Original article

History of cannabis and the endocannabinoid system

Marc-Antoine Crocq, MD

This article retraces the story of cannabis from the earliest contacts of humans with the plant to its subsequent global expansion, its medicinal uses, and the discovery of the endocannabinoid system in the 20th century. Cannabis was attested to around 12 000 years ago near the Altai Mountains in Central Asia, and since then, cannabis seeds have accompanied the migration of nomadic peoples. Records of the medicinal use of cannabis appear before the Common Era in China, Egypt, and Greece (Herodotus), and later in the Roman empire (Pliny the Elder, Dioscorides, Galen). In the 19th century, orientalists like Silvestre de Sacy, and Western physicians coming into contact with Muslim and Indian cultures, like O'Shaughnessy and Moreau de Tours, introduced the medicinal use of cannabis into Europe. The structure of the main psychoactive phytocannabinoid, tetrahydrocannabinol (THC), was determined in Israel by Mechoulam and Gaoni in 1964. This discovery opened the gate for many of the subsequent developments in the field of endocannabinoid system (ECS) research. The advances in the scientific knowledge of the ECS place the debate on cannabis liberalization in a new context.

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From the earliest dawn of history

Near the Flaming Mountains, a popular tourist spot in the Xinjiang-Uighur autonomous region of China, a middle-aged European-looking man was found with a large cache of cannabis. Further analysis revealed that the man carried almost 800 g of cultivated cannabis with a high Δ^9-tetrahydrocannabinol (THC) content. Contrary to a first impression, this is not a sensational news item about an adventurous tourist facing a prison sentence far away from home, but a scholarly archeological report about the excavation of the grave of a 45-year old male of high social status, probably a shaman, buried around 750 BC.[1] The tomb was associated with the Tocharian culture, a nomadic population speaking a now extinct Indo-European language, depicted as blue-eyed and fair-haired in ancient Chinese records. The botanical and phytochemical analyses indicated that the cannabis was not merely gathered from wild plants, but instead cultivated from strains of cannabis selected by humans based on their potent THC content. Male cannabis plant parts had been removed, as these are pharmacologically less psychoactive. Russo et al concluded that the cannabis was cultivated for its psychoactive properties, rather than only as fiber for clothing or as food. This story illustrates the long-standing link between human beings and cannabis as a psychotropic drug.

Paleobotanical studies attest that cannabis was already present about 11 700 years ago in Central Asia near the Altai Mountains.[2] South-East Asia has also been proposed as an alternative region for the primary domestication of cannabis.[3] Cannabis provided fibers for ropes and nets, food, and seeds for oil. Our ancestors would have chanced upon the euphoriant properties of heated cannabis and would have easily identified the resin produced by the distinctive female plants.

Author affiliations: Maison des Adolescents, Mulhouse, France; CAMUHA, University of Upper Alsace, Mulhouse, France. **Address for correspondence:** Marc-Antoine Crocq, MD, Psychiatrist, Maison des Adolescents, 8 rue des Pins, 68200 Mulhouse, France (email: marcantoinecrocq@gmail.com)

In this plausible scenario,[4] humans moved from gathering to cultivating cannabis and then started selecting strains either for fibers or for THC content. Some 12 000 years ago, after the last glacial period, cannabis seeds followed the migration of nomadic peoples and commercial exchanges. This joint migration is an example of a mutually beneficial symbiosis, in which humans and a plant contributed to each other's propagation over the planet. We established a similar evolutionary symbiosis with an animal species, the canids, which also helped us to colonize the planet.

The dispersal of cannabis over Eurasia from a central point is reflected by the fact that the plant is designated by related words in most languages of this huge landmass.[5] English *hemp* and German *Hanf* are etymologically cognate with Greek *κάνναβις*, Latin *cannăbis*, Italian *canapa*, and Russian *konoplja*. Even non-Indo-European languages use related words, eg, *qunnab* (قُنَّب) in Arabic, a Semitic language, *kendir* in Turkish, and *kanap'is* (კანაფის) in Georgian, a Caucasian language.

