

## Introduction

Medicine in the Western World has forgotten almost all it once knew about therapeutic properties of marijuana, or cannabis.

Analgesia, anticonvulsant action, appetite stimulation, ataraxia, antibiotic properties and low toxicity were described throughout medical literature, beginning in 1839, when O'Shaughnessy introduced cannabis into the Western pharmacopoeia.

As these findings were reported throughout Western medicine, cannabis attained wide use. Cannabis therapy was described in most pharmacopoeial texts as a treatment for a variety of disease conditions.

During the second half of the 1800s and in the present century, medical researchers in some measure corroborated the early reports of the therapeutic potential of cannabis. In addition, much laboratory research has been concerned with bioassay, determination of the mode of action, and attempts to solve the problems of insolubility in water and variability of strength among different cannabis specimens.

"Recreational" smoking of cannabis in the twentieth century and the resultant restrictive federal legislation have functionally ended all medical uses of marijuana.

In light of such assets as minimal toxicity, no buildup of tolerance, no physical dependence, and minimal autonomic disturbance, immediate major clinical reinvestigation of cannabis preparations is indicated in the management of pain,

chronic **neurologic** diseases, convulsive disorders, migraine headache, anorexia, mental illness, and bacterial infections.

Recently declassified secret U.S. Defense Department studies reconfirm marijuana's **congeners** to have therapeutic utility.

*Cannabis indica*, *Cannabis sativa*, *Cannabis americana*, Indian hemp and marijuana (or marihuana) all refer to the same plant. Cannabis is used throughout the world for diverse purposes and has a long history characterized by usefulness, euphoria or evil—depending on one's point of view. To the agriculturist cannabis is a fiber crop; to the physician of a century ago it was a valuable medicine; to the physician of today it is an enigma; to the user, a euphoriant; to the police, a menace; to the traffickers, a source of profitable danger; to the convict or parolee and his family, a source of sorrow.

This book is concerned primarily with the medicinal aspects of cannabis.

The Chinese emperor Shen-nung is reported to have taught his people to grow hemp for fiber in the twenty-eighth century B.C. A text from the period 1500-1200 B.C. documents a knowledge of the plant in China—but not for use as fiber. In 200 A.D., the use of cannabis as an analgesic was described by the physician **Hoatho**.<sup>44</sup>

In India the use of hemp preparations as a remedy was described before 1000 B.C. In Persia, cannabis was known several centuries before Christ. In Assyria, about 650 B.C., its intoxicating properties were noted.<sup>44</sup>

Except for Herodotus' report that the Scythians used the smoke from burning hemp seeds for intoxication, the ancient Greeks seemed to be unaware of the psychoactive properties of cannabis. Dioscorides in the first century A.D. rendered an accurate morphologic description of the plant, but made no note of intoxicating properties.<sup>10</sup>

In the thirteenth and fourteenth centuries, Arabic writers described the social use of cannabis and resultant cruel but unsuccessful attempts to suppress its non-medical use.<sup>44</sup>

Although Galen described the use of the seeds for creating warmth, he did not describe the intoxicating qualities of hemp. Of interest is the paucity of references to hemp's intoxicating properties in the lay and medical literature of Europe before the 1800s.<sup>44</sup>

The therapeutic use of cannabis was introduced into Western medicine in 1839, in a forty-page article by W. B. O'Shaughnessy, a thirty-year-old physician serving with the British in India.<sup>27</sup> His discussion of the history of the use of cannabis products in the East reveals an awareness that these drugs had not only been used in medicine for therapeutic purposes, but had also been used for recreational and religious purposes.

O'Shaughnessy is not primarily known for his discovery of hemp drugs, but rather for his basic studies on intravenous electrolyte therapy in 1831, and his introduction of the telegraph into India in the 1850s.<sup>26</sup>

After studying the literature on cannabis and conferring with contemporary Hindu and Mohammedan scholars O'Shaughnessy tested the effects of various hemp preparations on animals, before attempting to use them to treat humans. Satisfied that the drug was reasonably safe, he administered preparations of cannabis extract to patients, and discovered that it had analgesic and sedative properties. O'Shaughnessy successfully relieved the pain of rheumatism and stilled the convulsions of an infant with this strange new drug. His most spectacular success came, however, when he quelled the wrenching muscle spasms of tetanus and rabies with the fragrant resin. Psychic effects resembling a curious delirium, when an overdose was given, were treated with strong purgatives, emetics with a blister to the nape of the neck, and leeches on the **temples**.<sup>27</sup>

The use of cannabis derivatives for medicinal purposes spread rapidly throughout Western medicine, as is evidenced in the report of the Committee on Cannabis **Indica** of the Ohio State Medical Society, published in 1860. In that report physicians told of success in treating stomach pain, childbirth psychosis, chronic cough, and gonorrhoea with hemp products.<sup>25</sup> A Dr. Fronmueller, of Fuerth, Ohio, summarized his experiences with the drug as follows:

