

Absinthe, epileptic seizures and Valentin Magnan

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ABSTRACT Absinthe is an alcoholic liquor containing extracts from the wormwood plant. It was widely consumed in France in the late nineteenth century. Its production was banned in 1915, partly because it was thought to cause neurological disturbances, including mental changes and epileptic seizures. Modern knowledge of an acceptable content of the convulsant α -thujone in absinthe has allowed the lifting of the production bans, and called into question the experimental work of Valentin Magnan in the 1870s, which formed the scientific background to the campaign against absinthe. An examination of Magnan's published investigations suggests that his science was very adequate by the standards of his time, and that he had shown that an alcohol-soluble component of wormwood did produce lapses of consciousness, myoclonic jerks and tonic-clonic convulsions in animals. Whether that component, presumably thujone, was present at convulsant concentrations in some of the available absintnes of Magnan's time cannot now be known.

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INTRODUCTION

Absinthe is a bitter-tasting, greenish alcoholic liquor. Some of its constituents are, at least nominally, derived from the wormwood plant, *Artemisia absinthium* (see Figure 1). Absinthe was very frequently consumed in Western Europe, especially in France, in the latter part of the nineteenth century and came to achieve a notorious reputation, although alcoholic solutions containing wormwood-derived materials had been in medicinal use since ancient times without causing apparent problems. Wormwood itself was mentioned as a therapeutic agent in the Ebers papyrus^{1a} of the sixteenth century BC and in Pliny's first-century *Natural History*.^{1b} Wine of absinth (*oinos absinthites*) was described in the first-century *Greek Herbal of Dioscorides*. In this work, in the words of Goodyer's English translation of 1655,² the wine was reportedly 'made divers ways' and was:

good for ye stomach, ureticall, good for ye slow of digestion, for ye sick-liver, & ye Nepriticall, and ye Ictericall, for such as want appetite, & ye aggrieved at ye stomach & for ye long continued distension of ye Hypochondria and for inflations, & ye round-wormed, for ye restrained menstrual.

As the word 'absinth' has sometimes been applied to the wormwood plant and the very similar 'absinthe' to the beverage, to avoid confusion in the remainder of this paper 'absinthe' has been used to refer only to the drink and 'wormwood' to the plant, even when it was termed 'absinth' or its full botanical name was used in the original.

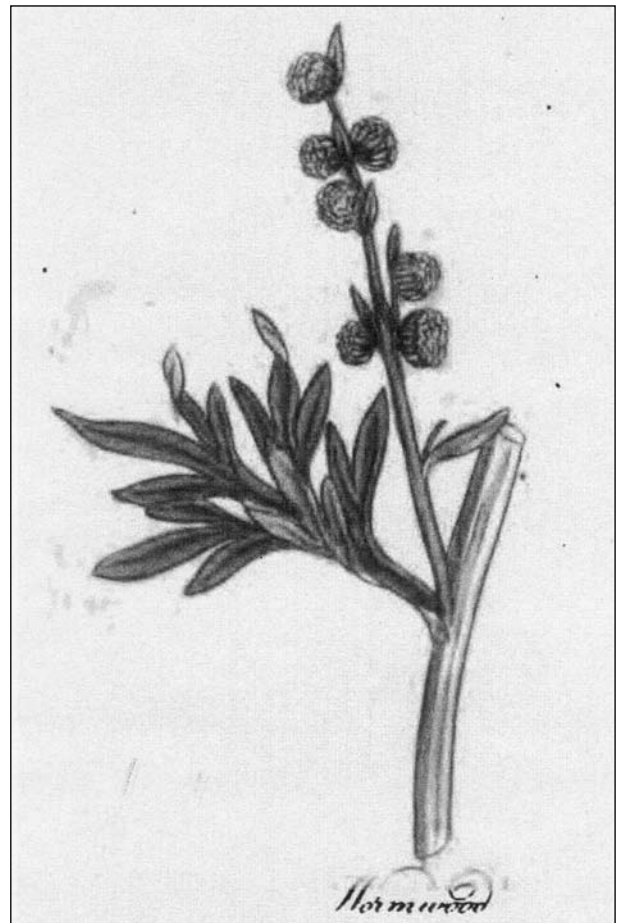


FIGURE 1 Illustration of wormwood from J Hill's *The family herbal* (Bungay: Brightly & Co; 1812).