Cannabis naturally belongs to the class of substances such as tobacco, alcohol, and caffeine, which are used regularly by all humanity

Reflecting the long association of cannabis and humans, some myths in India have cannabis emerge, as a divine ingredient, in the earliest stages of cosmogony, known as the churning of the ocean.[6] The god Shiva supposedly favored cannabis, which had a religious role as an agent for mystic inspiration. Under names such as *Vijaya*, cannabis has been used for thousands of years in ayurvedic medicine to reduce pain, nausea, and anxiety, improve appetite and sleep, relax muscles, and produce a feeling of euphoria.

The global dissemination of cannabis came to a finale when the plant reached Africa, and ultimately America. Spain introduced the cultivation of hemp in central Chile, in Quillota near Valparaíso, within the first decade after the *Conquista*.[7] Louis Hébert, an apothecary with a practice in Paris, is credited as being the first colonist to grow hemp in 1606 in Acadia (today, Nova Scotia).

Classical records of the medicinal and psychoactive properties of cannabis

China can boast some of the earliest records of the medicinal use of cannabis. The discovery of the curative virtues of plants is attributed to Shén Nóng (神农), a mythical emperor whose name means the Divine Farmer (c 2000 BC). Because of him, it has been claimed that the discovery of medicinal cannabis dates back to two millennia BC. However, this is probably exaggerated since the compendium (Jīng, 经) of 365 medical herbs (BěnCǎo, 本草) ascribed to Shén Nóng was written much later, during the Han dynasty (221 BC-AD 220). The common name for hemp and cannabis in China is Má (麻), and this character can appear in word compositions meaning numbness or anesthesia. This character has the same meaning and usage in Japanese. Huà Tuó (华佗), a Chinese surgeon of the Han dynasty, is said to have performed surgery under general anesthesia using a mixture of wine and herbal extracts, which might have contained cannabis, although the exact formula for this potion was not passed on.

The topical application of cannabis for inflammation is mentioned in the Ebers papyrus, written in Egypt in about 1500 BC. The medicinal use of cannabis has been reported on Assyrian clay tablets. According to Scurlock and Andersen, cannabis, called *azallû* in Akkadian,[8] was probably used as a medicine, apparently for depression.

A classical but ambiguous mention is found in Homer's Odyssey (Book IV),[9,10] around the late 7th or early 8th century BC. Zeus' daughter, Helen, served wine mixed with a drug called nēpenthés (νηπενθές) that quiets all pain and strife and brings forgetfulness of every ill. Helen served this mixture to Greek soldiers who had painful reminiscences of their comrades slain during the Trojan war, triggered by Telemachus' visit—a case of posttraumatic stress disorder. "Nē–Penthés" literally means "No–Grief." Homer's text tells us that this medication comes from Egypt; it might have been cannabis or opium.

Herodotus (c. 484-c. 425 BC) describes how Scythians, after a King's burial, prepare small chambers that are hermetically closed with woolen blankets laid on three posts sloping toward each other.[11] The participants crawl under the blankets and throw hemp seeds (κάνναβις) on red hot stones and are "delighted" (ἀγάμενοι) by the fragrant smoke. Herodotus

remarks that hemp either grows spontaneously or is sown and cultivated by the Scythians.

In the Roman Empire, the medical use of cannabis was mentioned by Pliny the Elder, Dioscorides, and Galen. Only the latter discussed the psychoactive effects. The *Naturalis Historia* by Pliny the Elder (c AD 23-79), the oldest extant encyclopedia from the Graeco-Roman world, is an exhaustive compilation of the knowledge available at the time.[12,13] In Book 19, the author described the cultivation of hemp for making ropes and nets. In Book 20, Pliny discussed the medicinal uses of cannabis, differentiating cultivated cannabis and a wild variety growing in forests (probably, *Althaea cannabina*, a different plant). Pliny indicated antalgic and anti-inflammatory properties: a decoction of the roots in water relieves arthritis and cures gout and similar maladies (*radix articulos contractos emollit in aqua cocta, item podagras et similes impetus*). Pliny did not mention the intoxicating or euphoriant properties. The Greek physician Dioscorides (c. AD 40-90) also confirmed, in his pharmacopeia, "*De Materia Medica*," that applications made with the boiled root of cannabis could lessen inflammation. Claudius Galen (AD 129-199/217) wrote that it was customary in Italy to serve small cakes containing marijuana for dessert. As cited by Brunner,[14] Galen remarked that the seeds create a feeling of warmth, and if consumed in large amounts, affect the head by emitting a warm and toxic vapor.

