophical Society on 10 October 1878 was entitled 'Further comments on the pituri group of plants', although it was principally concerned with the mydriatic properties of *D. myoporoides* and another solanaceous plant, *Anthocercis viscosa* (stickytail plant). Mueller also long assumed that *D. myoporoides* and *D. hopwoodii* would contain the same alkaloids; indeed, he wrote that the alkaloid he and Rummel had isolated from *D. myoporoides* would prob-

ably prove to be the same as piturine.[61] Mueller had initially dubbed his *D. hopwoodii* extract 'duboisine', but a year later modified this opinion in an appended correction to a report published, somewhat surprisingly, in Austria.[62] The English investigators Ringer and William Murrell also expected that *D. myoporoides* and *D. hopwoodii* extracts would exhibit similar properties, an expectation that appeared to be partially confirmed,[63] although it was clear that *D. myoporoides* exerted the more potent mydriatic effects.

Gerrard finally succeeded in late 1880 in obtaining from *D. myoporoides* a crystalline alkaloid as fine, colourless needles of more limited water solubility than the amorphous alkaloid, and hoped that the availability of this purified form might settle the question of its identity. According to many contemporary reviews,[64] the Paris pharmacist H. Duquesnel independently crystallized duboisine in the same year, but I have been able to locate only a short report on his 1881 presentation of duboisine crystals to the French Academy of Medicine, in which he indicated his intention to investigate the alkaloid further in collaboration with the physiologist Laborde.[65] The identity of Gerrard's alkaloid with the active principle of *D. myoporoides* was confirmed by its powerful mydriatic properties, a 1 in 32,000 solution being sufficient to rapidly dilate the pupil, but he was unable to decide whether the alkaloid was atropine.[66]

As early as February 1879, the medical student Louis Fauqué had published a doctoral thesis in Paris on his investigations of the pharmacological properties of duboisine in animals, conducted in collaboration with Petit in the prominent Laboratory for Experimental Pathology of Edmé Vulpian and in the clinic of Galezowski, indicative of the interest in the new drug.[67] Further animal investigations quickly followed, which confirmed that duboisine also possessed the other properties of *Duboisia* extracts: paralysis of the vagus, stimulation of vasomotor centres at lower doses but paralysis at higher doses, slowing of heart rhythm, increased blood pressure and accelerated respiration, inhibition of salivary and sweat secretion as well as of peristalsis, and paralysis of the oculomotor nerve (explaining its mydriatic action) but little effect upon sensory nerves or striated muscle function. In these actions it was similar to atropine, but much more potent.[68] Duboisine was also found to antagonize the actions of muscarine and pilocarpine, and its own toxicity could be ameliorated by administration of coffee or lemon juice.[69] In humans, 1 mg of the substance was reported to elicit 'sleepiness, delirium, twitching of the limbs, visual hallucinations, increase in pulse and respiration lasting for 10 hours'.[70]

In the same year as Gerrard's crystallization of duboisine, the authoritative German alkaloid investigator Albert Ladenburg announced that he had established the identity of duboisine with hyoscyamine, then regarded as the major commercial solanaceous alkaloid.[71] Duboisine was already being commercially prepared at this time by the firms E. Merck (Darmstadt) and Gehe & Co. (Dresden) for use as a mydriatic, but also as an injectable sedative and narcotic for psychiatric patients. Only later (in 1880) would Ladenburg discover that commercial 'amorphous hyoscyamine' contained a second alkaloid that he would dub, confusingly, 'hyoscine' (in the false belief that it was an isomer of hyoscyamine).[72] Prevailing technological limitations meant that commercial hyoscyamine and duboisine were both inevitably mixtures of hyoscyamine and scopolamine, and probably of further, unidentified alkaloids, with the relative amounts depending upon the source plant material and its preparation. Ladenburg's authority nevertheless sufficed to establish 'duboisine' as being identical in a practical sense with 'hyoscyamine',

despite frequent observations that it was much more potent. Motivated partly by the criticism of Erich Harnack,[73] Ladenburg finally re-examined the question in 1887 and found that commercial duboisine (E. Merck), a yellow-brown syrupy mass, was in fact principally scopolamine.[74] The Berlin firm Schering found, in contrast, that duboisine prepared as described by Bancroft consisted of nothing but hyoscyamine.[75] As late as 1897, the Scottish physician G. Sharp advocated the dropping of the name 'duboisine' on the basis that Ladenburg had demonstrated its identity with hyoscyamine.[76] The isolation in 1892 of yet another tropane alkaloid from *D. myoporoides*, 'pseudohyoscyamine' (= norhyoscyamine),[77] confused the picture even further, as it was still widely assumed at this point that a given medicinal plant contained a single active principle.

This controversy, one of many regarding the identity of alkaloids that enlivened chemistry at this time, persisted as the result of conflicting reports and of confusion of the names 'hyoscyamine' and 'hyoscine'. In the 1890s it would be recognized that hyoscyamine levels increase and scopolamine levels decrease with age in solanaceous plants, accounting for some of the reported discrepancies.[78] The early identification of duboisine with hyoscyamine was thus partially the result of the selection of raw materials and preparative processes employed by the firm E. Merck, highly esteemed for the purity of its alkaloid preparations. Ironically, amorphous hyoscyamine and amorphous duboisine would by the end of the century supplant the 'purer' (and more expensive) crystalline forms of each alkaloid in non-ophthalmological applications, as it would prove that the 'contamination' with scopolamine was responsible for most of their desirable pharmacological properties. Thoms recorded in his pharmaceutical reference work (1927–1929) that 'amorphous duboisine' and 'amorphous hyoscyamine' from Merck both consisted of racemic scopolamine,[79] while the 1925 edition of *Hagers Handbuch* noted that *D. myoporoides* contained hyoscyamine, scopolamine and an unidentified 'coniine-like' alkaloid.[80] George Barger and colleagues found in 1937 that an alkaloid extract they had prepared from *D. myoporoides* material contained no hyoscyamine but was rich in scopolamine, whereas commercial 'duboisine' (*Duboisinum purum crystallisatum* Merck) was almost pure hyoscyamine,[81] while the British pharmacist Mitchell was surprised in 1940 to find that the drug ('not often encountered in pharmacy') was entirely hyoscyamine-free.[82]

This issue was, in fact, not definitively resolved until the publication in 1945 of the findings of the Australians Colin Barnard (Council for Scientific and Industrial research [CSIR]) and Horace Finnemore (University of Sydney). They reported that there are geographical and climatic differences in the alkaloid content of *D. myoporoides* trees: scopolamine was the predominant alkaloid in samples from ten localities in Queensland and northern New South Wales, while hyoscyamine predominated in specimens from southern New South Wales.[83] Loftus Hills, Bottomley and Mortimer (Division of Plant Industry, CSIRO, Canberra) later reported that scopolamine content declined in favour of hyoscyamine from northern (warmer) to southern (cooler) regions of the Australian east coast,[84] while pyridine alkaloid content (anabasine, nicotine) was greater than that of tropane alkaloids in *D. myoporoides* from the Killarney Plateau (southern Queensland)[85] and New Caledonia.[86]

A related problem involved the confusion of 'pituri' and 'duboisine', and of their source plants, which also persisted for some time,[87] the issue being clouded by the indiscriminate sale of *D. myoporoides* and *D. hopwoodii* leaf in Europe as 'Duboisia'[88] and the fact that most European workers had never seen the fresh

source plants. This confusion was not completely eliminated until the early twentieth century; for example, *Merck's Jahresbericht* for 1916 erroneously noted that Gerrard had isolated 'piturine' from *D. myoporoides* (Gerrard had also concerned himself with the investigation of pituri[89]), while as late as 1911 handbooks on plant chemistry continued to confuse *D. myoporoides* and *D. hopwoodii*.[90] This necessarily led to confounding of the associated alkaloids and their pharmacological effects.

