

Chapter 1

THE PHARMACOHISTORY OF *CANNABIS SATIVA*

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I. INTRODUCTION

In his monumental *Handbuch der Pharmacognosie* Tschirch¹ devotes more than 500 pages to "Pharmakohistoria". This picturesque term which describes a somewhat neglected corner of knowledge deserves resurrection; hence the title of this chapter.

Cannabis sativa L. was one of the first plants to be used by man for fiber, food, medicine, and in social and religious rituals.² In the present survey I shall try to emphasize the therapeutic aspects. However, the distinction between use in religious or social ceremonies and medical use, in particular in ancient times, was blurred. A complete separation of these aspects may be misleading and is not attempted.

Abel has published a fascinating survey of the historical aspects of cannabis use,³ which is the most complete and competent review to date. Additional historical material overlapping to a certain extent with that in Abel's review and the present one can be found in the excellent book by the early modern pioneer Walton⁴ and the recent historical-ethnographic survey by Emboden.⁵ However, professional historians have mostly neglected this field of study which could give us new and interesting clues as to the social mores and culture throughout human history.

II. THE ANCIENT WORLD OF THE MIDDLE EAST AND EUROPE

A. Assyria

Campbell Thompson has compiled an Assyrian herbal based on 120 fragments of cuneiform plant lists and 660 tablets, most of them from the era of Ashurbanipal (died 626 B.C.).⁶ Several names for cannabis were used, mostly associated with the term azallu (to spin). The Sumerians used a similar name, azalla, indicating a very ancient origin. Towards the end of the eighth century B.C., qunnabu is mentioned for the first time in some Assyrian royal correspondence, along with myrrh (gum-resin from *Commiphora myrrha*, which is widely used in incense), apparently in reference to certain rites. Gan-zi-gun-nu (cf. Indian ganja, see below) is another name for cannabis. It was known as "the drug which takes away the mind".

Cannabis was used medically in several ways. Externally, it served for "binding temples", as a bandage, or as a constituent of various ointments for swellings and bruises. The seeds in juniper oil were used as an ointment against the evil eye. Azallu is also cited in association with the term "hand of the ghost", apparently an, as yet, unidentified disease. For arimtu (which seems to mean some loss of control of the lower limbs), roast azallu was added to a water bath to soak the legs. For depression of spirits, the crushed seeds (together with other seeds, probably those of *Mesembryanthemum*, a plant known to cause intoxication) were added to medical baths. Cannabis fumes were a drug for the "poison of all limbs" (presumably arthritis). Azallu, either as a drink or in the food, was prescribed for depression of spirits, for impotence, for "hand of the ghost", for kidney stones (together with ostrich egg shell, anemone, and thistle in date water or beer), and to annul witchcraft. The seeds, together with mint and saffron in beer, were given for a female ailment (apparently amenorrhea).

It is of interest that the term "harmum" is associated with cannabis. This word has its roots in the semitic term for boycott (ban), and one can only wonder whether it was allowed for use only by the priests and doctors but was forbidden for use by others. There are indications that this may have been true over many centuries in various cultural environments (*vide infra*) but an actual proof is lacking for obvious reasons.*

* However (referring to the ropes made from cannabis), "harum" could have meant also a "fishing net". In Hebrew the corresponding word "herem" means either boycott (ban) or a fishing net.

B. Ancient Egypt

Grapow,⁷ in his study on medicine in ancient Egypt, considers that the hieroglyph transliterated as “šmšm.t.” stands for *Cannabis sativa*. It was used in incense, as well as an oral medication for “mothers and children” (for an unstated purpose though probably in prevention of hemorrhage in childbirth, as in other cultures), in enemas (together with other herbs and honey),⁸ in eye medications and in ointments in bandages. Grapow refers to the Ebers, the Chester Beatty, Hearst (Berlin), and Ramasseum III papyri. Cannabis was apparently well known and used. The identification is based on the fact that the same plant was used both as fiber and as a medicament. The reference to religious use (incense) and the obvious relation to the use in Assyria (see above) strengthens the assumption that šmšm.t. is indeed *Cannabis*. It is, however, surprising that in view of the recent documented use by the ancient Egyptians of the water lily (*Nymphaea caerulea*), the mandrake (*Mandragora officinarum*), and the opium poppy (*Papaver somniferum*) to mediate ecstasis among the priestly caste,⁹ no reference to parallel use is found for *Cannabis sativa*. One can surmise, of course, that as many shamanistic ceremonies in ancient or primitive societies were of a secretive nature, written evidence would not be expected to be readily found.

C. The Scythians

The Scythians were a tribe of violent warriors who ruled the Crimea and, at different times, parts of southern Russia, the Balkans, Anatolia, and the Middle East around 700 B.C. Herodotus¹⁰ has described the strange funerary customs of the Scythians: hemp seeds (more probably dried flowering tops) were thrown on red hot stones and, on inhaling the smoke, “the Scythians howl in joy”. The same custom, though not associated with burial ceremonies, was prevalent among the inhabitants of islands on the Aras river in Turkish Armenia.¹⁰ There is also recent archeological evidence that hemp played a social role in Scythian life not associated with funerary customs, but we have no indication that it was used as a medicament.¹¹

D. Judea

There is no generally accepted direct evidence that cannabis in any form was known or used in ancient Judea¹² although Benet¹³ has made a case that the Biblical plant *kneh-bosem* (in Hebrew) was incorrectly translated in the Septuagint and by Luther as calamus but was in fact *Cannabis*. Kneh-bosem was one of the constituents of incense in the Temple, and as cannabis had the same use in Egypt, Benet's supposition is not unreasonable in view of the close etymological similarity between kneh-bosem and the semitic forms of the word (see below). It seems to me more probable, however, that *pannagh*, and unidentified product exported from, or transported through, Judea to Tyre, and mentioned by the prophet Ezekiel,^{13a} was in fact cannabis. Rabin has suggested^{13b} that *pannagh* was one of the original forms of the word cannabis (cf. in Sanscrit *bhanga* and in Persian *bang*), which later underwent a metathesis in Semitic (cf. Assyrian *qunnabu*, Syriac *qunnappa*, and classical Arabic *kunnab*), finally becoming *cannabis* in Greek.