West-Eastern Divan

Goethe's *West-östlicher Divan* (1814-1819), a collection of poems inspired by the Persian poet Hafez, initiated an age of fruitful exchange between Orient and Occident, between Christian and Muslim cultures. Europe rediscovered the medicinal and psychoactive properties of cannabis through the translation of Arabic books and manuscripts by scholars like Sylvestre de Sacy, followed by the scientific observations of physicians in the age of European colonial adventures, such as O'Shaughnessy in India and Jacques-Joseph Moreau de Tours in the Middle East.[15,16]

Goethe's *West-östlicher Divan* concludes with a dedication to Silvestre de Sacy (Paris, 1758-1838), the most renowned orientalist of his times, who compiled a bilingual "chrestomathy" from choice passages of Arabic authors of various epochs.[17] Subsequent authors, including O'Shaughnessy, have abundantly cited Sacy's chapter devoted to cannabis (*qunnab* or *qinnab*, or also *kaff*), including the following facts and anecdotes. Haydar (حيدر), a devout shaikh who died in Khorasan in AD 1221, is traditionally credited with serendipitously discovering the exhilarating properties of cannabis, and with sharing this knowledge with the numerous "fakirs" who congregated around him. Ibn al-Bayṭār (AD 1197-1248), the author of a renowned pharmacopeia in Andalusia, *Compendium on Simple Medicaments and Foods*, mentioned a variety of cannabis called *Qinnab hindī* (*Cannabis indica*) that he has seen nowhere else than in Egypt, where it was cultivated in gardens. This comment prefigured O'Shaughnessy's report that oriental strains of cannabis have a much higher content of psychoactive substances. In a fairytale atmosphere of *One Thousand and One Nights*, Sacy tells us that a place called *al-Junayna* (the small garden), in the district of Cairo anciently called *Ṭabbāla* (الطبّالة) (ie, the Drummer-Girl, or *la Timbalière*), was known for the sale of powerfully inebriating hashish. When used in excess, hashish induced a kind of dementia (*ru'ūna*, الرُّعُونة) and ultimately agitated psychoses (*zhnūn*, الجنون), corresponding to the apathy and psychoses later reported by Moreau de Tours. Periods of tolerance already alternated visibly with periods of repression; for example, in 1378, an emir decided that the teeth of those who consumed hashish would be extracted.

William Brooke O'Shaughnessy (1809 Limerick, Ireland-1889 England) studied medicine at the University of Edinburgh and moved to Calcutta, where he published the results of his observations on cannabis in 1839.[18] He noted that the intoxicating effect of cannabis was then unknown in Europe, except a few youths experimenting with "hasheesh" in Marseilles (Napoleon's soldiers brought back cannabis from the Egypt campaign). O'Shaughnessy noted that the effects of cannabis depended on a "resinous secretion" that seemed absent in European hemp, likely because of differences of climate since the European and South-Asian plants looked identical. He described various preparations traditional in India, including Gunjah, Bang, and Majoon—a green buttery electuary, obtained by boiling in fat and adding sugar, whose name derives from the Arabic participle Ma'jūn (kneaded معجون).