Medical Applications for Duboisine

Duboisine sulfate was listed as early as 1880 in the Prussian *Arzneitaxe* (= scale of charges for medications), and had entered the Dutch and Spanish pharmacopoeias by 1893.[91] Neither duboisine nor *Duboisia* preparations (*Folia duboisinae myopoiridis* and *extractum duboisinae*), on the other hand, were ever listed in German or British pharmacopoeias (in contrast to atropine sulfate and *Folia belladonnae*, for example), although they were regularly discussed in auxiliary publications such as *Martindale's Extra Pharmacopoeia*, Dorvault's *L'officine* and *Arzneimittel, welche in dem Arzneibuch für das Deutsche Reich nicht enthalten sind*.[92]

Ophthalmology

Bancroft, Tweedy and others had quickly identified the mydriatic properties of *D. myoporoides* extracts, and the initial employment of the new alkaloid was in ophthalmology. The first of many reported medical applications of duboisine were published in early 1878 by the Paris ophthalmologists Wecker — who had received his duboisine 'at a very moderate price' from Petit and suggested that it should replace atropine in ophthalmology where idiosyncratic responses to the latter caused problems[93] — and Galezowski, who presumably received the alkaloid from the same source.[94] Soelberg Wells at King's College Hospital, London, reported in 1879 treatment of ciliary muscle spasm with a duboisine solution provided by the Sydney physician Fortescue; it was more effective than atropine, although he had concerns as to whether it might also induce glaucoma.[95] The first American report of the employment of duboisine sulfate in ophthalmology appeared the same year in the *Philadelphia Medical and Surgical Reporter*.[96]

Duboisine, without irritating the eye or conjunctiva, was usually reported to elicit rapid pupil dilation and subsequent paralysis of accommodation; mydriasis occurred sooner with duboisine (6–8 minutes) than with atropine (14–15 minutes), and the duration of its effect was longer.[97] Duboisine was also employed in the treatment of near-sightedness, keratitis and spasms of accommodation, as well as for temporary paralysis of the ciliary muscles.[98]

Duboisine intolerance was not infrequently reported.[99] An early report was that of the Oslo doctor Berner. Having applied a small amount of the sulfate to his own eye, he experienced four hours of thoroughly unpleasant motor restlessness and autonomic inconvenience that ultimately ended in sleep. His pupils, however, remained dilated for six days, and, on the day after his experiment, 'there was a disagreeable sweat over the whole body, with depression, and irritability, and physical and moral prostration'.[100]

Reports of duboisine intolerance prompted Tweedy to remark: 'I have long felt that duboisin [sic], like many other new remedies, has been, and still is, extravagantly abused. It is of immense power and value, and necessary only in special cases, for which it should be reserved.'[101] Veasey similarly cautioned in 1896 that 'the idiosyncratic intolerance of duboisine is not by any means rare, a fact which should be borne in mind when handling this powerful alkaloid'.[102] But the danger associated with duboisine as a topical agent was judged

differently by various physicians, and variations in the potency of preparations (the crystalline version was generally regarded as harbouring the greater risks) and inappropriate dosages, combined with idiosyncratic patient responses, may have underlain some of the problems experienced. Indeed, many physicians regarded duboisine as a safer alternative to atropine.[103]

Sedative and Hypnotic

The sedative effects of duboisine in agitated delirium had been recognized as early as 1879.[104] Fauqué noted with some surprise in his doctoral dissertation that one excited patient, who could not be controlled with either morphine or chloral, was rapidly sedated by 1 mg duboisine, and proposed that this effect, stronger than that elicited by atropine but comparable with that of the other solanaceous plant popular in French clinics, *Datura stramonium*, might usefully be employed in hyperkinetic disorders.[105] Mabille and Lallemant reported in 1892 that they had been employing it in France for the past two years,[106] and Dupuy listed 'alcoholic delirium' in his 1889 alkaloid handbook as an indication for its use.[107] The sedative properties of duboisine achieved greater attention, however, following the publication in 1890 by Nicolaus Ostermayer of Budapest of a study comparing the effects of subcutaneous atropine, scopolamine and duboisine. He found that the yellow hygroscopic powder duboisine sulfate was a rapid and intensive sedative (after 10–15 minutes) and hypnotic (20–30 minutes), and was safer for treating excited states in psychiatric patients than the then standard scopolamine.[108] A number of other European authors similarly applied it subcutaneously,[109] although a few also found it to be effective as an oral medication.[110] In Germany, duboisine was recommended by Gellhorn in 1891 as a rapid and safe sedative for psychotic patients, especially when injected; he noted that duboisine in tablet form for injection (*tablettae hypodermicae*; à 1 mg) had recently become available from Dr August Oetker of Bielefeld, renowned for the firm based on his improved American baking powder.[111]

The Australian naturalist Joseph Henry Maiden (1859–1925) commented in 1893 that most exported *Duboisia* leaf was sold in Germany.[112] Duboisine was also employed as a sedative in other countries, including Switzerland and Russia,[113] but the 1898 edition of the herbal manual *King's American Dispensatory* noted that neither *Duboisia* nor its alkaloid were employed internally to any great degree in the United States.[114] The following entry in the naturopath physician Ellingwood's *American Materia Medica, Therapeutics and Pharmacognosy* (1919) suggests, however, that its employment was not totally unknown:

> It has been given in some cases of *maniacal excitement*, but it must be given in the enfeebled cases and not when there is fullness — engorgement of the circulation of the cerebral organs. It has been used in the treatment of *emotional insanity* and *delirium* with excitement… It is also used in *muscular tremblings*, *paralysis agitans* and *epilepsy*.[115]

The usual dosage, whether oral or subcutaneous, was $^{1}/_{2}$ to 1 mg per day, although as much as 2 mg per day was reported. Accumulation was sometimes a problem, eliciting symptoms of belladonna intoxication, so that 'drug holidays' were instituted at eight-day intervals where chronic administration was necessary.[116] Injection of duboisine elicited dryness of the throat, pupillary dilation, slight visual problems, thirst, accelerated pulse and some muscular paralysis. Stupor lasting several hours could also be observed; the patient remained responsive to questioning but otherwise languid and apathetic. Higher doses could lead to reduced circulation or even coma and death. Reduced cardiac performance and gastrointestinal disturbances leading to weight loss could

develop during longer periods of administration. Therapeutic and toxic effects of duboisine were thus essentially similar to those of atropine and scopolamine.[117]

Paralysis Agitans (Parkinson's Disease)

Duboisine was not a true hypnotic, such as chloral or morphine, as this effect was not seen where insomnia was of psychiatric origin, as in depression or paranoia. But Emanuel Mendel in Berlin had noted that muscle relaxation preceded the onset of sleep induced by duboisine in psychiatric patients, so that it was his practice to employ duboisine wherever motor unrest prevented sleep. He therefore treated twelve parkinsonian patients with duboisine, rarely without success; within fifteen minutes, tremor was reduced to the extent that writing was again possible, and this effect lasted three to five hours. Toxic signs could appear at doses as low as 0.2 mg, and included pupil dilation, dryness of the mouth and increased pulse. Mendel abandoned the use of scopolamine in parkinsonism in favour of duboisine because of the less marked toxic effects and because of the lower dose required (2–3 doses of 0.2–0.3 mg/day).[118]

Duboisine was also a popular antiparkinsonian agent in France,[119] but was not adopted to any great degree outside continental Europe. Perhaps most surprisingly, it does not appear to have been used in this capacity in Australia. Duboisine continued to be mentioned sporadically in German literature as an antiparkinsonian medicament until the 1920s, although generally negatively.[120] The name 'duboisine' was still current as late as 1938, when the Italian physician Panegrossi surprisingly listed it beside atropine and hyoscyamine as one of the alkaloids of the belladonna root.[121]

Other Disorders

Duboisine was also applied with some success in a number of other nervous disorders, including Basedow's (= Grave's) disease, epilepsy and nystagmus, as well as for the management of night sweats and morphine addiction.[122] All these applications were consistent with the nineteenth century approach of treating these disorders with atropine and/or scopolamine.

What Was 'Duboisine'?

After duboisine salts became commercially available — the alkaloid chemist Carl Scriba wrote in 1925 that he first prepared them at Merck (Darmstadt) in 1881[123] — the sulfate was preferred in medicine to pure duboisine base (the hydrochloride and hydrobromide were also available in the 1890s), being more soluble and easy to crystallize. The clinical activity of 'duboisine' was generally linked by the beginning of the twentieth century with its scopolamine content, especially as the sedative and antiparkinsonian value of hyoscyamine was also recognized by this time as being attributable to its 'contamination' with scopolamine. But it was also apparent that commercial 'duboisine' consisted of several alkaloids in varying relations; the Lausanne doctor Rabow, for instance, noted in 1893 that duboisine was more dangerous than scopolamine, as at toxic doses it could elicit convulsions, rarely seen with scopolamine.[124] Merck described their duboisine sulfate in 1916 as 'the sulfate of the total ether-soluble alkaloid content' of the leaf, the 'entire active content of the plant material'.[125] More specifically, the firm established in 1912 that their duboisine sulfate, which was more stable than the amorphous alkaloid, consisted of 18–20% scopolamine and 1–1.5% hyoscyamine, the rest being composed of unidentified bases.[126]

Interest in *Duboisia* declined with the recognition that 'duboisine' was not a distinct alkaloid species. New research was correspondingly scant at the beginning of the twentieth century. Apart from reviews by Joseph Maiden,[127] the only major publi-

cations were a 1912 report by the British chemists Carr and Reynolds that the principle alkaloid in *D. myoporoides* (obtained from the Philippines) was hyoscyamine,[128] and a series of papers by James Petrie (University of Sydney) in 1917 on the chemistry of poisonous *Solanaceae*.[129]