The absinthe available for human consumption in the past two centuries, with its high concentration of ethyl alcohol (45–75%), was developed from a formula that originated in Switzerland late in the eighteenth century.^{3,4} Classically, the beverage was made by distilling an alcoholic extract of the dried above-ground parts of the wormwood plant. Further quantities of materials obtained from wormwood and various other herbs (most commonly anise and fennel) were then added to a particular fraction of the distillate. The green colour finally obtained was due to extracted chlorophyll.

As the years passed, many modifications of the original method were devised in making marketed absinthes. Various additional herbal materials and dyes were sometimes added to provide a satisfactory colour, as well as certain chemicals to achieve other desirable visual and gustatory properties. The alcohol concentration in different absinthes varied, although it was always high enough to keep any added plant-derived oils in solution. At times, it seems that some commercial absinthes contained no material that originated from wormwood.⁵

By the mid-nineteenth century, absinthe had become a favourite aperitif of the French middle classes. Elaborate rituals were often involved in its preparation preliminary to intake. In brief, before drinking, the strongly alcoholic solution was slowly diluted with water containing dissolved sugar (to counter the bitterness of the absinthe) until the mixture became cloudy as the water-insoluble herbal oils began to separate from solution.

In the wake of the widespread infestation of the French vineyards with *Phylloxera* in 1864, there was a shortage of both wine and grape-derived alcohol. Absinthes then began to be made with cheaper, industrially produced ethyl alcohol. It was soon realised that such absinthe had become the cheapest source of drinkable alcohol generally available in France. As a result, absinthe rapidly became the most popular form of alcoholic beverage drunk by the lower classes. It was also favoured by many French literary and artistic figures of the time, including Charles Baudelaire, Arthur Rimbaud, Emile Zola, Paul Gauguin and Henri de Toulouse-Lautrec, as well as by artists and writers from other countries, such as Edgar Allan Poe and Oscar Wilde. The mental disturbances of Vincent van Gogh have been attributed to his excessive intake of absinthe.⁵

By the end of the nineteenth century, absinthe had come to be regarded as a significant cause of mental illness and epileptic seizures. The existence of a syndrome, absinthism, involving substance dependence, hallucinations, epileptic seizures and mental deterioration, was postulated. As a result, absinthe production was banned in France in 1915, and in various other Western European countries and in the United States between 1905 and 1923. The bans continued until recent times in the European Union and still exist in the US.

With the advent in recent years of sensitive and specific analytical methods, it became possible to investigate the composition of various absinthes and, in particular, to measure their contents of the chemical thujone, which was thought responsible for the alleged neurotoxicity of absinthe. The European Commission in 2003 specified what it considered safe contents of thujone for various strengths of alcoholic beverage.⁶ This knowledge permitted the lifting of the ban on absinthe production in Western European countries.

An awareness of a reputedly safe thujone concentration in alcoholic beverages and the widened commercial availability of absinthe have resurrected the question of whether late nineteenth-century absinthes really possessed any toxicity beyond that attributable to their high alcohol concentrations.^{7,8} Padosch et al.⁴ and Lachenmeier et al.⁹ concluded that, purely on the basis of thujone content, it would seem unlikely that absinthe made according to the original Swiss recipe would have carried any major risk of neurotoxicity. As a consequence of this information, present-day writers^{10,11} have sometimes criticised the scientific work and interpretations of Valentin Magnan, whose laboratory and clinical studies in the 1870s and subsequent advocacy played a significant part in the banning of absinthe production in France nearly a century ago.

In fairness to Magnan, it is now impossible to know whether the actual compositions of the various absinthes that were available in France in his day were as modern-day analytical chemistry suggests they should have been. Consequently, little additional light can be thrown on the justification of Magnan's assessment of the neurotoxic menace of the absinthe of his time. Rather, the present paper explores the adequacy of Magnan's investigational science in relation to the clinical issue of absinthe intake, its neurotoxicity and potential for producing epileptic seizures, and the contributions to the understanding of epileptic seizure mechanisms that emanated from Magnan's investigations.