Jacques-Joseph Moreau de Tours, a disciple of Esquirol, traveled through the Middle East between 1836 and 1840, accompanying one of his mentor's patients. Moreau quoted the report of Louis Aubert-Roche on the use of hashish to

treat the plague in Egypt.[19] He experimented with cannabis upon himself, using a preparation called *dawamesk*,[20] made of cannabis leaves and flowers, boiled in a liquid mixed with butter, and subsequently flavored with rose, jasmine, or honey to produce an electuary very similar to O'Shaughnessy's majoon. He also shared dawamesk within a circle of Parisian poets and novelists, including Théophile Gautier.

Moreau noticed that hashish produced pure bliss, but also disorganization of ideas and temporal distortions. He hoped that studying the effects of cannabis on the mind would help him to elucidate the mechanisms of madness and delusions. Moreau wrote about the psychoses and abulia induced by cannabis.

The first Golden Age of medical cannabis

Cannabis became persona grata in Western medicine in the late 19th, early 20th century. Queen Victoria took cannabis for painful menses, and Empress Elisabeth (Sissi) of Austria took it for cough, and possibly also to stimulate the appetite. Sissi was generally wary of medicines and appreciated that cannabis was a natural remedy.[21]

J. Russel Reynolds, a very influential British physician, was appointed in 1878 as physician-in-ordinary to Queen Victoria's household. In 1890, he summarized more than 30 years' experience with cannabis in the *Lancet*.[22] A major obstacle to the use of cannabis was the fact that the active ingredient had not yet been isolated—THC would be identified only in 1964. Therefore, plant extracts could not be made uniform, because "the hemp grown during different seasons, and in different places, varies in the amount that it contains of the therapeutic agent." The toxicity due to overdosing was made all the more unpredictable by the idiosyncratic sensitivity of the patient. Therefore, Reynolds tried to always obtain cannabis from the same source to prepare a "tincture." The dose, taken in drops on a small piece of sugar or bread, would be increased cautiously. The author found cannabis a most useful drug in a variety of painful illnesses (facial neuralgia, migraine, dysmenorrhea, and "numbness and other paresthesiae so common in the limbs of gouty people" [an indication already mentioned by Pliny the Elder]). Reynolds' indications agree with modern studies of medicinal cannabis registries, which show that pain syndromes account for 42.4% of cases.[23] Reynolds mentioned a pediatric use of cannabis that we would refrain from today: teething problems.

In several medical indications, cannabis was displaced by the discovery of other sedative and analgesic drugs such as aspirin. Throughout the 20th century, a series of obstacles restricted the use of cannabis, particularly in the United States. These successive measures were the Marihuana Tax Act in 1937; the removal of cannabis from the American pharmacopeia a few years later; and the 1961 United Nations Single Convention on Narcotic Drugs that placed cannabis under the strictest control regime (Schedule IV) along with heroin. The Golden Age of cannabis came to a definite end in 1970 when it was declared a Schedule 1 drug in the USA, and research into the effects of cannabis was practically made impossible. Psychiatrists had additional reasons to be wary of cannabis when a 15-year follow-up in a cohort of 45 570 Swedish conscripts established that cannabis is an independent risk factor for schizophrenia.[24] However, an alternative explanation of the association between cannabis use and schizophrenia might be that pathology of the cannabinoid system in schizophrenia patients is associated with both increased rates of cannabis use and increased risk for schizophrenia, without cannabis being a causal factor for schizophrenia.[25]

The discovery of the endocannabinoid system, and the renewed debate on cannabis liberalization

More than 100 cannabinoids have been isolated from cannabis; the two significant compounds are cannabidiol (CBD) and Δ^9-THC. CBD was first isolated from marijuana in 1940, and its structure was reported in 1963.[26] However, since CBD was not psychoactive, it was neglected and eclipsed by THC. The structure of the main psychoactive phytocannabinoid, THC, was determined in Israel by Mechoulam and Gaoni in 1964.[27,28] Raphael Mechoulam had survived the Holocaust as a child in Bulgaria and emigrated to Israel, where he worked at the Weizmann Institute. He managed to obtain 5 kg of seized cannabis from the police, separated several compounds on a column, and identified one of these compounds as psychoactive by testing it on monkeys.[29] Afterward, he further characterized that compound by feeding it with cake to healthy volunteers. He thereby observed a variety of psychological reactions (laughing, panic attacks, openness to discussion) according to the subjects' personalities. Mechoulam's seminal discovery gave the impetus for the exploration of a novel receptor system, the endocannabinoid system (ECS). Subsequently, Devane et al characterized a