Merck nevertheless continued to manufacture 'duboisine sulfate' until exhaustion of the available supply of Australian plant material in 1916, peaking in 1905–1906 with the processing of 400 kg leaf (with an alkaloid yield of about 0.8%); extraction was resumed at a reduced level in 1921 and continued until the mid-1930s.[130] But the Dresden firm Gehe & Co. had already noted in 1891 that the price of duboisine was hindering its fortunes:

> Although duboisine is certainly still accessible, there has been a decline in its employment, which, given its current price, determined by the expensiveness of the raw material, is hardly surprising, particularly as in ophthalmological applications it possesses not the slightest advantage over atropine sulfate.[131]

The same firm noted in their April 1891 report that duboisine was 'a medically almost forgotten alkaloid',[132] but also remarked that its sedative properties had only been recently identified, so that its most important possibilities were probably not yet apparent to the firm. Joseph Maiden wrote in 1893 that the Merck list price for duboisine sulfate in 1889 (7 s. 6 d. for 15 grain; packed leaf was exported for between 4 d. and 1 s. per pound) was 'almost prohibitory' but not 'excessive, considering the difficulties importers have to contend with in getting supplies of the raw material'; he further noted that the habit of collectors chopping down whole trees instead of pruning them was 'killing the goose with the golden eggs, and such conduct will bring its own punishment.'[133] Another Australian commentator noted in 1891:

> It is used in ophthalmic surgery, but not at present to any great extent; this we conclude is the very natural result of Ladenburg's investigations… It is a rather more powerful mydriatic than atropine but is generally considered to be otherwise inferior… The future of duboisia undoubtedly depends either on its yielding duboisia very cheaply (for ophthalmic surgery), or in more extended trials therapeutically establishing uses not yet suggested for it, but which its pharmacological peculiarities give a foundation for.[134]

The Merck list price for duboisine sulfate in Australia by 1912, however, was £5 per ounce, a considerable drop from the quoted 1893 level.[135]

On the other hand, Näcke (1892) and Rabow (1893) both noted that duboisine was much cheaper than scopolamine,[136] and the figures listed in the official German pharmaceutical price list, the *Preußische Arzneitaxe*, also indicate that the price of duboisine throughout the 1890s was lower than that of hyoscyamine and scopolamine, but higher than that of atropine (1892 price per 10 mg: 10, 25, 15 and 5 Pf., respectively). By 1917, all four alkaloids were available for similar prices (15, 15, 10 and 10–20 Pf.), but a sharp rise in price in the course of 1925 rendered duboisine noncompetitive (30, 5, 5 and 5 Pf.; prices according to new *Reichsmark*), a situation that persisted until the 1930s, after which duboisine was no longer manufactured commercially. The prices listed for the various alkaloids in the 1896 American catalogues of Gehe & Co. (Dresden) and Merck & Co. (New York) similarly indicate that duboisine was less expensive at this point than hyoscyamine, hyoscine and scopolamine (all listed separately).[137]

In contrast to the gloomy attitudes cited above, the German neurologist Emanuel Mendel proclaimed in 1893 before the Berlin Society for Psychiatry and Nervous Diseases the great value of duboisine for psychiatric practice: 'Given the short life that most modern so-called medications enjoy, allow me to draw attention today to one which, at least in certain cases, represents an enrichment of our pharma-

cological armoury.'[138] This difference of opinion reflects the fact that duboisine was principally employed in English-speaking countries at the end of the nineteenth and the beginning of the twentieth century in ophthalmology — 'Duboisine sulfate is a sedative, hypnotic, and mydriatic of variable strength. Its principal use is in ophthalmology; as a mydriatic it is much more powerful than atropine, and is applied as "drops" (0.2 to 0.5 per cent.)'[139] — whereas its use in psychiatry was largely limited to continental Europe. Its price in England thus needed to be competitive with that of atropine rather than that of scopolamine, but the reverse applied in Germany, where its popularity in sanatoria and similar institutions prolonged its commercial success. But even here, only very small amounts were required. Further, although hyoscyamine and scopolamine are mydriatic to a similar degree, the stimulant effects of the first oppose the depressant effects of the latter, so that it might be preferable in some situations to employ a defined alkaloid rather than the mixture 'duboisine' to achieve a reliable and consistent sedative effect.

The status of the *D. myoporoides* 'industry' immediately before the Second World War was concisely addressed by Arthur Penfold (1890–1980), economic chemist and curator of the Sydney Museum of Applied Arts and Sciences,[140] at the end of his 1936 presidential address to the Royal Society of New South Wales:

> There have been numerous enquiries for supplies of *Duboisia myoporoides* from Europe, but an extensive business has not developed, although there is a considerable demand for natural sources of atropine alkaloids. There does not appear to be any difficulty in supplying the required leaves, but complaints have been received concerning the variable content of hyoscyamine. The chemistry of the leaves of *Duboisia myoporoides* was worked out by Dr Petrie. There is certainly need for a critical investigation of the alkaloidal content of leaves of *Duboisia myoporoides*, particularly concerning the age of the leaves, climatic, soil, and other conditions operating, whereby the alkaloid varies both in content and chemical composition from time to time. The investigation is warranted, as there is a demand for approximately 100 tons of leaves per annum.[141]

'Duboisine drops' continued to be employed in ophthalmology as late as the 1950s, but increasingly rarely.[142] The official end for 'duboisine sulfate' was perhaps heralded by its being omitted from the 27th edition of *Martindale Extra Pharmacopoeia* in 1967. The French firm Ciba Vision Ophthalmics, however, still marketed a hyoscyamine preparation as 'Sulfate de Duboisine Martinet' between 1993 and 2000.[143] 'Duboisia' and 'duboisine sulfate' are still employed today by homeopathic physicians for the treatment of various ocular problems, and specifically in cases where vision is impaired by a red spot.[144]

Duboisia in the Second World War

The recognition that 'duboisine' was actually a mixture of alkaloids available from other sources might have proved the end of the medical importance of the genus *Duboisia*, but events took an unexpected turn. Scopolamine had been introduced by Steinbüchel in Germany at the turn of the century as an agent for easing the pain of childbirth, inducing the so-called 'twilight sleep'.[145] This form of anaesthesia, whereby the pain of childbirth was neither experienced nor remembered despite full consciousness, was then introduced into general surgery, usually in combination with morphine. Scopolamine was also regarded as the most effective treatment for the tremor characteristic of the parkinsonian syndrome that developed as a sinister long-term after-effect of encephalitis lethargica, an epidemic that killed and incapacitated many young people between 1916 and 1930. The scope for the employment of scopolamine had thus increased significantly since 1900, and its role was

even more crucial during the Second World War: large quantities were required as a sedative (including its use in pre-surgical anaesthesia and for the management of shell shock), as well as for the control of sea-sickness, a major issue in both the Pacific and Atlantic theatres. The problem for the Allied nations was that most scopolamine was still produced in Germany.

Shortly after the outbreak of war, the CSIR initiated arrangements for the introduction to Australia of medicinal drug plants regarded as important by the Australian Medical Equipment Control Committee (MECC), including hyoscyamus and belladonna.[146] In a brief note in the *Australasian Journal of Pharmacy* in November 1939, Horace Finnemore suggested that *D. myoporoides* might also be explored as a local alternative to belladonna for tropane alkaloids; he had examined its properties over many years, and was presently exploring suitable galenic preparations of the plant.[147] The CSIR therefore contacted Finnemore in June 1940 with the request that he conduct the pharmaceutical assays and analyses in a drug plant project to be overseen by Colin Barnard; corresponding biological tests were to be the responsibility of Professor Roy Douglas Wright of the University of Melbourne, while collaboration with State Departments of Agriculture and Forestry was also sought.[148] By 22 August 1940 Finnemore could deliver a report in which he noted that *D. myoporoides* could 'easily' supply all the scopolamine required domestically, but also urged that leaf exports be strictly controlled, as Arthur Penfold had told him that ten tons had already been exported to England;[149] an embargo on leaf exports was in place by mid-1942.[150] Within twelve months of Finnemore's report, the CSIR concluded that a 'method for the extraction of the hyoscine has been developed by Mr H. Finnemore of the University of Sydney' and that, in contrast to other medicinal plants, no supply problems were foreseeable;[151] Finnemore himself saw 'no great difficulty in cultivating … all our requirements of these drugs'.[152]