Creighton¹⁴ has tried to show that many Biblical stories, such as Jonathan's breaking of an unspecified taboo (presumably use of hashish, but most probably eating on a day of fast); or Saul's gradual change of character; Ezekiel's phantasmagoria of composite creatures, of wheels, and of brilliant play of colors; Daniel's interpretation of Nebuchadnezzar's dream (“Nebuchadnezzar was driven from men and did eat *grass* as oxen”); and many others are indications of hashish use.

The above attempts of historical proof are at best indications. The historical background and setting, however, makes it difficult to believe that the ancient Jews were unaware of cannabis and its medical and hedonistic properties as well as its ritual use.

The ties between Egypt and the ancient Jews were long standing. As cannabis apparently was used in Egypt (see above) it is quite inconceivable that when the Jews left Egypt (*circa* 1220 B.C.) they were completely unaware of it. The Scythians, for whom cannabis was central in their religious rites, swept down through Palestine to Egypt *circa* 630 to 610 B.C. A town south of Tiberias was named Scythopolis during the Hellenistic period as some Scythians settled there. Again, it is doubtful that the nearby Jewish population knew nothing about their customs.

While most Scythians were only temporary visitors to the Middle East, the Assyrians were one of the major military powers in the area for hundreds of years and their influence was powerful. As mentioned above, the Assyrians employed cannabis, apparently quite extensively. The contacts between the Jews and the Assyrians were prolonged and wide. During certain historical periods the trade of Judea depended on Assyria; the cultural-religious impact of the Nineveh court and temples penetrated not only the royal and priestly class in Jerusalem but also the lower classes. Gradually in the 7th century B.C. even the Assyrian cult of heavenly constellations was adopted; the ancient forms of augury were revived; in the Temple itself an image of the Assyrian "queen of heaven" was erected; within the Temple young women offered their bodies in honor of the deity. During the reigns of the Assyrian kings Esarhaddon (681 to 669 B.C.) and Ashurbanipal (669 to 626 B.C.), the Jewish King Menasseh, who was their vassal, fought beside them in their wars with Egypt and probably also in Transjordan in order to secure the commercial roads for drugs and spices. The influence of the kings of Nineveh ("the bloody city, full of lies and robbery") in Judea was immense. It can be assumed that under these conditions Assyrian medicine and drugs were known and used, at least among the ruling class.

After the death of Ashurbanipal, the decadent and hedonistic kingdom of Assyria swiftly disappeared from history. The Jewish King Josiah (628 B.C.) is known to have taken advantage of the Assyrian decay to remove vigorously all pagan influence from Jewish life and religious customs. Hashish, presumably a symbol of Assyrian moral laxity, would have been banned. This is, of course, an assumption but it fits the historical background, the insular character of the Jews at the time, and the needs of the independent Judean state. It explains the strange absence of the word *cannabis* in the Bible (or its cursory mention, assuming that *panagh* is indeed *hashish*).

E. Ancient Greece and Rome

In a recent article, Brunner¹⁰ has summarized the rather skimpy knowledge of cannabis available to the ancient Greeks and Romans. Hemp was undoubtedly used in Greece and Rome for the production of textiles and a vague early mention is made of its medical use in Greece: "a mixture of cannabis, ashes and honey is a remedy for an ulceration in the lower back."¹⁰

Surprisingly the Romans and Greeks were completely unaware of the psychotropic properties of cannabis. These fun-loving nations would have undoubtedly used hashish extensively had they known about it, and one can only surmise what Virgil, Ovid, or Apuleius would have written about it.

At the turn of the modern era, cannabis was established as a medicament. Pliny the Elder (died *circa* 79 A.D.) described its use in detail: "Its seed is said to make the genitals impotent. The juice from it drives out of the ears the worms and any other creature that has entered them, but at the cost of a headache; so potent is its nature that when poured into water it is said to make it coagulate. And so, drunk in its water, it regulates the bowels of beasts of burden. The root boiled in water eases cramped joints, gout too and similar violent pains. It is applied raw to burns, but is often changed before it gets dry."¹⁰

The above paragraph, though close, is not identical to the descriptions given by

Pliny's contemporary Dioscorides. It was extensively copied during the Middle Ages. Brunner¹⁰ also quotes several other ancient authors, claiming that "warm juice pressed from *Cannabis* seeds is useful in treating ear aches" (Pseudo-Theodorus) as well as that "mixed with grease may serve to reduce swelling of the chest and a pounded mixture of *Cannabis* seed, nettle seed and vinegar can be applied in treating cold sores" (Pseudo-Apuleius).

Pedanius Dioscorides¹⁵ (died *circa* 90 A.D.) described two types of *Cannabis* in his *Herbal*, which was one of the most influential drug books over 16 centuries. One of these types was used to make strong ropes and had a round seed which, "being eaten of much doth quench geniture, but being juiced when it is green is good for the pains of the ears." The roots of the other "being sodden & so laid on ye force to assuage inflammations & to dissolve Oedemata & to disperse ye obdurate matter above ye joints."

Galen (died *circa* 199 A.D.)^{10,16} finds the seeds "hard of digestion, hurtful to the stomache and head, and containeth in it all ill juyce"; it "drieth up the seed if too much is eaten of it." He also finds the juice to be an analgetic for pains caused by ear obstruction. Al-Kindi (800 to 870 A.D., in Iraq)¹⁷ quotes Galen: "hasheesh which is called 'the trembling' eases the muscles of the limbs," however "it produces senseless talk."

Pliny, Dioscorides, and Galen remained for 16 centuries the main original sources from which the European (and to a large extent the Near Eastern) physicians learned their pharmacology.

Additional information was available but was not widely known. Thus a Syrian manuscript on anatomy, pathology, and therapeutics, probably compiled in the first centuries A.D.,¹⁸ recommends that for painful teeth with cavities, extract of fresh Kunbare (*Cannabis*) should be injected into the nose of the patient; if the tooth had to be pulled out the extract was to be rubbed on the gums.

III. EUROPE, THROUGH THE MIDDLE AGES TO THE 19TH CENTURY

As in many other areas of human knowledge, the Middle Ages did not advance the understanding of drugs and their use very far.