VALENTIN MAGNAN'S CAREER

Valentin Jacques Joseph Magnan was born at Perpignan, in France, in 1835.^{11,12} He studied medicine at Montpellier and then worked at hospitals in Lyon before competing successfully in 1863 for an internship in Paris at the Bicêtre Hospital under Louis Marcé and at the Salpêtrière Hospital under Jean Pierre Falret. In 1867 he came to the attention of influential figures in Paris when he treated the Prince Imperial, the son of Louis Napoléon. Soon afterwards he was appointed to be in charge of the Admissions Office of the newly opened Sainte-Anne Asylum in Paris. All instances of mental illness that came to the attention of the Paris police were assessed initially at this institution, and their more definitive management was then organised. Magnan occupied this

influential appointment for the remainder of his professional career, retiring in 1912 and dying four years later. Although passed over in 1877 for the newly created Chair in Mental Disease in Paris, Magnan became perhaps the most considerable figure in French psychiatry of his time, and the leader of one of its main schools of thought.

Magnan's professional achievements lay in three main areas. In the late 1860s and the following decade he worked on the clinical consequences of alcohol abuse, in particular of absinthe, and carried out animal experimentation relevant to these matters. He continued to campaign against these abuses throughout the remainder of his life, but from the 1880s his interest expanded into the classification of mental illness.¹² He believed that such illness should be categorised on the basis of its life-long course and took up Bénédict Augustin Morel's idea that was so influential in French psychiatry, viz that such illness was a moral degeneration.

Magnan modified this interpretation, minimised its religious connotations and formed the view that there were two types of degeneracy, one being inherited and the other a chronic delusional insanity. Either type, but particularly the latter, could develop into dementia. Magnan's ideas were not universally accepted in French psychiatric circles.¹³ The subsequent controversies in the national professional community resulted in a considerable delay to its acceptance of Emil Kraepelin's subdivision of psychotic illness (apart from general paralysis of the insane) into manic-depressive disease and dementia praecox (later called schizophrenia).

Towards the end of his professional activities and in his retirement, Magnan was before his time in advocating less enforced restriction of the mentally ill and the abandoning of straitjackets and other forms of restraint, and employing an open-ward policy with the early return of the sufferer into the community.

Magnan's research relating to absinthe

Magnan was not the first to note a possible association between excessive absinthe intake and the occurrence of epileptic seizures and mental disturbance. He himself gave credit for this to Auguste Motet at the Bicêtre, who in 1859 described instances of the association in a doctoral thesis submitted to the University of Paris.¹⁴ Marcé, whom Magnan referred to as his 'master' at the Bicêtre, had also reported the matter in a paper published in 1864.¹⁵ Marcé claimed absinthe possessed a special action beyond that of its alcohol content because, unlike simple alcohol intoxication, it rapidly produced stupor, hebetude (dullness of mind), terrifying hallucinations and intellectual enfeeblement. He found that giving dogs 2–3 g of wormwood essence produced trembling, mental dullness and stupor, and led to the appearances of profound terror. Doses of 3–8 g of wormwood essence