Finnemore, however, was heftily criticized in internal correspondence by the Chief of the Division of Plant Industry, Bertram T. Dickson (1886–1982) for his sharing his results with only one of several interested drug firms — Drug Houses of Australia (DHA) — 'especially when the information is based on investigations financed by the Commonwealth Government through the Medical Equipment Control Committee.'[153] As early as September 1940, Finnemore had supplied 50 kg of Grafton leaf to the Sydney firm Elliott Bros, part of DHA, for 'experimental large scale extraction'.[154] While Dickson noted that DHA was profiting from the research Finnemore had conducted under the aegis of the CSIR, in that DHA had exported all scopolamine produced since March 1941, Finnemore had refused to assist, for example, F. H. Faulding with their extraction of *Duboisia* material.[155] In April 1943, Barnard wrote to Sir David Rivett (Chief Executive Officer, CSIR) that:

> Relations with Mr Finnemore have … never been satisfactory. Considerable friction occurred between him and ourselves (Dr Dickson and myself) over the way the Duboisia work was handled. The handling of the morphine investigations has been equally unsatisfactory & unsatisfactory is a mild term for what I think of it. It is however a long story & certain action was taken to remedy the position.[156]

Significantly, an internal CSIR report from 1943 noted that 'close contact [had] been maintained with [interested] commercial firms', particularly Cox, Findlayson & Co. and Burroughs Wellcome; DHA was not mentioned, although contact with Finnemore continued.[157]

Duboisia research in the private sector had certainly also been stimulated by the wartime emergency. Early one morning in October 1940, the Chairman of the MECC,

Sir Alan Newton, placed a telephone call to Wilfred Russell Grimwade (1879–1955). Grimwade was a partner in Felton, Grimwade & Duerdins Pty Ltd (since 1929 part of DHA), a small company by international standards but one of the leading Australian chemical firms; it would later become DHA (Victoria).[158] The Chairman informed Grimwade that Australia required 11 oz scopolamine (about 312 g) per year, and that stocks were dangerously low (in a memorandum to the CSIR, the MECC estimated that Australia annually imported 40 oz at a cost of £800, and 200 oz atropine for £600).[159] It could still be procured in America at this point but, at a cost of about £25 per ounce, it would have represented a high demand on Australia's dollar reserves. Grimwade, still wrapped in the towel he had donned as he stepped from the shower, replied quickly that the Government should save its money; remembering Bancroft's paper on *D. myoporoides* from sixty years earlier, he announced confidently that his laboratory could manufacture scopolamine from *Duboisia* with little problem.[160]

Grimwade noted later that this was a rather brave promise, partly motivated by the fact that he wished to avoid dripping more water onto his wife's best carpet; he was not even certain that *Duboisia* leaf actually contained scopolamine, let alone how it might be efficiently extracted. Scopolamine had been produced on a modest scale in Australia before the war, but even this was from imported belladonna.[161] Grimwade's previous attempts to grow belladonna on his Westerfield property near Frankston (Victoria) were frustrated by low alkaloid yields and the high labour investment required. His chief chemist, E. I. Rosenblum, wrote that they thus 'somewhat anxiously … accepted the challenge'.[162] Nevertheless, within seven weeks 7oz (about 200 g) of British Pharmacopoeia standard scopolamine had been extracted on the laboratory benches of Grimwade and Rosenblum (presumably facilitated by Finnemore's advice, although this is not mentioned in Grimwade's account) from about 50 kg leaf supplied by Finnemore, as noted above. Further work was facilitated by the fact that the American consul had heard of Grimwade's initial success; the Americans recognized the need for stockpiling larger quantities for the coming Pacific War and were willing to pay well for a steady supply. This led to the establishment of the first plant in Australia for industrial scopolamine extraction, which by the end of 1941 was producing $1^1/_2$ kg of alkaloid per week.[163]

On 1 December 1941, the British Ministry of Supply wrote to Australia House in London that it had received a telegram from the Washington office of the British Purchasing Commission that 'Australia is now producing hyoscine under control of Medical Equipment Control Committee, Melbourne and can supply 500 ounces [~14.2 kg] to UK up to June '43 without difficulty … Owing to shortage of supplies in this country' the Ministry wished to confirm that this was the case and that the quoted price of £AU12 7 s. 6 d. per ounce was also correct. Australia House confirmed the information on 16 December, noting that the 500 oz to be delivered in instalments by June 1943, half of which was to be forwarded to London and half to Washington, represented the total capacity of Australia's producers. The drug was duly despatched in 25 or 50 oz lots during the agreed period, with only one package ever being lost — due to a direct bomb hit on a British post office.[164] It was initially noted with consternation in Britain that the delivered substance exhibited a higher melting point and optical rotation than recorded in the British Pharmacopoeia, a fact that Rosenblum attributed to the company's success in producing scopolamine of 'reagent quality'.[165]

Demand for scopolamine continued to rise during the course of the War, and

Australia became the sole supplier to the Allied forces, as noted in an application in August 1944 to the Defence Committee by the MECC for priority status for the erection and equipment of a new factory by Grimwade's firm: 'Atropin [sic] and Hyoscine … are absolutely essential in Medical Practice and there is a world shortage. As they can be extracted from a locally grown tree, Australia has now become the general source of supply for the Allied Nations'.[166] Huge quantities were employed, for instance, for the preparation of the troops participating in D-Day, prompting the Australian historian Geoffrey Blainey to write in 1977: 'Here, in 1944, was the greatest armada in the history of man, setting out towards a turning point in history; and much of the success of that armada depended on a drug which had been discovered by forgotten men and women in ancient Australia.'[167] Those involved in transport of the alkaloid soon recognized that increased shipments were indicative of pending major amphibious operations by the Allies.[168] As a curiosity, it might also be mentioned that '*Hyoscine*' was the American naval codeword for Adelaide (South Australia) during the War.[169]

The 7000 oz (~200 kg) of scopolamine produced from *Duboisia* during the War reputedly exceeded all previous production of the alkaloid.[170] Peak annual production was achieved in 1946 (~205 kg), after DHA had opened a new and safer (due to efficient ventilation) plant in 1945, despite the reservations of the Defence Committee.[171] By 1954, over five tons of various alkaloids had been produced, equivalent to 8,000 million average doses; the increased supply resulted in a decline in price from £25 to £4 per ounce.[172]

Hyoscyamine/Atropine

Commercial extraction of hyoscyamine for conversion to atropine proved more difficult, but also commenced in 1942, primarily from *D. leichhardtii* leaf. An anonymous reviewer noted at this point:

> 'One of the most striking examples of local enterprise is the extraction of *atropine* from the native duboisias, following exhaustive experiments by research workers. Adequate amounts of *atropine* will soon be available. Small quantities of *belladonna* have also been grown in Victoria.'[173]

It had been recognized as early as 1895 that the alkaloid content of *D. leichhardtii* was higher than that of *D. myoporoides*,[174] and that this increased yield consisted mostly of scopolamine, with little contamination by pyridine species. It was, however, not systematically studied; Petrie published a review in 1917,[175] after which it was again neglected until the Second World War, at which time the CSIR found that available samples were predominantly hyoscyamine-containing.[176] Variation in *D. leichhardtii* alkaloid levels was not as apparent as for *D. myoporoides*, although both hyoscyamine-dominant and scopolamine-dominant stands have since been identified.[177]

Commercial Duboisia *Plantations*

Until 1944, leaf collected from wild-growing trees had been employed for scopolamine preparation. Boy Scouts, amongst others, were initially deployed to harvest the leaf, before local farmers realized the value of the once-hated tree and the number of willing collectors grew. The harvest was relatively simple: branches were cut from the trees and air-dried together with the leaves, which were then removed for processing; the branches were later mechanically chopped and the leaf separated from the woodchip for artificial drying. The trees regenerated sufficiently to allow repeated harvest twelve months later.

By 1944, however, demand for the drug had become too great to be satisfied by these means, having grown from 15,000 pounds (6.8 tonne) in 1942 to 93,000

pounds (42.2 tonne) in 1944 (and to 189,000 pounds [85.7 tonne] in 1948).[178] There was even some fear that *D. myoporoides* and, more seriously, *D. leichhardtii*, might be exploited to the point of extinction. Research by the Division of Plant Industry of the CSIR/CSIRO between 1940 and 1954 improved yield and extraction, one of the major initial breakthroughs being the discovery that *Duboisia* could be more efficiently grown from cuttings than from seed, although this was true only to a limited extent for *D. leichhardtii*. It was also recognized that natural hybrids of the two species were present in areas where both *D. myoporoides* and *D. leichhardtii* occurred, some of which offered advantages over the individual species. This stimulated directed research into the production of new crosses, with the — ultimately fulfilled — hope that alkaloid production might be increased by these means.[179] In contrast, attempts to cultivate belladonna, henbane and *Datura* species, also pursued with some vigour and some success by the CSIR and MECC,[180] met with disappointing results, with viral and insect attack representing problems not affecting the native *Duboisia* to the same degree.[181] Nevertheless, *Duboisia* farming was fraught with natural difficulties, and was 'not to be recommended as a crop for amateurs or the average farmer, but rather for the skilled horticulturalist.'[182]