Hildegard of Bingen¹⁹ (born 1099) in her *Physica* mentions that "hempseed" is considered a relief for pain. Peter Schoofer²⁰ in his herbal *Der Gart der Gesundheit*, published in Mainz in 1485, gives a good drawing of the *Cannabis* plant and indicates that it is prescribed for distended stomachs, dropsy, pains in the anal region, and as a plaster for boils and carbuncles. Applied to wounds it relieved pain, and a decoction of its roots and seeds mixed with white lead and oil of roses was used to treat erysipelas. The vapors eased headaches. Later herbals, which copied, summarized, or compiled existing knowledge, presented mostly the views of Pliny, Dioscorides, and Galen, in addition to a few novel uses which may have either originated from lost writings of Galen or been added by unknown herbalists over the ages.

John Parkinson²¹ the king's herbalist (1640) quoting Matthiolus, Tragus, Ruellius, Fuschius, and Lugdunensis (herbalists of the preceding centuries) in addition to Galen and Dioscorides, states:

. . . the seede of Hemepe consumeth wind, and by the much use thereof. . . it dryeth up the natural seede of procreation, therewith: for it is hard of digestion, hurtful to the head and stomack and breedeth ill blood and juyce in the body, yet being boyled in milke and taken, helpeth such as have a dry and hot cough. . . make an Emulsion out of the seede, and give it with good success to those that have the Iaundice, especially in the beginning of the disease if there be no ague accompanying it, for it openeth the obstructions of the gall, and causeth digestion of choller therein: but as Matthiolus saith, the women in Germany went a wrong course, to give their children the decoction of Hemepe seede for the falling sickness, which it did rather

augment, then helpe to take away: the Emulsion or decoction of the seede, stayeth laskes and fluxes that are continuall, easeth the paines of the collicke: and allayeth the troublesome humours in the bowels: also doe stay bleedings herewith, whether at the mouth or nose, or at other places by frying the leaves with some of the blood that hath come from them that bleed, and so given them to eate: it is held very good to kill the wormes in man or beast, as also the wormes in the eares, or the juyce dropped therein, or to draw forth any other living creature that hath crept therein; the decoction thereof, powred into the holes of earthwormes, will draw them forth, and fishermen and anglers have used this feate to get wormes to baite their hookes. The decoction, of the roote is sayd to allay inflammations in the head or any other part the herbe it selfe . . . easeth the paines of the goute, the hard tumours, or knots of the joynts, the paines and shrinking of the sinewes, and other the like paines of the hippes: it is good to be used, for any place that hath beene burnt by fire, if the fresh juyce be mixed with a little oyle or butter. Matthiolus saith, that Hempe seede, given to Hennes in the winter, when they lay fewest egges, will make them lay more plentifully.

Later herbals such as the famous Gerard¹⁶ and Culpeper²² herbals had little new to add. The Middle Ages in Europe stayed their course, as regarded medical and not-so-medical use of cannabis, till the 19th century.

IV. MEDIEVAL ARAB SOCIETY

Rosenthal²³ has recently described and analyzed in detail the use of hashish among the Arabs in a book appropriately entitled *The Herb Hashish versus Medieval Muslim Society*. Hashish use, which was formally prohibited over most of a millennium, was nevertheless so common, especially among the poor, as to occupy a prominent place in Arab literature. The medical applications of hashish were, however, apparently negligible, for its reputation was of a drug which "people who use it habitually have proved its pernicious effect, it enfeebles their minds by carrying them to maniac affections, sometimes it even causes death" (Ebn-Beitar, died 1248 A.D.).²⁴ It is possible, however, that due to its rejection by the rulers its medical use was mostly outside the established medical channels and was unrecorded. Thus Ibn al-Badri, in a treatise on hashish written around 1464 (preserved in Paris in manuscript form) tells that the poet Ali ben Makki visited the epileptic Zahir-ad-din Muhammed, the son of the Chamberlain of the Caliphate Council in Baghdad, and gave the reluctant Zahir-ad-din hashish as medication. It cured him completely but he could not be without the drug ever after.²⁵ The unexpected use against a neurological disease in this particular case may be due to influence of Indian medical traditions. Baghdad at the time had close medical ties with India where cannabis was widely used against spasms.

The Jewish philolosopher and physician Maimonides (died 1204), who lived much of his active life in Cairo, mentions²⁵ cannabis among the most frequently employed drugs which "warm to the first degree and which dry to the first degree." No further details are presented, but later he quotes a 10th-century Arab physician, Al Tamini,²⁶ that "hempseed oil provides benefit to cold earaches, heals chronic (ear) illnesses and dissolves it (ceruminous) obstruction." Al Tamini's indications obviously stem from the writings of Pliny, Dioscorides, and Galen.

Cannabis is mentioned again by Maimonides in his *Glossary of Drug Names*,²⁷ yet again no therapeutic indications were given for this "frequently used" drug. One wonders whether his reticence had some connection with the prevalent ban on cannabis in both Arab and Jewish societies.

Illicit use of hashish was, and still is, widespread in most Arab countries. It is not employed as a medicament.

V. INDIA AND PERSIA

A. India

Cannabis was part of the religious lore of the Aryans, a nomad tribe, which invaded

India from the north *circa* 2000 B.C. It is mentioned²⁸ in the sacred Vedas and is associated there with the god Siva, who brought the plant for the use and enjoyment of his people. In the fourth book of the Vedas, the Atharvaveda (written in Sanscrit, *circa* 1500 to 1200 B.C.), the plant is described as a sacred grass,²⁸ and bhang, the mild drink prepared from cannabis, is mentioned as an antianxiety herb in the verse: "Five kingdoms of plants, with Soma as their chief, we address: Soma, darbha, bhangas, Saha, yava; may they free us from distress."²⁹ Over the centuries, its use and its place in religious and social ceremonies spread throughout India. In a fascinating review on "The Religion of Hemp" Campbell^{30,31} states, "To the Hindu the hemp plant is holy. As the wife of Vishnu, the preserver, lives in the hysteria-curing *tulsi*, or Holy Basil, and as Shiva dwells in the dysentery-scaring *bel*, Aegle marmelos, so the properties of the bhang plant, its power to suppress the appetites, its virtue as a febrifuge and its thought-bracing qualities show that the bhang leaf is the home of the great Yogi or brooding ascetic Mahadev." Bhang was associated with rites required to clean away evil influences; oaths were taken on the bhang leaf; offerings of bhang to the gods and in particular to Baldev, the older brother to Lord Krishna,²⁸ were made. Initially the medical properties of bhang were closely tied to religion. Thus according to an account in the Ayurveda (a supplement to the Vedas), fever is possession by the hot angry breath of the great gods Brahma, Vishnu, and Shiva. If the fever stricken performs certain religious rites with bhang, the god Shiva is pleased, his breath cools, and the portion of his breath in the body of the fever stricken ceases to inflame.³¹ Although the use of bhang retained its ties to religion, not all medical applications had mythological background. Cannabis was described in the Suśruta-samhitā, one of the two major medical treatises written after the Ayurveda. The Suśruta-samhitā probably originated in the last centuries B.C. and became fixed in its present form around the 7th century. Cannabis leaves were recommended as antiphlegmatic, as a remedy for catarrh accompanied by diarrhea, and as a cure for biliary fever.²⁸ The term "antiphlegmatic" had a much wider meaning than it has today, as "phlegm" for the Hindu was one of the three elemental substances of the body, the other two being the spirit (residing below the navel), and the bile (residing between the heart and the navel). The phlegm was seated above the heart.