I have used hemp many hundred times to relieve local pains of an inflammatory as well as neuralgic nature, and judging from these experiments, I have to assign to the Indian hemp a place among the so-called hypnotic medicines next to opium; its effects are less intense, and the secretions are not so much suppressed by it. Digestion is not disturbed; the appetite rather increased; sickness of the stomach seldom induced; congestion never. Hemp may

consequently be employed in inflammatory conditions. It disturbs the expectoration far less than opium; the nervous system is also not so much affected. The whole effect of hemp being less violent, and producing a more natural sleep, without interfering with the actions of the internal organs, it is certainly often preferable to opium, although it is not equal to that drug in strength and reliability. An alternating course of opium and Indian hemp seems particularly adapted to those cases where opium alone fails in producing the desired effect.<sup>25</sup>

Because cannabis did not lead to physical dependence, it was found to be superior to the opiates for a number of therapeutic purposes. Birch, in 1889, reported success in treating opiate and **chloral** addiction with cannabis,' and Mattison in 1891 recommended its use to the young physician, comparing it favorably with the opiates. He quoted his colleague Suckling:

With a wish for speedy effect, it is so easy to use that modern mischief-maker, hypodermic morphia, that they [young physicians] are prone to forget remote results of incautious opiate giving.

Would that the wisdom which has come to their professional fathers through, it may be, a hapless experience, might serve them to steer clear of narcotic shoals on which many a patient has gone **awreck**.

Indian hemp is not here lauded as a specific. It will, at times, fail. So do other drugs. But the many cases in which it acts well, entitle it to a large and lasting confidence.

My experience warrants this statement: cannabis *indica* is, often, a safe and successful anodyne and **hypnotic**.<sup>23</sup>

In their study of the medical applications of cannabis, physicians of the nineteenth century repeatedly encountered a number of difficulties. Recognizing the therapeutic potential of the drug, many experimenters sought ways of overcoming these drawbacks to its use in medicine, in particular the following:

Cannabis products are insoluble in water.

The onset of the effects of medicinal preparations of cannabis takes an hour or so; its action is therefore slower than that of many other drugs.

Different batches of cannabis derivatives vary greatly in strength; moreover, the common procedure for standardization of cannabis samples, by administration to test animals, is

subject to error owing to variability of reactions among the animals.

There is wide variation among humans in their individual responses to cannabis.

Despite these problems regarding the uncertainty of potency and dosage and the difficulties in mode of administration, cannabis has several important advantages over other substances used as analgesics, sedatives, and hypnotics:

The prolonged use of cannabis does not lead to the development of physical dependence.“, <sup>13, 14, 24, 39, 44</sup>

There is minimal development of tolerance to cannabis products. <sup>\*11, 13, 14, 24, 44</sup>

Cannabis products have exceedingly low toxicity.<sup>9,21,22,24</sup> (The oral dose required to kill a mouse has been found to be about 40,000 times the dose required to produce typical symptoms of intoxication in man.)<sup>21</sup>

Cannabis produces no disturbance of vegetative functioning, whereas the opiates inhibit the gastrointestinal tract, the flow of bile and the cough reflex.<sup>1,2,24,44,46</sup>

Besides investigating the physical effects of medicinal preparations of cannabis, nineteenth-century physicians observed the psychic effects of the drug in its therapeutic applications.<sup>4,27,33</sup> They found that cannabis first mildly stimulates, and then sedates the higher centers of the brain. Hare suggested in 1887 a possible mechanism of cannabis' analgesic properties :

During the time that this remarkable drug is relieving pain a very curious psychical condition manifests itself; namely, that the diminution of the pain seems to be due to its fading away in the distance, so that the pain becomes less and less, just as the pain in a delicate ear would grow less and less as a beaten drum was carried farther and farther out of the range of hearing.

This condition is probably associated with the other well-known symptom produced by the drug; namely, the prolongation of time.<sup>16</sup>

Reynolds, in 1890,<sup>33</sup> summed up thirty years of his clinical experience using cannabis, finding it useful as a nocturnal sedative in senile insomnia, and valuable in treating dysmenorrhea, neuralgias including tic douloureux and

\* Loewe notes a slight “beginner’s habituation” in dogs, during the first few trials with the drug, as the only noticeable tolerance effect.<sup>20</sup>

tabetic symptoms, migraine headache and certain epileptoid or choreoid muscle spasms. He felt it to be of uncertain benefit in asthma, alcoholic delirium and depressions. Reynolds thought cannabis to be of no value in joint pains that were aggravated by motion and in cases of true chronic epilepsy.