Grimwade also oversaw the introduction of commercial farming of both species in south-east Queensland and northern New South Wales, both by natural means and selective breeding; an experimental farm was also established in Victoria, but growth was slower than further north, and plants were also eaten with apparent impunity by local deer. Grimwade, by now official botanical adviser to the Australian Army (with the rank of Major-General), was also involved in a number of other successful wartime projects that advanced his vision of local drug-growing and essential oil industries, including the extraction of an olive oil ersatz from apricot kernels and the introduction to Australia of the straw method of opium extraction from poppies, whereby the time-consuming slicing of the plant is spared. This latter success ultimately led (despite an interruption to cultivation following the Second World War) to Australia now supplying more than half of the world's legal opiates. Other medicinal (digitalis, ephedrine, ergot, quinine) and fruit plants were also explored in Australia by the CSIR during the War as the emergency forced the country to look to its own resources.[183]

After the Second World War

The success of wartime forays into applied medical botany led to the establishment of the 1945 *Australian Phytochemical Survey*, which aimed to identify further native plants that might be useful in a medical or industrial context.[184] *Duboisia* in particular was seen by some as the flagship of research into the pharmacological qualities of indigenous Australian plants: 'we know relatively nothing about the possibility of finding sources of some of these drugs from our indigenous plants. Only recently has *Duboisia myoporoides* become noteworthy as a source of hyoscine and hyoscyamine and this can serve as a good example of the possibility.'[185] Grimwade and Rosenblum were 'confident' that the industry that had developed under wartime conditions would continue to flourish in the post-war period,[186] and there was some expectation that '*Duboisia* might rank again as a strategic raw material' after it was found that 'atropine was the best antidote for some of the new nerve gases being developed for chemical warfare.'[187]

But government support for the phytochemical industry was at best lukewarm after the wartime emergency had passed. As early as May 1943, the improved world situation allowed a reassessment of Department of Primary Industries (DPI)

priorities, whereby the focus of interest was now defined as plants 'bearing pharmacological and insecticidal' substances. At this stage, interest in *Duboisia* research was still buoyed by hopes that crops standardized with respect to alkaloid content might allow Australia to 'become the source of world supply'; Kevin Loftus Hills had commenced work with this aim for the CSIR, overseeing experimental plots in Nambour and Canberra.[188]

In September 1945, however, Colin Barnard wrote to R. D. Wright that post-war medicinal plant research would be greatly curtailed as a result of reduced funding for the DPI, prompting Wright to despatch a bitter letter to the Prime Minister, Ben Chifley. After enumerating the wartime achievements of the CSIR and others in medicinal plant research, Wright concluded:

> I have regarded your Government as at least offering a hope for the development of technological strength of the country … the present sort of performance, however, is one which, even though not calculated, could not have been better designed to add to the emigration of scientists from Australia. It is surely time we called halt in this direction.[189]

Many within the CSIR were outraged by this direct action, but Wright's fears for the future of the industry proved all too justified, particularly following the election of the conservative Menzies government in 1949. As the result of lobbying by growers' groups, the *Duboisia* leaf export embargo, which had previously assured control of market volume and price of the raw product and which DHA saw as prerequisite to the profitability of local extraction efforts, was lifted in 1954.[190] Even before this point, an English procurist for the chemical, oils and drug company Biddle, Sawyer & Co., Herbert Berens, was surprised to find that *Duboisia* leaf sales were rather 'haphazard':

> Firms that required the leaves bought them only when they wanted them. No arrangements had ever been made with the collectors to furnish supplies regularly, consequently interest in the collection of leaves was waning.[191]

Berens made 'satisfactory arrangements' to purchase whatever was available from a Ford automobile dealer (!) who had recently established his own plantation of *D. leichhardtii*, the species now attracting most commercial attention, but this lack of organization did not bode well for the future of the industry.

By 1945, the DHA plant had been extracting twelve commercial substances from *Duboisia*, including chlorophyll, then fashionable as a deodorant,[192] but the new circumstances also led to the rapid closure of what was by this time the world's most advanced alkaloid purification plant, and extraction moved to countries with lower labour costs — ironically, Germany and Japan. DHA ceased major involvement in alkaloid extraction, and CSIRO research — which had at various stages entailed co-operation with the NSW and Queensland Departments of Forestry, the Queensland Department of Agriculture and Stock, and the Departments of Pharmacy at the University of Sydney and Physiology at the University of Melbourne — was gradually curtailed, although important research into the alkaloid constitution and variability of *Duboisia* species and hybrids continued to be published by Peter Inkster Mortimer, Warwick Bottomley and Kevin Loftus Hills until the late 1950s.[193] Research into the biochemistry of alkaloid production in *Duboisia* continued to be pursued in Australia during the immediate post-war period; Edward Trautner's group at the University of Melbourne found, for example, that alkaloid synthesis occurs principally in the roots, from whence the compounds are transported to the aerial parts of the plant, in a fashion similar to that since described in European *Solanaceae*.[194] It was also found that controlled environmental conditions could be

employed to regulate the relative amounts of hyoscyamine and scopolamine.[195] In a letter to the CSIR Chairman at the end of 1954, Loftus Hills admitted to 'feeling rather bitter' that he could no longer pursue various research directions he had been exploring, with the only consolation being that Ray F. Dawson (Columbia University, New York), one of the leading authorities on alkaloids, had actually asked whether Loftus Hills would object, under the circumstances, if 'a botanical team at Columbia working with the Brookhaven National Laboratory should take over the biogenesis work on Duboisia at the stage where Bottomley, Mortimer and [Loftus Hills] had to leave it in 1952'. Loftus Hills had recognized 'the unique opportunity presented by the Duboisia species of solving some of the most perplexing problems of alkaloid biogenesis', and regretted that he had had no choice but to give the American researchers his blessing.[196]

The general manager of Burroughs Wellcome & Co. (Aust.) wrote to Walter Ives of the CSIRO on 4 August 1959 that his firm had been supplying leaf to the English parent company for extraction at Dartford, but now planned to extract the alkaloid itself and was also aiming to 'put the cultivation and collection of leaf on a less empirical basis'; the firm was thus seeking CSIRO assistance, as Burroughs Wellcome had 'come up against problems, both botanical and ecological', that were beyond its capacity. Burroughs Wellcome's interest in alkaloid extraction from *Duboisia* and the establishment of a plant for these purposes in Rosebery (Sydney) was to form part of its investigation of native species in the framework of a 'Natural Products Research Group'. But Ives replied on 7 August 1959: 'As far as Duboisia is concerned we pretty well wound up our interest in this seven years ago. We did a lot of work on it during the war and a few years afterwards.'[197]

Grimwade expressed his regrets for lost opportunities in a 1954 paper that he had previously submitted to the Minister for External Affairs, Richard Casey, in the (disappointed) hope that he might reverse his decision to lift the leaf export embargo:

> The bulk of the world's atropine is being manufactured abroad from Australian leaves by pharmaceutical manufacturers who enjoy much cheaper labour conditions than those prevailing in Australia. A modern and efficient extracting and refining plant which during the war and the period of the embargo was working around the clock, to-day stands idle … not less than 12 alkaloids and their salts are now manufactured in Australia. This technical success has now become an economic impossibility owing to lack of governmental support. Australia has few, if any, articles of commerce that have originated from its natural resources and it is unfortunate that lack of official recognition of the circumstances is causing her to lose world dominance in the supply of irreplaceable pharmaceuticals that could have been easily within her grasp.[198]

Grimwade was subsequently attacked by an English importer for defending nothing more than the profits of DHA; he retorted, somewhat disingenuously, that there would have been no interest in *Duboisia* in the first place without the efforts of his firm.[199]

Colin Barnard still believed in 1952 that the *Duboisias* 'have prospects for replacing, at least greatly supplementing, Atropa and Hyoscyamus as sources of hyoscine and hyoscyamine.'[200] But a survey of European countries during 1952 by and on behalf of DHA found that there existed only limited possibilities for Australian exports of scopolamine and atropine to these markets,[201] especially as Germany itself had exported product to the value of 3,666,000 DM in 1951.[202] Another major problem for the *Duboisia* industry at this time was that the development of synthetic antiparkinsonian compounds in the immediate post-war years, part of an explosion in new agents emerging from the

chemical–pharmaceutical industry at this point, caused a shift from scopolamine to these newer pharmaceuticals as antispasmodic and antiparkinsonian agents.[203] Halothane anaesthesia was also replacing scopolamine in the operating theatre, while employment of *Duboisia*-derived eye-drops was now largely limited to Australia and Great Britain.