Later Hindu medicine scarcely developed. For centuries, up till modern times, the Ayurvedic system of medicine continued to be the dominant medical system throughout India. Evidence of the medical use of cannabis during this period abounds. It was described in the Rajanighanta of Narahari Pandita^{28,32} (300 A.D., republished in 1500) as "excitant, heating, astringent: it destroys phlegm . . . sharpens the memory, and excites appetite." In later books³² one finds that ganja was "soporific and corrects derangements of the humours, which produces a healthy appetite, sharpens the wits, and acts as an aphrodisiac;" that bhang "increases infatuation, the power of the voice, and the digestive faculty;" and that "ganja destroys leprosy, creates energy," etc. It was considered an "elixir vitae". Obviously the Greek-Roman medical dogmas of the 1st to 2nd centuries A.D. had not imposed their weight on Indian medicine, for the medical uses of cannabis by the two systems differ considerably. However, a book written by Islamic author Makhzan-el-Adwiya states³³ that hemp seeds are "cold and dry meaning stimulant and sedative . . . drops of the juice of the leaves thrown into the ear allay pain and destroy worms . . . restrain the seminal secretations . . . a poultice of the boiled roots are used for allaying neuralgic pains." These are statements close to the prevailing tradition of Dioscorides. This is not surprising, since contacts existed throughout the Middle Ages between India and the Arabs. Thus evidence exists that the great Caliph Haroun-al-Rashid accepted the preeminence of Indian medicine and imported Hindu physicians to organize hospitals and a medical school in Baghdad.³⁴

However, Moslems in territories further East developed their own medical traditions. Rumphius (1695)³⁵ found that the Moslems in Amboyana (today Indonesia) used the male cannabis plant for virulent gonorrhoea, asthma, and "stiches on the side" (apparently herpes zoster).

The Indians had a much better understanding of cannabis than the Europeans. Their emphasis on the nervous system is much closer to contemporary understanding of cannabinimimetic activity. Cannabis-derived drugs were used in the treatment of cramps, convulsions in children, headaches (migraine?), hysteria, neuralgia, sciatica, and tetanus. Early in the 19th century Sir W. B. O'Shaughnessy³⁶ experimentally showed that many of these claims were well founded. His work will be discussed later.

Hemp drugs were also used with considerable success in dysentery and cholera. Today we know that THC reduces intestine motility, hence the use against dysentery (and cholera) makes some therapeutic sense.³⁷

In the treatment of diseases of the respiratory organs hemp drugs were used in hay fever, bronchitis, asthma, and coughs.²⁸ Modern work (see Chapter 8) has shown that, at least as regards asthma, Indian tradition had a factual basis.

One of the most common uses was (and probably still is) for the relief of pain and as a febrifuge, the drug being used either locally or given orally. Poultices were applied over inflamed, painful parts, even over the seat of pain in liver and bowel diseases. Small fragments of charas were placed in a carious tooth to relieve toothache. Systemically the drugs were used for labor pains, as well as pain produced by dysmenorrhea, menorrhagia, and as mentioned above in neuralgia, cramps, and in minor operations (circumcision).²⁸

In various parts of India cannabis was used for a large number of diseases and to improve the physical and mental states of the user.²⁸ It was believed to be an appetite promoter and a general tonic, to alleviate fatigue, to give staying power under severe exertion, to be a diuretic, to reduce delirium tremens, to shrink swelling of the testicles, etc. The view that cannabis was an aphrodisiac was widespread. As a general comment to this ubiquitous popular use, one can only quote again the Indian commission, "The medicinal use seems to merge sometimes into the popular use, where the drugs are used, ostensibly at least, for purposes akin to medical."

B. Persia

Eliade³⁸ in his definitive work on shamanism has noted that "there is no doubt that the most elementary technique of [shamanic] ecstasy, intoxication by hemp, was known to the ancient Iranians." Although there is no proof that Zarathustra (7th century B.C.), the founder of Persian religious thought, used cannabis, there is evidence that its religious use was considerable, and the importance of cannabis intoxication for shamanic ecstasy was widely disseminated from Iran through Central Asia. It is also possible that the role of hashish in Islamic mysticism was due to pre-Islamic Iranian influence.

The therapeutic use of cannabis in ancient Persia apparently was not widespread though it is mentioned numerous times in Schulenz's history of pharmacy.³⁹

VI. CHINA

Chinese traditional medicine is not strictly folk medicine. It evolved not only from the knowledge of practicing magicians-physicians of plant lore but was (and still is) a well-organized system of medical values and facts, based on observations, experiments, and clinical trials. The importance of drugs in this system is mainly to restore the harmony between the Yin (the weak, passive, feminine force) and the Yang (the strong, active, masculine force) which when in disharmony cause disease. The medical classics

in China were well recorded and reverently copied and were generally followed for centuries or even millennia to an extent much wider than in other ancient societies.⁴⁰⁻⁴²

The Yellow Emperor Huang Ti (*circa* 2600 B.C.) is reputed to be the author of *Nei Ching*, a canon of internal medicine, parts of which are still in use. A second medical classic is traditionally assumed to have been written shortly thereafter by the Emperor Shen Nung. In its present form it dates from the 1st century A.D. It is known as *Shen Nung Ben Ts'ao* and describes about 300 medicines including cannabis ("ma" in Chinese).^{40,41} "Ma" has a negative connotation in Chinese and this may indicate that its undesirable psychotropic properties were known in early Chinese society.⁴¹ Cannabis was recommended in *Ben Ts'ao*, together with other herbs, for rheumatic pains, disorders of the female reproductive tract, absentmindedness, and malaria (probably for the headache caused by the disease), as well as for beriberi. If, however, the fruits of hemp were taken in excess they could cause "seeing devils".⁴²

The famous surgeon Hua T'o is reputed to have used cannabis in wine as anesthetic in major operations, *circa* the 3rd century A.D.⁴³ As cannabis is only a minor pain killer one can only assume that large stupefying doses were administered (see Reference 36 for a 19th-century description of total catalepsy in man produced by large doses of cannabis resin).