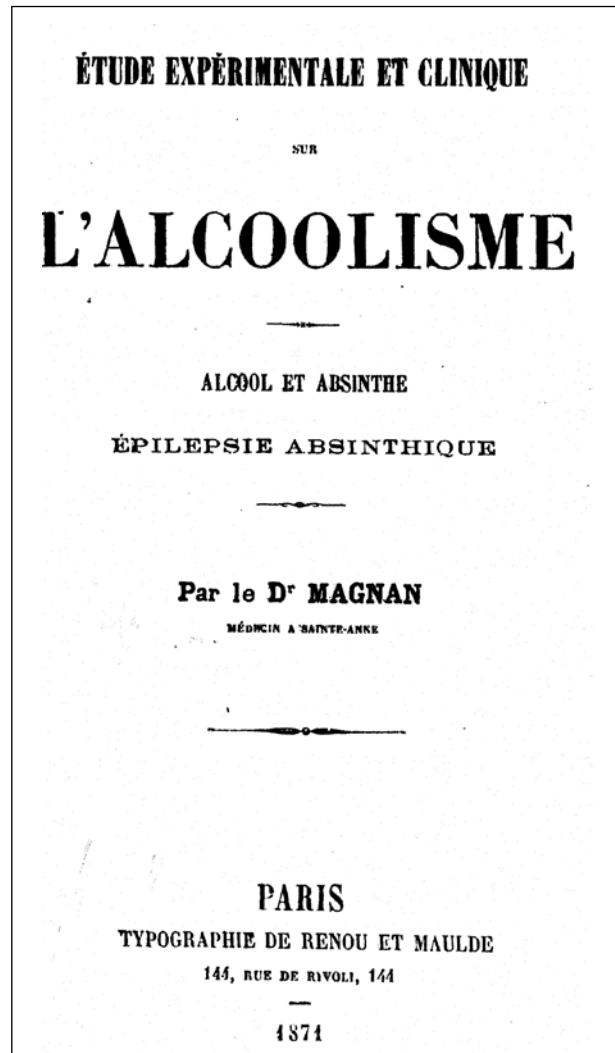


FIGURE 2 The title page of Valentin Magnan's 1871 monograph on alcoholism and absinthic epilepsy.

caused epileptiform clonic convulsions, incontinence, stertorous respirations and death.

An association between absinthe and convulsing had also been noted by the great French clinician Armand Trousseau.¹⁶ Trousseau described the case of Mr W., aged 38 in 1861, who when aged 25 'had well-marked epileptic fits, probably due to his excessive use of absinthe, for the fits disappeared after two years, and on his giving up drinking absinthe'. The time factors suggest that somewhere between 1850 and 1861 Trousseau had recognised the association between absinthe and seizures, so that he probably had priority over the Bicêtre alienists in observing the association.

Magnan's own work in the area began in 1864,¹⁷ while he was collaborating with Marcé. There were major publications from Magnan in 1869,¹⁸ a short monograph, *Étude expérimentale et clinique sur l'alcoolisme*¹⁹ (Figure 2), and a long paper²⁰ in 1871 and a major monograph, *De l'alcoolisme, de diverses formes de délire alcoolique et*

de leur traitement, in 1874,²¹ soon afterwards translated into English by Greenfield. Magnan also summarised his work in an English language paper which appeared in *The Lancet* in 1874.²² He reported some of his earlier investigations on more than one occasion in his later publications. It seems unlikely that all of his experimental observations were published under his name since, while he mentioned that he had worked on dogs, cats, rabbits, guinea pigs and various birds,¹⁸ nearly all his experimental details traced in print refer to studies carried out in dogs. However, Robert Amory, who had earlier collaborated with Magnan, published some of his own original data, some joint work with Magnan including studies in non-canine species and some of Magnan's earlier work in North American medical literature.²³

In 1864, Magnan described a 30-year-old male who on three separate occasions experienced *vertiges* (a term then used for brief non-convulsive epileptic seizures with impaired consciousness) and convulsive epileptic seizures at times when he was drinking absinthe, but never when he abstained.¹⁷ Magnan stated that he had encountered further instances of the association. From the experimental design of his laboratory studies, it seems that Magnan was aware of the need to distinguish between the roles of alcohol and of other absinthe constituents in provoking epileptic seizures and other manifestations of neurotoxicity.¹⁸ He took the precaution of always using wormwood oil from the same reputable manufacturer, and reported that alcoholic extracts of the following components of contemporary absinthes, given individually to dogs, even in large intragastric doses, did not evoke seizures: essences of anise (aniseed, *Pimpinella anisum*), badian (star-anise, *Illicium anisatum*) and angélique (*Angelica archangelica*); sweet flag (*Calamus aromaticus*), origen (oregano, *Origanum vulgare*), menthe (mint, *Lamiaceae* species) and mélisse (*Melissa officinalis*).¹⁹ Nor did alcohol itself.

In contrast, 5 g of wormwood essence caused tonic-clonic seizures and 'hallucinations' (i.e. behaviour as if the animal was hallucinating), whereas lower doses caused *vertiges* and brief *secousses* (i.e. myoclonic jerks or jolts) involving the head and anterior parts of the body. On the other hand, chronic daily alcohol intake in increasing quantities in a dog produced widespread tremblings, paraplegia (i.e. hind limb weakness – alcoholic peripheral neuropathy was not then widely known) and coma, all increasing after each intake of alcohol. The combination of alcohol and essence of wormwood in another dog resulted in tremblings, alcoholic paraplegia and epileptiform seizures.