first cannabinoid receptor (CB_1R) in rat and human brains.[30] Only 4 years later, the same author isolated the first endocannabinoid, arachidonoylethanolamide (AEA).[31] AEA was also termed anandamide by reference to the Sanskrit word ānanda (आनन्द), which means bliss, happiness, or pleasure, and is a good description of what the Scythians experienced when inhaling cannabis fumes in Herodotus' excerpt quoted earlier. The long association of humans with cannabis made sense now that it was shown that our brain produced its own cannabinoid, although anandamide is entirely different from cannabis by its chemical class.

Today, the ECS is understood as comprising a few known endocannabinoids (principally, AEA and 2-arachidonoylglycerol [2-AG]), and the two primary cannabinoid receptors (CB_1R, present mainly in the central nervous system, and also in digestive organs, and CB_2R, implicated in the regulation of immunity and inflammation).[32] A singularity of the ECS is retrograde signaling, ie, the signaling initiates in postsynaptic neurons and acts upon presynaptic terminals. AEA and 2-AG are produced in the postsynaptic neuron and released into the synaptic space, then travel in a retrograde direction to the presynaptic terminal to interact with CB_1Rs, which leads to a decrease in neurotransmitter release by the presynaptic neuron.[33] The articles by Di Marzo, by Maldonado et al, and by Morrison and Murray, in this issue of *Dialogues in Clinical Neuroscience (DCNS),* reflect the extraordinary expansion of knowledge about the ECS in the last few years. The ECS emerges as a complex and widespread brain signaling system that plays a role in affective and cognitive functions, and psychotic disorders, and might be the target for the act of various therapeutic compounds. The elucidation of the ECS also sheds light on the human fascination for cannabis, which appears to be the only plant that produces a potent phytocannabinoid activator of the CB_1R.[34]

The debate about the relaxation of cannabis prohibition, or even its legalization, had resurfaced in the 1960s. It was carried in Western societies by a generation that came of age after the deprivations of WWII. It culminated with the hippie philosophy on a background of opposition to the Vietnam War. The tremendous advances in the scientific exploration of the ECS place this continuing debate in a new context. In this issue of *DCNS*, Hall and Marcu discuss the problems associated with legalizing cannabis or allowing its recreational or medicinal use. These decisions should be in accord with scientific evidence. The conclusion of the 2017 report from the US National Academy of Medicine on "The Health Effects of Cannabis and Cannabinoids—The Current State of Evidence and Recommendations for Research" confirmed the limitation of scientific knowledge.[35] The National Academy of Medicine report stated that conclusive or substantial evidence that cannabis or cannabinoids are effective is limited to only three domains. The recognized therapeutic uses were as follows: (i) alleviation of chronic pain in adults (cannabis); (ii) as antiemetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids); and (iii) the improvement in patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids). At a time of cannabis liberalization, essential unsolved questions persist. For instance, we know little about the psychotomimetic effect of THC, even in persons without a history of mental disorders. Also, contrary to earlier expectations, the protective effect of CBD in association with THC is not proven.[36]

Although considered a congener of heroin by the 1961 UN Single Convention, cannabis naturally belongs to the class of substances such as tobacco, alcohol, and caffeine, which are used regularly by all humanity. It might have less somatic toxicity than alcohol and tobacco. A risk of marijuana is the induction of psychosis or cognitive deficits when consumed during the neurodevelopmental period. Mechoulam's milestone discovery that Δ^9-THC is the primary psychoactive principle, and the ensuing elucidation of the ECS, opened the gate for a new era in cannabis history. ■

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