During the 7th century (Tang Dynasty) an expanded major new book of *materia medica* was written by T'ao Hung Ching (reputedly with the help of 2000 scholars). About 900 years later, during the Ming Dynasty the scholar Li Shih-chen collected, over 27 years, all the published knowledge on medicines (reputedly in 800 books), interviewed scholars and peasants, and finally wrote the 52-volume *Ben-Ts'ao Kang Mu* (1578 A.D.). This great pharmacopoeia remained the standard drug book for centuries. It described more than 1000 plants and 1000 animals in great detail, classifying them into 62 divisions. An appended work added more than 8000 prescriptions. Many of the prescriptions of the great *Ben Ts'ao* are still followed today.^{40,44} Most of the cannabis medical applications described below come through the *Ben Ts'ao Kang Mu*.

The Chinese were aware of the dual nature of cannabis. A 10th-century herbal points out: "Ma-fen is used for waist diseases and injuries; it clears blood and cools temperature . . . it undoes rheumatism; it discharges pus. If taken in excess it produces hallucinations and a staggering gait. If taken over a long term it causes one to communicate with spirits and lightens one's body."⁴⁵

Ma was scarcely used in China as an illicit drug. Li⁴⁵ has suggested that this was due to a basic incompatibility with Chinese temperament, philosophy of life, and traditions. Cannabis with its erratic effects, due to the fantasy and uncoordinated thoughts caused by it, was likely to induce acts that might bring shame to the user or his family. In tradition-bound Chinese society this would have been contrary to the prevailing system of social values based on the family as well as contrary to the generally accepted Confucian values of moderation and uprightness.

While the medicinal value of cannabis was well recognized (for examples, see below), it was apparently not a very popular medicament.

Touw has recently described the use of cannabis in China in the past.⁴² This publication as well as that of Hubotter⁴⁶ should be consulted for full details and references. Modern use apparently is minimal as it does not appear in most contemporary compilations of Chinese medicinal plants.⁴⁰

The "kernels" (not necessarily meaning the seeds alone) were used both as laxative and in diarrhea, to "render the flesh firm and prevent old age" as well as against vomiting. The latter use was widespread in India as well and was confirmed during the 19th century in Europe (see below); it was rediscovered in the 1970s in the U.S., though

none of the many articles on the subject refers to ancient or 19th-century use and experience.

Cannabis kernels, oil, and leaf juice were widely employed externally for various skin and lymph diseases, ulcers, wounds and eruptions, leprosy, and even for falling hair. The well-documented topical antibiotic properties of the cannabinoids described in the 1950s and 1960s⁴⁷ fully justify the use in appropriate skin diseases. The use in leprosy in China (in preparations containing also the well-known anti-leprosy drug chaulmoogra oil) deserves further investigation. The cannabinoid acids, present in cannabis, and the chaulmoogra acids, present in chaulmoogra oil, have certain common physicochemical properties, such as *high lyposolubility* due to the long aliphatic chains and *anionic centers* due to the carboxyl groups in both groups of compounds.

In spite of the early use as an anesthetic, cannabis was not widely employed as analgetic except for severe pain (probably when it was administered in very high doses). It was used, however, as an antirheumatic drug.

Cannabis was widely used after childbirth to stop hemorrhages as well as for "menstrual disorders". These properties of cannabis were widely known in other cultures, as mentioned elsewhere in this chapter, and were substantiated during the 19th century (*vide infra*). Cannabis was apparently also used as antidiabetic and in many degenerative diseases.

The use of cannabis as an antihelmintic is of interest, as it is mentioned throughout many centuries in various cultural regions. A modern antihelmintic, hexylresorcinol, has a chemical structure closely related to the structure of the cannabinoids. Experimental work in this area with cannabinoids has not been reported. It might yield interesting results, for if nonpsychotropic cannabinoids are found to possess antihelmintic activity, the doses administered could be very high due to the documented lack of toxicity and side effects of such compounds.

VII. WESTERN EUROPE AND NORTH AMERICA IN THE 19TH AND EARLY 20TH CENTURIES

During the first decades of the 19th century cannabis was not used as a drug in Europe, although information on its medicinal properties was available from the much-copied herbals and plant-medicinal texts.

Napoleon's soldiers brought back from Egypt stories of hashish "paradise" easily achieved by smoking through a nargilah (water pipe) or eating a sweet containing hashish.⁴⁸ These lurid stories gradually infiltrated the open-minded Parisian literary circles and led to the establishment of "le Club des Hachichins" (*circa* 1846), whose best-known members were Théophile Gautier and Charles Baudelaire. While the cultural importance of the club was considerable, in particular in literature, its medical influence was marginal except in psychiatry. Moreau, in 1845, in one of the first publications on *experimental* psychiatry to be published,⁴⁹ claimed that hashish induced temporary insanity and could be used as a model of this disease. There is little in common between psychotic diseases and hashish intoxication, but the obvious differences did not prevent researchers from drawing the same conclusions more than a century later when working with LSD. Moreau recorded that hashish was not an antidepressive drug; in some cases of delirium he had positive results but quite sensibly declined to claim the discovery of a new drug.

The main figure behind the resurgence of cannabis as a medicinal agent is undoubtedly the British scientist and physician O'Shaughnessy^{36,50} who not only meticulously recorded the popular and medical uses of the various preparations in India but also conducted animal and human experiments and applied his knowledge in the clinic.

First, as befitted a then-modern scientist, he administered small doses of *churus* resin

to dogs and "three kids." The dogs received *circa* 650 to 1300 mg extract; the kids only 650 mg. The dogs "became stupid and sleepy," "staggered to and fro," "assumed a look of utter and helpless drunkenness," and "lost all power of the hinder extremities." As to the kids, "In one no effect was produced; in the second there was much heaviness, and some inability to move; in the third a marked alteration of countenance was conspicuous, but no further effect." In none of these or several other experiments was there the least indication of pain or any degree of convulsive movement observed. These experiments apparently proved to O'Shaugnessy that "no hesitation could be felt as to the perfect safety of giving the resin of hemp an extensive trial in the cases in which its apparent powers promised the greatest degree of utility," and clinical trials were initiated.