By present-day standards, the numbers of dogs Magnan studied would appear inadequate to permit well-based conclusions, although it is not clear whether Magnan had additional supporting data and had simply published accounts of representative experiments. If the latter was

the case, Magnan had provided reasonable evidence that the components of wormwood essence that should have been present in absinthe could have conferred convulsant and other neurotoxic properties on the beverage. His studies also suggested that the pattern of absinthe-related epileptic events to be expected in humans would involve lapses in consciousness (absences, petit mal), myoclonic jerks and generalised tonic-clonic epileptic seizures, i.e. phenomena resembling those of a primary generalised epilepsy of juvenile myoclonic type.

Was this the pattern of the reported seizures associated with human absinthe abuse? Magnan described only the presence of generalised tonic-clonic seizures in several of his human cases. However, in Case XI in Greenfield's translation of Magnan,²¹ the continued intake of absinthe was associated with 'sudden faintings', increasing 'absences' or faints and epileptic seizures. In Case XII, a 42-year-old male who drank absinthe and brandy to excess over some years experienced attacks of 'vertigo' (probably a translation into English of *vertiges*, i.e. minor non-convulsive epileptic seizures), muscle twitchings and then fits. Unless these two of the five human cases reported in Magnan's monograph were instances of causally unrelated primary generalised epilepsy, it seems that absinthe in humans provoked epileptic phenomena of a pattern similar to that which occurred in animals given essence of wormwood. At the time of Magnan's studies, Herpin²⁴ had very recently published the first clear description of what was to become known as the juvenile myoclonic type of primary generalised epilepsy. Therefore Magnan may not have appreciated the importance of the lapses and jerkings that he saw in his patient.

Magnan carried out additional work on epileptic seizures provoked by wormwood extract that was not directly relevant to the absinthe-epilepsy question. For instance, in two pigeons he showed that seizures induced by wormwood essence continued after the cerebral hemispheres had been removed surgically.¹⁹ In a dog kept alive by artificial respiration after its neuraxis had been severed at the cervico-medullary junction, he reported that intravenous wormwood essence caused jerking in the upper part of the animal's body, followed by clonic and then generalised convulsing as the wormwood dose was increased. In 1873 he used an ophthalmoscope to look for retinal vessel changes during wormwood-induced seizures in a dog, and in another animal made a trepan hole in the skull to inspect the superficial cerebral arteries during wormwood-induced seizures.²⁰

Presumably Magnan was seeking evidence of the cerebral circulatory alterations that were at the time believed to underlie epileptogenesis, although he seemed to leave it to his readers to deduce the rationales of his experiments, and to interpret them. Some of Magnan's observations had pharmacokinetic implications, which he again did not make explicit. In 1871 he reported that if

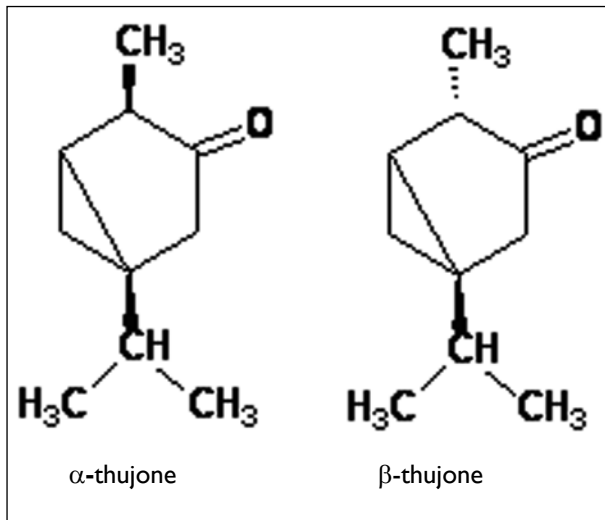


FIGURE 3 Structural formulae of thujone enantiomers.

essence of wormwood was given to a dog together with alcohol, the expected convulsion was deferred for several hours, even though the smell of absinthe appeared rapidly on the animal's breath.¹⁹ Did the alcohol delay the absorption of the convulsant agent in absinthe or slow its entry into the brain? Magnan provided an answer when a second dog was given alcohol by mouth. In this animal, subsequent intravenous essence of wormwood produced convulsing at the expected time. Therefore alcohol probably delayed the absorption of the convulsant component present in wormwood essence.