As previously in the *Duboisia* story, a renewal of interest was prompted by developments external to Australia. With its introduction in 1951 of *N*-butylscopolamine ('Buscopan')[204] as an antispasmodic agent to replace previously employed but not unproblematic *Datura* extracts, the German firm Boehringer Ingelheim required a reliable supply of raw scopolamine. This interest led to a revival of *Duboisia* research in Australia, as this supply could not be guaranteed by the *Duboisia* stocks then available: genetic variability, low germination and striking rates, and variability in alkaloid content related to locational factors needed to be addressed if a viable *Duboisia* industry was to again emerge. It should be remarked that these efforts by Boehringer to improve the alkaloid content in a previously wild medicinal tree represented a rather bold strategy in light of the fact that some authorities regarded the dominant role of environmental factors as precluding long-term success with attempts to improve secondary phytometabolite yield genetically, especially as it remains unclear what role tropane alkaloids play in the plant.[205] Grimwade, on the other hand, had believed that 'cultivation is superior to natural sources as a source of any drug',[206] although early attempts at selective breeding suggested that environmental factors determined alkaloid yield to a greater extent than genetic character.

Partly in collaboration with the Queensland Department of Primary Industries and the University of Queensland (Department of Parasitology), Boehringer invested greatly from the early 1960s in research into issues of germination, cultivation, alkaloid isolation, cloning and phytopathology. This research led to a number of vital innovations, including improved genetic stock based on already available hybrids and novel varieties drawn from natural populations, with improved resistance to climatic conditions and insect attack, as well as optimized patterns and levels of alkaloid production. Commencing with about twenty promising plant parents, more than 12,000 crosses produced by conventional horticultural means had been investigated by the year 2000, of which twenty were ultimately selected for commercial propagation. Experimentation with seed pre-treatment and vegetative propagation produced major improvements in these areas, as did later investigations of tissue culture propagation techniques.[207]

Improved growing conditions (vegetative propagation, more intensive cropping with consequently higher yields, weed and pest control, fertilizer use) and mechanized harvesting (since the mid-1970s) also contributed to significant increases in scopolamine yield with concurrent reduction of production costs. Mechanized harvesters with filtered, air-conditioned cabins for the operators, for example, allow rapid harvest of the raw material during peak alkaloid production instead of protracted collection throughout the summer, and also reduced exposure of workers to dangerous air-borne alkaloids. Even casual exposure to *Duboisia* dust can cause mydriasis, accommodation problems and conjunctivitis ('cork eye'), but chronic occupational exposure can also elicit neurological effects, including lethargy, euphoria and retrograde amnesia.[208] As a result of this investment and research, Australia remains the world's leading supplier of raw material for scopolamine and atropine extraction.[209]

Research into the biochemistry, pharmacology and propagation of *Duboisia* species and hybrids was also conducted independently of Boehringer. William ('Bill') J. Griffin was particularly interested in the investigation of *Duboisia* species after he joined the School of Pharmacy at the University of Queensland in 1963; he was a recognized authority in pharmacognosy, a subfield of pharmacy dealing with substances of natural origins, especially plants. Together with John Fred Coulsen, he published a pair of important papers in 1967–1968 in which they reported that *D. myoporoides* leaf and stem contained no less than thirteen different alkaloids (including four novel identifications), and that its root produced eight alkaloids (one new identification).[210] Griffin also identified an annual cycle in alkaloid content, with scopolamine levels declining from January to June, a decline that could be ameliorated by treatment with a cytokinin-containing seaweed spray.[211] Investigations in other countries similarly examined the variation in leaf alkaloid content according to developmental stage and location on the stem,[212] and a diurnal rhythm has also been reported.[213] Griffin continued to conduct research into enhanced *Duboisia* cultivation and alkaloid analysis into the early 1990s, fostering several doctoral theses concerning *Duboisia*, and published a comprehensive overview of the chemotaxonomy of tropane alkaloids in 2000.[214]

Duboisia research has also been pursued outside Australia. Considerable investigation of *Duboisia* propagation and alkaloid analysis has been conducted in Japan (especially at Nagasaki University),[215] where *Duboisia* species have been cultivated since the early 1960s.[216] Of the 196 papers published on *Duboisia* since 1975 (as listed in the *SciFinder* database), 106 were published by Japanese groups, 47 of them in Japanese journals. Similarly, significant research has been undertaken in India, a major importer of Australian *Duboisia* leaf and where *D. myoporoides* has been cultivated under the aegis of the Central Institute of Medicinal and Aromatic Plants (at Lucknow and Bangalore) since 1980,[217] as well as in Pakistan (around Karachi, since the mid-1980s),[218] although these countries have not yet produced commercial crops.[219] There is, however, some indication of a decline in interest in *Duboisia* research since the mid-1980s as judged by the frequency of published papers (Fig. 4).

Research has also revealed that far from including the single alkaloid assumed by the first investigators of *D. myoporoides*, the plant produces at least twenty tropane alkaloids and six non-tropane alkaloids (Figs 1, 5; Appendix 1). In perhaps the only published study of the alkaloid content of the *D. myoporoides* fruit, the surprising discovery was made that the pyridine alkaloid nornicotine dominated during growth, while the major alkaloids of the mature fruit were tetramethylputrescine and scopolamine.[220] Not all alkaloid species depicted in Figs 1 and 4 are found in all geographical stands of *D. myoporoides*, the chemical constitution varying greatly according to location, both in Australia (as discussed above) and elsewhere.[221] Interest in the non-alkaloid components of *D. myoporoides* has been in comparison quite restricted, although the use of ursolic acid, first isolated from *D. myoporoides* in 1947, for pest control and as a chemoprotective agent has recently been discussed.[222]

But none of these 'other' alkaloids or the aliphatic components have achieved the cultural, scientific or commercial significance of atropine and scopolamine — with perhaps one small exception.

Excursus: Tigloidine

As mentioned above, scopolamine had long been regarded as useful in the management of parkinsonian tremor, and atro-

pine-based and belladonna-based therapies had dominated antiparkinsonian therapy since the nineteenth century. Synthetic anticholinergic agents had largely displaced the older phytotherapeutic approaches in the course of the 1950s, but it remained clear that the ideal antiparkinsonian agent was yet to be identified.[223]

Tigloidine was first isolated from *D. myoporoides* by Barger and colleagues in 1937 as a 'thin colourless syrup'. It is an analogue of atropine, with the tropate moiety replaced by tiglate and tropine by its 3-epimer pseudotropine (in which the 3-substituent is *exo* rather than *endo*).[224] Tigloidine hydrobromide ('Tiglyssin'; T. & H. Smith, Edinburgh) was reported in widely spaced Australian papers to achieve improvements in a small number of parkinsonian, Huntington's disease and spastic paraplegic patients; as predicted by preclinical studies, it reproduced all the desired effects of atropine, but without its side effects.[225] Edward Trautner, a German-born physiologist–biochemist at the University of Melbourne involved in *Duboisia* research since the end of the War, and colleagues (including the psychiatrists Charles Noack and Samuel Gershon) noted the similarities in the structures of atropine analogues and of tigloidine, but remarked that most of the pharmacological effects of atropine analogues appeared to require the esterification of the basic portion of the molecule with an arylalkanoic acid, a feature lacking in tigloidine. Delayed recovery (the phenomenon whereby atropine and similar drugs induce rapid fatigue in repeatedly stimulated muscle), on the other hand, required an unsaturated carboxylic acid attached to the tropine moiety: tigloidine thus produced the effects on muscle that were believed to underlie the benefits of atropine in Parkinson's disease, while lacking its undesirable central vegetative effects. The investigators were also impressed by the fact that only involuntary motor activity was affected by the agent; even at higher doses, voluntary movements were not impaired. Some patients experienced euphoria during treatment with the drug, but there did not appear to be a direct association of this effect with its motor

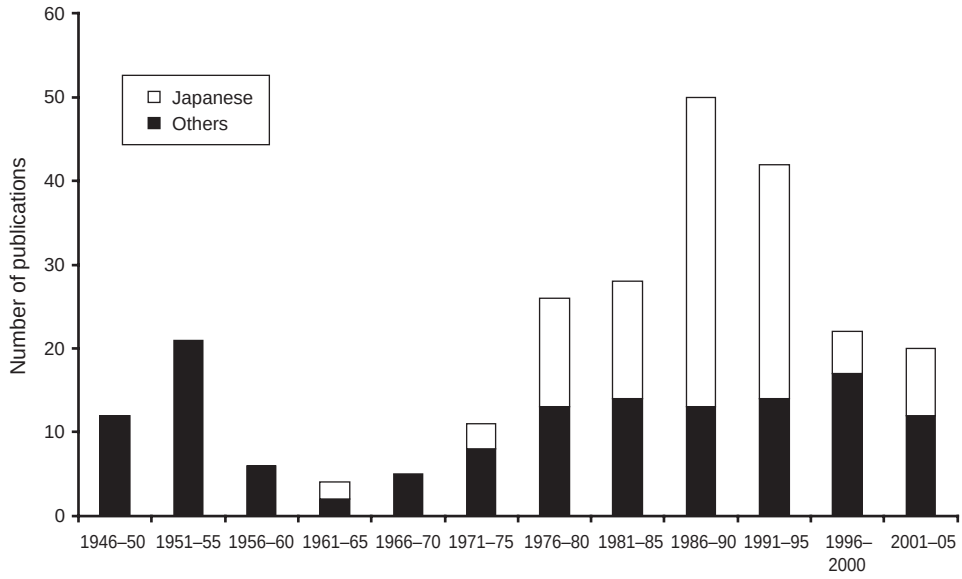


Figure 4. Publications concerning *Duboisia myoporoides* or *Duboisia leichhardtii* since 1975, according to SciFinder databank (available at http://www.cas.org/SCIFINDER/, accessed 30 January 2006).