Ethanol extracts (tincture) of cannabis resin (*circa* 65 to 130 mg per dose) were administered to patients with rheumatism, tetanus, rabies, infantile convulsions, cholera, and delirium tremens. These diseases were chosen in order to confirm well-established local medical traditions (see above). In the case of rheumatism two out of three cases were "much relieved . . . they were discharged quite cured in three days after." In both cases the huge doses caused side effects such as total catalepsy or uncontrollable behavior, which today would be considered quite unacceptable. The third patient "experienced no effect whatever, and on further inquiry it was found that he was habituated to the use of Gunjah in the pipe." This is an early report on tolerance, which was also noted in some additional cases.

Further trials with lower doses gave closely analogous effects: "alleviation of pain in most — remarkable increase of appetite in all — unequivocal aphrodisia, and great mental cheerfulness. The disposition developed was uniform in all, and in none was headache or sickness of stomach a sequel of the excitement."

Convulsions and spasms associated with rabies and tetanus were well controlled with rather high doses of cannabis tincture. In the case of tetanus cannabis was considered to improve the prognosis and was administered in 650-mg doses to "perfectly hopeless cases." Relaxation of the muscles and an "interruption of the convulsive tendency" was observed. Encouraging results were also reported in cases of infantile convulsions.

Surprisingly good results were observed in the treatment of cholera: "We know no remedy equal to it as a general and steady stimulant when given to Europeans in the dose of half a drachm during the tractable stage of this disease." In native cases success was less striking due to apparent tolerance to the drug, as most of the Indian patients apparently were long-time users of bhang.

An important observation made by O'Shaugnessy was that cannabis was a potent antiemetic agent. As mentioned above, this property was rediscovered in the U.S. about 120 years later; no credit has been given to O'Shaugnessy in any of the numerous contemporary publications on this topic.

The reports by O'Shaugnessy were received in England with considerable interest. Gradually Indian hemp became an accepted drug in therapy, originally in England and later, to a limited extent, in other European countries and in North America.

Shortly after O'Shaugnessy's publications Clendinning⁵¹ was able to report, on the basis of numerous clinical cases, that, "I have no hesitation in affirming that [cannabis administration] has usually and with remarkably few substantial exceptions been followed by manifest effects as soporific or hypnotic in conciliating sleep; as an anodyne in lulling irritation; as an antispasmodic in checking cough and cramp; and as a nervine stimulant in removing languor and anxiety, and raising the pulse and spirits; and that these effects have been observed in both acute and chronic affections, in young and old, male and female."

In 1845 Donovan confirmed the above observations.⁵² He found that cannabis tincture made from resin from India (local Irish cannabis being of little value) was highly

effective in cases of violent neuralgic pain in the arms and fingers, inflammation of the knee, facial neuralgia, sciatica affecting the hip, knee, and foot, etc. The doses employed are difficult to determine today but in most cases best results were obtained at levels which also produced some side effects. He also observed the effect of exciting hunger and suggested the use in anorexia nervosa.

Part of these results were independently corroborated and expanded by Corrigan.⁵³ He described several cases of chorea and neuralgia which were successfully treated with cannabis tincture. Like most other clinicians he noted the variability of the drug. In one case 20 drops of the tincture caused "temporary loss of power in almost all the muscles, followed by sleep, while a similar dose has been taken by other patients three times daily for weeks with impunity and advantage."

The most detailed review of the therapeutic uses of cannabis in the mid-19th century is presented by Christison.⁵⁴ The analgetic power of hemp extract (tincture) is stressed, in particular in rheumatic pain, sciatica, and tooth pain. He describes the marked mitigation of various types of spasms, the relief of asthmatic paroxysms, and the hypnotic effects. Of particular interest is his emphasis on the "remarkable power of increasing the force of uterine contractions, concomitant with a significant reduction of labour pain." He compared the action of ergot and cannabis: (1) hemp acted within minutes and was faster than ergot; (2) ergot action lasted longer, cannabis action being of very short duration; and (3) cannabis action was much more energetic than that of ergot. Christison also noted that cannabis restrained uterine hemorrhage and claimed that it was the most efficacious preparation available, the effects being very marked. It is quite strange that these claims based on previous popular use and later confirmed by others have not been investigated recently.

Grigor⁵⁵ found oxytocic activity in about half of his cases; in those cases when activity was observed the contractions were reported to acquire great increase in strength and frequency immediately on swallowing the drug. The expulsive action was stronger than that of ergot, no anesthetic effects were observed, and when the effects were subsiding they could be kept up by addition of further amounts of cannabis.

In 1859, J. Russel Reynolds⁵⁶ described numerous successful and unsuccessful cases of treatment with cannabis. Thirty-one years later, an F.R.S. by this time, he summarized his long clinical experience:⁵⁷ "... Indian hemp when pure and administered carefully is one of the most valuable medicines we possess." He found cannabis to be "absolutely successful for months, indeed years without any increase in dose" in cases of senile insomnia ("senile ramollissement"). In mania cannabis was "worse than useless;" in depression it was seldom used. In "almost all painful maladies" Indian hemp was found to be "by far the most useful of drugs." Neuralgias of several kinds were successfully treated for years. He emphasized the use in trigeminal neuralgia, but found it useless in sciatica and all pains which "occur only on movement." In cases of migraine he found that "very many victims of this malady have for years kept their sufferings in abeyance by taking hemp at the moment of threatening or onset of the disease." Contrary to previous reports, he found cannabis useless in epilepsy, tonic spasms, general chorea, or tetanus but very valuable in "nocturnal cramps of old and gouty people" and in cases of "simple spasmodic dysmenorrhoea." He also found that cannabis in some cases relieved spasmodic asthma.

Silver in 1870 treated cases of menorrhagia with cannabis tincture.⁵⁸ He recorded that "the medicine acted like magic, both pain and discharge totally ceased after a few doses."

The above observations were repeatedly recorded and expanded in England up till the end of the century. Douglas⁵⁹ gave support to Corrigan's use of cannabis in chorea but regretfully noted that other colleagues preferred "Dr. Hughes's favourite and useful remedy — rhubarb steeped in port wine."