THE NEUROTOXIC AGENT IN WORMWOOD

Magnan's seemingly well-designed investigations made it clear that if absinthe possessed convulsant and other forms of neurotoxic activity, that activity probably resided in its wormwood-derived components. With advances in analytical chemistry it has been shown that wormwood oil contains thujone, a known convulsant, and that the bitter taste of wormwood derives at least in part from the content of absinthin.⁹ Other terpene lactones are also present. Thujone exists in two stereoisomeric forms (Figure 3), both of which possess convulsant properties. Some 70–90% of the total thujone in wormwood oil is in the form of the β -enantiomer,⁵ but the main biological activity resides in the α -enantiomer.²⁵

α -Thujone is a GABA_A receptor non-competitive antagonist.²⁵ Because its molecular structure resembles that of part of the cannabinoid molecule, it was at one time suggested that a cannabinoid-type action might be responsible for the hallucinatory and other psychological effects claimed for absinthe.²⁶ More recent evidence does not support this interpretation.²⁷ Thujone induces cytochrome P₄₅₀ activity,²⁵ and is porphyrinogenic.²⁸ Because of this latter effect it was suggested that thujone in absinthe may have caused Vincent van Gogh's hallucinations since he also happened to suffer from unrecognised porphyria.²⁸

Other GABA_A receptor antagonists such as picrotoxinin and pentylentetrazole (Metrazole)²⁹ cause epileptic seizures in experimental animals and in humans, and the induced seizure pattern resembles that of a primary generalised epilepsy, with its interruptions of consciousness, multiple myoclonic jerks and, at higher dosages, generalised tonic-clonic convulsing. For a time pentylentetrazole seizures were considered a model for human absence epilepsy, although the seizures produced resembled myoclonic jerks more closely than absence ones. It is also known that the oxazolidinedione family of drugs, effective in humans against petit mal absence seizures, prevents thujone-induced seizures in animals.³⁰

Taken together, these facts make it probable that α -thujone in the wormwood-derived component of absinthe was responsible for the association between absinthe intake and epileptic seizures that was noticed by Magnan and his contemporaries. While safe concentrations for thujone in alcoholic beverages have now been determined, and recent studies have shown that present-day absinthes prepared according to the original Swiss recipe should not have had dangerous thujone concentrations, it remains possible that some of the absinthes drunk by Magnan's patients may have had higher thujone concentrations. It is also possible that some of Magnan's patients may have had a genetic predisposition to juvenile myoclonic epilepsy, even though they had no past history of clinical seizures. Such persons might be expected to be unusually vulnerable to the epileptogenic consequences of thujone-induced GABA_A receptor blockade.

DISCUSSION

Modern scientific evidence lends some support to the belief of Magnan and some of his Parisian contemporaries that the absinthe of their time possessed the capacity to cause convulsing and other neurotoxic manifestations. Whether its convulsant principle (α -thujone), as distinct from alcohol itself, explained the reported hallucinatory and other psychological effects of excess absinthe intake is less clear. However, there can be little doubt that Magnan²² was being far-sighted when, in *The Lancet*, he wrote that the 'essence of absinthe is a valuable agent for the study of the mechanism of epilepsy.'

Magnan himself used absinthe for this purpose, as described above, and it was employed by other investigators in the late nineteenth century to provoke epileptic seizures in experimental animals and then to study the effects of various cerebral manipulations on the induced seizure phenomena.^{31–35} In the early decades of the twentieth century, Howard Florey³⁶ used it in his investigations on the cerebral circulation carried out in Charles Sherrington's laboratory in Oxford.

Wormwood, as suggested by its name, has been a remedy for intestinal worms since ancient times, although herbals such as those of Dioscorides² and Culpeper³⁷ were not particularly enthusiastic concerning its efficacy. At least from the Middle Ages onwards, intestinal worms were commonly regarded as a cause of epileptic seizures, particularly in children (for example by Bernard of Gordon,³⁸ early in the fourteenth century). Although some nineteenth-century authors were more sceptical,^{39,40} the great neurological figure Sir William Gowers held as late as 1881 that:

Acute convulsions frequently result from the irritation of various forms of intestinal worms in children and sometimes in adults. Usually, however, they cease when the worms are expelled.⁴¹

Because of the generations-old popular perception that there was a relationship between intestinal worms and convulsions in children and the continuing medical endorsement of this idea, it seems possible that the use of wormwood (with its content of convulsant thujone) to treat intestinal worms when their presence was recognised may have sometimes contributed to the occurrence of the convulsions it was intended to prevent.

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