benefits. This unique pharmacological profile was naturally of great interest, but its excessive cost prohibited extensive use; only 0.5% of the alkaloid content of *D. myoporoides* consists of tigloidine, and even Trautner and Noack conceded that the continuation of clinical trials was thereby precluded.[226]

Current Situation for the *Duboisia* Industry

Australian plantations of *Duboisia* species and hybrids remain the major world sources of scopolamine and atropine (~70% of world supply). Since 1980, all exported *Duboisia* leaf has been derived from cultivated plants. Plantations of *D. myoporoides* and *D. leichhardtii* and of hybrids of the two species (which have the dual advantages of higher tropane and negligible pyridine alkaloid levels) produce leaf with an alkaloid content of up to 5–7% by dry weight, of which about half is scopolamine.[227] The principle producers are 100–150 growers in the Kingaroy area of south-east Queensland, 40% of whose plantations are associated with Boehringer, maintaining a steady and reliable supply of leaf. The Australian 'Boehringer Ingelheim Plantations' cover 1100 hectare and produce up to 1000 tonne leaf annually;[228] according to the Department of Primary Industries, the mean density of 1250 trees per hectare produces between 500 kg in a dry year and 1250 kg leaf in a good season.[229] Although precise total production figures are difficult to locate because the industry is small, competitive and somewhat secretive, Australian Bureau of Statistics data indicate that both leaf exports and their dollar value have been fairly constant for the past decade (for year ended 30 June 2002: 994,678 kg; $6,604,439).[230] Boehringer Ingelheim also maintains *Duboisia* crops at Solana Farm, near Arapongas, Paraná in Brazil, covering 1300 hectares and producing 600 tonne leaf annually.[231]

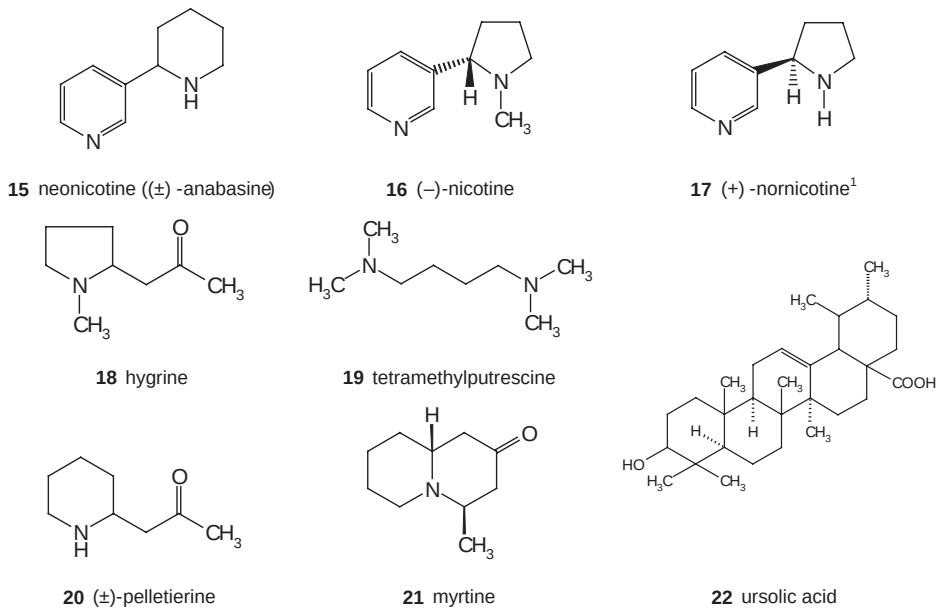


Figure 5. Non-tropane alkaloids identified in *Duboisia myoporoides*, and ursolic acid. 15–17, Nicotinic acid-derived, pyridine alkaloids; 18, ornithine-derived (as are the tropane alkaloids) pyrrolidine alkaloid; 19, tetramethylputrescine; 20, lysine-derived, piperidine alkaloid; 21, quinolidizine alkaloid.

Efforts to optimize *Duboisia* alkaloid synthesis continue unabated and take full advantage of modern plant biotechnology, including plant tissue culture, cell culture and molecular biological techniques, fostering hopes of further advances in tropane alkaloid production. Callus cultures and regenerated shoots have proved to be poor alkaloid sources, but may be useful for the selection of chemically interesting *Duboisia* hybrids. The possibility of producing tropane alkaloids in differentiated root cultures, particularly *Agrobacterium*-genetically transformed hairy root, on the other hand, has been the subject of intense research since the mid-1980s,[232] although the commercial viability of this approach remains to be established; a trial conducted in Spain by Boehringer Ingelheim suggested that regeneration of shoots from such cultures offered no advantage over conventional farming of *D. myoporoides–D. leichhardtii* hybrids.[233]

Contrary to comments in a recent (2001) handbook that 'there is as yet no scopolamine produced on a commercial scale in Australia',[234] two Australian companies are currently active in local alkaloid extraction, namely Alkaloids of Australia (Kingaroy), a small family-owned company founded in 1986 by the Crumpton family and the industrial chemist Greg Bowling,[235] and, to a lesser extent, Phytex Australia (Sydney; founded in 1982 by Reg Smith), the focus of which is the preparation of drug specialties rather than mass production. The major extractors, however, remain Boehringer Ingelheim in Germany and Boehringer Nippon in Japan, and the value-added final products are prepared overseas. For example: the gross value of the *Duboisia* crop (1991–1992) was about $US2 million; the value of extracted alkaloids, however, was estimated at this time to be $US5–15 million, and that of the final product to be $US100–150 million.[236] In addition, biotechnology patents relevant to *Duboisia* are held by Boehringer, increasing the danger of plant material being cultivated outside Australia, resulting in the total loss of control of an essentially native industry.

The reasons for the failure of Australian interests to control the industry are many, but foremost were certainly the lack of co-operation between producers regarding research, development and marketing, and Commonwealth Government indifference to the industry after the Second World War. There was, for instance, a clear lack of initiative with regard to potential joint ventures of local interests with Boehringer (or other overseas firms) in the exploitation of *Duboisia*. On the other hand, the relative lack of an Australian popular tradition in plant-based medicine, particularly with regard to local products — when compared, for example, with Europe, where phytomedicine is not only accepted as a major component of both self-treatment and physician-prescribed therapy, but often explicitly supported by national healthcare systems — as well as the limited tradition in the commercial exploitation of plant natural products (apart from timber) represented daunting barriers to developments in this direction. The loss of control can ultimately be justified in terms of its being compensated by the achievement of a stable market for *Duboisia* leaf. Further, it cannot be overlooked that the power of Boehringer in the international market for formulated products has been a great advantage with respect to both research and marketing, particularly with respect to an industry for which the growth potential was inherently limited. The combination of commercial farming and research and development activities fostered by Boehringer Ingelheim has provided the continuity necessary for commercialization of plantation crops: eight to ten years may elapse, for instance, between identification of a promising new hybrid clone and the first significant harvest. The possibility that Boehringer might have located an alternative scopolamine source — for example, *Datura innoxia* in South America[237] — also

militated against the development of an autonomous local industry.[238]

Duboisia is one of the few Australian native non-timber plants to have been commercially exploited to any significant degree. Nevertheless, the export of raw materials and the import of the processed, value-added product is a scenario all too familiar in Australia. As Grimwade noted in 1954, 'technical successes are delicate plants; no matter how good the gardener, they cannot thrive in an atmosphere of official indifference and neglect.'