Dobell⁶⁰ described a case of spasmodic asthma successfully treated prophylactically with cannabis tincture. However when "the stock of tincture at the Infirmary became exhausted and fresh supply was procured" the new cannabis tincture produced severe side effects, which prevented further use. This observation was not an isolated one. Oliver⁶¹ summed up his experience as follows: "Indian hemp for some time back has been vaunted as a medicine of some therapeutic value in cases of dysmenorrhoea; to me, however, its action seems so variable, and the preparation itself so unreliable, as to be hardly worthy of a place on our list of remedial agents at all." Oliver's negative attitude towards cannabis was strongly challenged. Brown⁶² admitted that in dysmenorrhoea it had not proved of much benefit, but in menorrhagia "there is no medicine which has given such good results. . . . The failures are so few that I venture to call it specific in menorrhagia." He found no major side effect when the drug was given in low doses. The same view was taken by Batho,⁶³ who considered cannabis tincture the remedy *par excellence* for menorrhagia, with no disagreeable physiological effects observed.

Cannabis was still widely used in Britain around the turn of the century. Fox, in a review on headaches,⁶⁴ on discussing the treatment of migraine states: "But I am accustomed to rely much upon *Cannabis sativa* having had a pretty large experience of this remedy. The extract, often combined with Cascara sagrada [a purgative] has controlled many, if not most, cases of migraine." He preferred to use the fresh extract which he administered "in good many instances to the point of intoxication." He found it useful only in "high-tension headaches," caffeine citrate being better for the "low-tension" ones.

The British physicians in India, having access to fresh, high-quality cannabis, used it quite extensively. In addition to the uses recommended by physicians in Britain, they found it valuable in the treatment of diarrhea.⁶⁵ Rennie reported that in dysentery "it is the sub-acute and chronic forms of the disease that the medicine gives the best results. It acts also in the acute forms, but not with the same certainty."⁶⁶ Birch, in 1889, reported from Calcutta that cannabis was very valuable in the treatment of chloral and opium addiction.⁶⁷ He found that cannabis immediately appeased the "appetite for the chloral or opium" and restored the ability to appreciate food.

In the U.S., cannabis, "this abnegated and nearly obsolete agent,"⁶⁸ was well known though apparently rarely used. Authentic Indian resin was not available, hence extracts of powdered local hemp leaves were used. These, when collected on time, were quite potent and, as described in great detail by Wood, could cause what can be defined today, a marihuana overdose reaction.⁶⁹

The publications by O'Shaughnessy and the British physicians were known in the U.S. and were widely cited in numerous local medical journals (see References 68 to 73), but few new applications or insights were recorded. Severe attacks of neuralgia, including trigeminal neuralgia, were treated with success. MacKenzie⁷² reported that, if continued for some time, cannabis was the most valuable remedy he had met with in the treatment of persistent headache. Low doses acted as pleasant hypnotics and calmatives; various preparations were employed in chorea ("more particularly in that form connected with hysteria"⁷⁶), in cases of neuralgic dysmenorrhea, in menorrhagia, as an oxytocic, in spasmodic asthma, in spasm of the glottis, and generally in cases of hysteria.

Several papers stressed the antiemetic effect of cannabis. Wright⁷³ reported that the drug relieved morning sickness, while Aulde found that when cannabis (together with other extracts) was administered to patients with delirium tremens it arrested their vomiting and they "gradually fall into a natural-like sleep."⁷¹ Aulde also states that "the same method of treatment is particularly applicable to that form of nausea and

vomiting with excruciating pain which now and then attacks persons previously in tolerable good health."

While the clinical descriptions of the U.S. physicians, even by the standards of the era, leave something to be desired, U.S. firms were not to be blamed for lack of cannabis preparations on the market. The *Merck Index* of 1896 alone lists six different Merck preparations, two of which are copied below.

"Cannabin Resinoid Merck (not "Cannabine"!)-- -- 15 gr. vial. 35

Also in 1, $\frac{1}{2}$, $\frac{1}{4}$ & $\frac{1}{8}$ oz. vials.

Fr. Cannabis sativa, L., var. indica (Indian Hemp). — Greenish-black, extr.-like mass. — Sol. A., E. — Hypn., Nar., Analg., & Aphrod. — Uses: Hyst., delir. trem., neural., insom., gout, rheum., ment. depres., insanity, & c.

Cannabine Alkaloid Merck (not "Cannabin"!)— Pure -- -- 15 gr. vial 10.00

Also in 10 & 5 grain vials.

Fr. Cannabis sativa, L., var. indica — Fine need. — Hypn., without danger. second. effects. — Dose $1\frac{1}{2}$ —4 grains (0.097—0.26 Gm)."

One can only wonder what were the fine needles of "Cannabine Alkaloid Merck", which cost \$10 (in 1896) and were hypnotic without "danger. second. effects."

Cannabis was known as a medicament in continental Europe during the second half of the 19th century but was rarely used. In a review of the medicinal properties of cannabis, Michel,⁷⁴ although considering British therapeutics "excentric" ("La thérapeutique des médecins anglais est trop souvent porté à l'exagération, j'allais dire à l'excentricité. . . ") finds British use of cannabis as oxytocic important enough to be repeated in France. Indeed, administration of cannabis to patients with uterine hemorrhage was found to be always successful. It was better than ergot as an oxytocic and was strongly recommended: "Notre propre expérience et nos observations, déjà assez nombreuses, nous font approuvés sans restrictions les conclusions du praticien écossais."

An earlier report by Binard⁷⁵ described the topical treatment of ocular pain and inflammation with cannabis tincture. No modern work on this topic seems to have been reported. This is possibly due to the difficulty of solubilization of cannabinoids in aqueous media.

Grimault⁷⁶ found that cannabis oil was helpful in cases of rheumatic pain; Benzenet⁷⁷ reported on the diuretic action of cannabis.

In Germany one of the few practitioners employing cannabis was Frohmüller, who has summarized his experience:⁷⁸ "Of all anaesthetics ever proposed, Indian hemp is the one which produced a narcotism most closely resembling the natural sleep without causing any extraordinary excitement of the vessels, or any particular suspension of secretions, or without fear of a dangerous reaction, and consecutive paralysis. It acts neither as violently nor as surely as opium. It can be given in all acute inflammatory diseases as well as typhoid affections. It is well adapted as an alternate with opium in case this ceases to act. Its best mode of administration consists in pills of the alcoholic extract and powdered seed."

Sée⁷⁸ reported in 1890 some original observations on cannabis in gastric disorders. Low doses of extract which did not produce unpleasant effects were found to give relief from pain and increased the appetite in many cases regardless of the causes of the pain and loss of appetite. It was found to relieve vomiting and cramp of the stomach. Cannabis was said to be "a true sedative to the stomach without causing any of the inconveniences experienced after the administration of opium, chloral, or the bromides."

Although occasional articles on the therapeutic potential of cannabis continued to be published for decades after the turn of the century, its medical use slowly declined. There are two major reasons for this:

1. The constituents of cannabis had not been isolated in a pure form. Hence, crude plant preparations or extracts had to be used. Cannabis is notorious for its chemical variability and its easy deterioration. Therefore, reproducible clinical effects were not always obtained.
2. Legally, in many countries, cannabis was linked to the opiates. The use of these drugs was officially controlled and frequently made difficult. However, the opiates due to their medical indispensability continued to be widely employed; cannabis use declined.

Interest in cannabis was renewed between 1940 to 1950 as a result of the chemical research of Adams⁸⁰ and Todd⁸¹ and the pharmacologic research of Loewe.⁸² Although the active principle had not yet been isolated, compounds with cannabimimetic activity were synthesized and these were tested in animals and examined in the clinic. The most widely tested compound was pyrahexyl (synhexyl) $\Delta^{6a,10}$ -THC hexyl isomer (see Appendix I for structure).

Thompson and Proctor⁸³ found that pyrahexyl and related compounds were beneficial in the treatment of withdrawal symptoms from the use of alcohol to a marked degree, and in the treatment of withdrawal symptoms from the use of opiates to a less marked, but still significant degree. About 85% of 70 patients had their symptoms of alcohol withdrawal alleviated by the administration of pyrahexyl; 11 cases did not show improvement. Ten out of twelve cases of Demerol (an opioid) addiction were able to withdraw from the drug completely in 1 week's time without having to resort to other types of medication. In some cases of barbiturate addiction, ameliorization of symptoms was noted.

Kubie and Margolin reviewed the therapeutic properties of cannabis derivatives and concluded that these compounds could be useful as aids to psychotherapy.⁸⁴

Stockings administered synhexyl to 50 depressed patients.⁸⁵ At doses from 5 to 15 mg in normal subjects and 60 to 90 mg in depressive patients, synhexyl was a powerful euphoriant. He concluded that

... the general effects in man consisted of a pleasant feeling of happiness and exhilaration with a marked sense of physical well being and self confidence. There was a sense of relief from tension and anxiety and the threshold for unpleasant effect is markedly raised. Hallucinatory phenomena and distortion of the temporospatial perception sense of cannabis-mescal type are not found, although elementary visual sensations in the form of photopsias and simple color patterns may occur when the eyes are closed or the subject is in darkness. On the motor side there may be a slight restlessness in the early stages similar to what is found with moderate doses of 'Benzedrine'. Hyperreflexia is common, but ataxia and motor incoordination are seen only with the largest doses. Catatonia and rigidity as seen with mescaline are never found.

Of the fifty cases tested, 36 showed a definite improvement in affective reaction, while 14 were unaffected or made worse. Twenty-seven of the series were neurotic-depressives, 20 of whom showed improvement; of these 27, 12 were typical chronic mental hospital cases, of whom 9 benefited from the drug.

The neurotic patients apparently were helped more than the psychotic. However, later Pond⁸⁶ was unable to confirm the work of Stockings. At doses (20 to 40 mg) considerably lower than those used by Stockings (60 to 90 mg), no evidence was found that the drug was valuable in the treatment of depression. In this study synhexyl was compared to an amphetamine. Today amphetamines are not considered to be antidepressive compounds and the comparison is of little value.

Parker and Wrigley⁸⁷ also could not confirm the work of Stockings although synhexyl was found to have marked pharmacological activity and it was recommended that further work on this and similar substances be continued. It should be pointed out that smaller doses of synhexyl (10 to 12 mg daily) were used than were reported by Stockings. A total of 62 patients were treated, of which 16 were outpatients. These patients represented a wide selection of diagnoses and some improvement was seen in

those exhibiting neurotic depressions. Attempts to confirm this activity in a double-blind study were unsuccessful.

Davis and Ramsey⁸⁸ studied the antiepileptic action of two isomers of the synthetic $\Delta^{6a,10a}$ -THC dimethylheptyl isomer (named DMHP; see Appendix I for the structure of DMHP). Five institutionalized epileptic children, who showed grand mal epilepsy with mental retardation, inadequately controlled with phenobarbital and Dilantin, were administered DMHP for 3 to 7 weeks. Three responded as well as to previous therapy; the fourth became almost completely and the fifth entirely seizure free. The optimal dosage was 1.2 to 1.8 mg daily. Although further research was recommended, none was later reported. As the active constituents had not been isolated in pure form and were not available for biological research, interest soon declined again.

In 1964 the major psychotropically active constituent, Δ^9 -tetrahydrocannabinol (Δ^9 -THC), was isolated in a pure form and its structure was elucidated.⁸⁹ It was shown that it could be easily obtained from the psychotropically inactive, crystalline major constituent, cannabidiol, or by synthesis.⁹⁰ Since 1964 about 6000 papers on the chemistry, pharmacology, metabolism, and clinical effects of Δ^9 -THC and the cannabinoid family of natural and synthetic compounds have appeared. The actual and prospective therapeutic uses of cannabinoids in the clinic will be discussed in the following chapters.

VIII. CONCLUSION

The cannabis story is a fascinating chapter in pharmacohistory. Its past use in medicine and in social and religious ceremonies deserves a more thorough professional investigation than it has received up till now. Maybe we can learn more of the taboos and social structures in many old societies on the basis of their relation to cannabis as a therapeutic and social drug and a shamanistic agent. Such investigations, with other drugs, in particular in South American cultures, have yielded a rich crop of important results.

For the medical scientist use of cannabis as a therapeutic agent in the past may serve as a clue to future drug development. Many of the therapeutic properties of cannabis have been verified with pure natural or synthetic cannabinoids. In several fields, however, no modern work exists. The most blatant examples are the antihelmintic, anti-migraine, and the oxytocic effects. Are we missing something?

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