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136. Näcke, 'Duboisinum sulfuricum bei geisteskranken Frauen' (n. 110); Rabow, 'Über Duboisinum sulfuricum' (n. 78).
137. Gehe & Co. (October 1896): atropine sulphate (SO_4) 8 s. 2 d. (1 oz); duboisine crystal 7 s. (1 g); duboisine SO_4 1 s. 10d. (1 g); hyoscyamine crystal or SO_4 2 s. (1 g); hyoscine hydrobromate (HBr)/hydroiodate (HI) 3 s. (1 g); scopolamine HBr/HI/hydrochlorate (HCl) 3 s. (1 g). Merck & Co. (August 1896): atropine SO_4 $4.00 (1 oz); duboisine SO_4 10–14¢ (1 g); hyoscyamine SO_4 20–25¢ (1 g); hyoscine crystal or HBr/HI/HCl 32–60¢ (1 g); scopolamine HBr 13–15¢ (1 g). My thanks to Maggie Heran, Director of the Lloyd Library and Museum (Ohio, USA) for supplying me with these figures.
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154. NAA: A9778, B30/2/41 (n. 152).
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165. Rosenblum, 'Developments in Drug Manufacture in Australia' (n. 158).
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171. NAA: A5799/15, 157/1944 (n. 166).
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173. Anonymous, 'The Development of Drug Manufacture in Australia: A Remarkable Wartime Achievement', *Australasian Journal of Pharmacy*, 23 (1942), 765–766.
174. Lauterer, 'Chemical and Physiological Notes' (n. 78).
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Appendix 1. Chronological list of alkaloids identified in *Duboisia myoporoides*

Novel alkaloids identified in *D. leichhardtii*, including scopadonnine (K. Kagei *et al.*, 'Studies on *Duboisia* species. 4. Minor alkaloids in leaves of *Duboisia leichhardtii*', *Yakugaku Zasshi*, 100 [1980], 216–220), calystegines (A. Kato *et al.*, 'Calystegine alkaloids from *Duboisia leichhardtii*', *Phytochemistry*, 45 [1997], 425–429) and dihydroxynortropanes (N. Asano *et al.*, 'Dihydroxynortropane alkaloids from calystegine-producing plants', *Phytochemistry*, 57 [2001], 721–726), have not yet been identified in *D. myoporoides*. Plant parts: fr, fruit; lf, leaf; r, root; rb, root bark; rw, root wood; st, stem

Alkaloid	Year	Plant part	First description in *D. myoporoides*
Tropane alkaloids			
Hyoscyamine	1880	rb, rw, st, lf	A. Ladenburg, 'Über das Duboisin', *Berichte der deutschen chemischen Gesellschaft*, 13 (1880), 257–258
Scopolamine = hyoscine	1887	rb, rw, st, lf, fr	A. Ladenburg, F. Petersen, 'Ueber das Duboisin', *Berichte der deutschen chemischen Gesellschaft*, 20 (1887), 1661
Norhyoscyamine = pseudo-hyoscyamine, solandrine	1892	st, lf	E. Merck, 'Ueber das Pseudohyoscyamin, ein neues Alkaloid aus Duboisia myoporoïdes', *E. Merck, Darmstadt. Bericht*, 6 (1892), 11
Noratropine	1912	st, lf	F.H. Carr, W.C. Reynolds, 'Nor-hyoscyamine and nor-atropine; alkaloids occurring in various solanaceous plants', *Journal of the Chemical Society*, 101 (1912), 946–958
Atropine[A]	1917	rb, st, lf	J.M. Petrie, 'The chemical investigation of some poisonous plants in the natural order Solanaceae. IV. The chemistry of the *Duboisias*', *Proceedings of the Linnean Society of NSW*, 42 (1917), 118–135
Tigloidine = 3β-tigloloxytropane	1937	lf	G. Barger, W.F. Martin, W. Mitchell, 'The minor alkaloids of *Duboisia myoporoides*', *Journal of the Chemical Society* (1937), 1820–1823
Valeroidine		rw, st, lf	
Isoporoidine[B]	1938	lf	G. Barger, W.F. Martin, W. Mitchell, 'The minor alkaloids of *Duboisia myoporoides*. Part II. Poroidine and *iso*Poroidine', *Journal of the Chemical Society* (1938), 1685–1690
Poroidine[B]		lf	
Acetyltropine	1967	lf	J.F. Coulson, W.J. Griffin, 'The alkaloids of *Duboisia myoporoides*. I. Aerial parts', *Planta Medica*, 15 (1967), 459–466. Butropine and valtropine had previously been identified in *D. leichhardtii* (W. Deckers, J. Maier, 'Über zwei neue Alkaloide aus *Duboisia leichhardtii*', *Chemische Berichte*, 86 [1953], 1423–1428; E.I. Rosenblum, 'Alkaloid variation in wild and cultivated *Duboisia leichhardtii* F. Muell.', *Australian Journal of Applied Science*, 5 [1954], 51–62), as had tropine (W.J. Griffin, 'The alkaloids of *Duboisia leichhardtii*', *Australasian Journal of Pharmacy*, 46 [1965], S128–S131); the latter had been identified even earlier in a *D. myoporoides* hybrid (K. Loftus Hills, E.M. Trautner, C. Rodwell, 'A tobacco-Duboisia graft', *Australian Journal of Science*, 9 [1946], 24–25)
Aposcopolamine		rb, rw, st, lf	
Butropine		st, lf	
Norscopolamine		st	
Tigloyltropine = α-tigloyloxytropane		lf	
Tropine[A]		rb, rw, st, lf	
Valtropine		rb, rw, st, lf	
Littorine (phenyl-lactoyltropine)	1989	lf	[C]W.J. Griffin, G.D. Lin, 'The isolation of littorine from a *Duboisia* hybrid', *Naturwissenschaften*, 76 (1989), 582
7β-Hydroxyhyoscyamine	1989	lf	[C]K. Ishimaru, K. Shimomura, '7β-Hydroxyhyoscyamine from *Duboisia myoporoides*-*D. leichhardtii* hybrid and *Hyoscyamus albus*', *Phytochemistry*, 28 (1989), 3507–3509
6β-Hydroxyhyoscyamine (anisodamine)	1991	lf	W. Gritsanapan, W.J. Griffin, 'Alkaloid variation within *Duboisia myoporoides*', *Phytochemistry*, 30 (1991), 2667–2669. Previously isolated from a *Duboisia* hybrid: Griffin, W.J., 'Isolation of 6-hydroxyhyoscyamine from a *Duboisia* hybrid', *Naturwissenschaften*, 62 (1975), 97
Apoatropine	1992	lf	Y.N. Shukla, R.S. Thakur, 'Tropane alkaloids from *Duboisia myoporoides*', *Phytochemistry*, 31 (1992), 4389–4390. Apoatropine previously isolate from a *Duboisia* hybrid: Y. Kitamura, Y. Sugimoto, T. Samejima, K. Hayashida, H. Miura, 'Growth and alkaloid production In *Duboisia myoporoides* and *D. leichhardtii* root cultures', *Chemical & Pharmaceutical Bulletin*, 39 (1991), 1263–1266
Tropine nonanoate		lf	

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Appendix 1. Continued

Alkaloid	Year	Plant part	First description in *D. myoporoides*
Non-tropane alkaloids			
Nicotine	1953	r, lf	K. Loftus Hills, W. Bottomley, P.I. Mortimer, 'Occurrence of
Nornicotine		r, lf, fr	nicotine together with hyoscine in *Duboisia myoporoides* R Br.', *Nature*, 171 (1953), 435–435
Anabasine = neonicotine	1957	r, lf, fr	P.I. Mortimer, S. Wilkinson, 'The occurrence of nicotine,
(Iso)pelletierine[D]		lf	anabasine, and *iso*pelletierine in *Duboisia myoporoides*', *Journal of the Chemical Society* (1957), 3967–3970
Tetramethylputrescine	1968	rw, rb, fr	J.F. Coulson, W.J. Griffin, 'The alkaloids of *Duboisia myoporoides*. II. Roots', *Planta Medica*, 16 (1968), 174–181. Previously identified in *D. leichhardtii*: W.J. Griffin, 'The alkaloids of *Duboisia leichhardtii*: tetramethylputrescine', *Australasian Journal of Pharmacy*, 48 (1967), S21–S22
Myrtine	1989	r	P. Bachmann, L. Witte, F.-C. Czygan, 'The occurrence of β-phenylethylamine derivatives in suspension culture of *D. myoporoides*', *Planta Medica*, 55 (1989), 231
Hygrine	1991	fr	W. Gritsanapan, W.J. Griffin, 'Alkaloid variation within *Duboisia myoporoides*', *Phytochemistry*, 30 (1991), 2667–2669

[A]First reports in which the presence in *D. myoporoides* was mentioned specifically.
[B]Poroidine and isoporoidine constituted the 'base Z' in Barger *et al.* 'The Minor Alkaloids of *Duboisia myoporoides*' (see under 'Tigloidine' in table).
[C]Not yet reported in pure *D. myoporoides*.
[D]The designation isopelletierine is no longer used, as it proved to be identical with pelletierine; Mortimer was the first to correctly elucidate its structure (*Australian Journal of Chemistry*, 39 [1958], 1263–1266).