Reynolds stressed the necessity of titrating the dose of each patient, increasing gradually every third or fourth day, to avoid “toxic” effects:

The dose should be given in minimum quantity, repeated in not less than four or six hours, and gradually increased by one drop every third or fourth day, until either relief is obtained, or the drug is proved, in such case, to be useless. With these precautions I have never met with any toxic effects, and have rarely failed to find, after a comparatively short time, either the value or the uselessness of the drug.<sup>33</sup>

Concerning migraine headache, Osler stated in his text: Cannabis *indica* is probably the most satisfactory remedy.<sup>11,28</sup>

In his definitive survey of the literature and report of his own studies, deceptively titled *Maribwana, America's New Drug Problem*, Walton notes that cannabis was widely used during the latter half of the nineteenth century, and particularly before new drugs were developed:

This popularity of the hemp drugs can be attributed partly to the fact that they were introduced before the synthetic hypnotics and analgesics. Chloral hydrate was not introduced until 1869 and was followed in the next thirty years by paraldehyde, sulfonal and the barbitals. Antipyrine and acetanilide, the first of their particular group of analgesics, were introduced about 1884. For general sedative and analgesic purposes, the only drugs commonly used at this time were the morphine derivatives and their disadvantages were very well known. In fact, the most attractive feature of the hemp narcotics was probably the fact that they did not exhibit certain of the notorious disadvantages of the opiates. The hemp narcotics do not constipate at all, they more often increase than decrease appetite, they do not particularly depress the respiratory center even in large doses, they rarely or never cause pruritis or cutaneous eruptions and, most important, the liability of developing addiction is very much less than with opiates.<sup>44</sup>

The use of cannabis in American medicine was seriously affected by the increased use of opiates in the latter half of the nineteenth century. With the introduction of the hypodermic syringe into American medicine from England in 1856 by Barker and Rupper, the use of the faster acting, water-soluble opiate drugs rapidly increased. The Civil War helped to spread the use of opiates in this country; the injected drugs were administered widely and often indiscriminately to relieve the pain of maimed soldiers returning from combat. (Opiate addiction was once called the “army disease.”<sup>41</sup>) As the use of injected opiates increased, cannabis declined in popularity.

Cannabis preparations were still widely available in legend and over-the-counter forms in the 1930s. Crump\* in 1931 mentioned the proprietaries “Piso’s Cure,” “One Day Cough Cure” and “Neurosine” as containing cannabis.<sup>44</sup> In 1937 Sasman listed twenty-eight pharmaceuticals containing cannabis.<sup>36</sup> Cannabis was still recognized as a medicinal agent in that year, when the committee on legislative activities of the American Medical Association concluded as follows:

... there is positively no evidence to indicate the abuse of cannabis as a medicinal agent or to show that its medicinal use is leading to the development of cannabis addiction. Cannabis at the present time is slightly used for medicinal purposes, but it would seem worthwhile to maintain its status as a medicinal agent for such purposes as it now has. There is a possibility that a re-study of the drug by modern means may show other advantages to be derived from its medicinal use.<sup>32</sup>

Meanwhile, in Mexico, the poor were smoking marijuana to relax and to endure heat and fatigue. (Originally marijuana was the Mexican slang word for the smoking preparation of dried leaves and flowering tops of the Cannabis sativa plant—the indigenous variety of the hemp plant.)

The recreational smoking of marijuana may have started in this country in New Orleans in about 1910, and continued on a small scale there until 1926, when a newspaper ran a six-part series on the use of the drug.<sup>44</sup> The fad subsequently spread up the Mississippi and throughout the United States, faster than local and state laws could be passed to discourage it. The use of “tea” or “muggles” blossomed into a minor

\* Chairman, Investigating Committee, American Medical Association.

“psychedelic revolution” of the 1920s Narcotics officers encouraged the enactment of local prohibitory laws and eventually succeeded in bringing about restrictive Federal legislation. In 1937 Congress passed the Marihuana Tax Act, the finale to a series of prohibitory acts in the individual states. Under the new laws, the already dwindling use of cannabis as a therapeutic substance in medicine was brought to a virtual halt. In 1941, cannabis was dropped from the National *Formulary and Pharmacopoeia*.

Around the time of the passage of the Marihuana Tax Act, Walton postulated sites of action for cannabis drugs. Cortical areas, he found, are affected at low dosage, while at high dosage there seems to be a depressant effect on the thalamo-cortical pathways. Hyperemia of the brain appears to be a local phenomenon, unless centers controlling vasodilation might be located in the thalamo-cortical region. Similar possible mechanisms are suggested for the phenomenon of mild hypoglycemia, usual hunger and thirst and occasional lacrimation and nausea.<sup>44</sup>

Despite restrictive legislation, a few medical researchers have had the opportunity to continue the investigation of the therapeutic applications of cannabis in recent years. In his study of the medical applications of cannabis for Mayor La Guardia's committee, Dr. Samuel Allentuck reported, among other findings, favorable results in treating withdrawal of opiate addicts with tetrahydrocannabinol (THC), a powerful purified product of the hemp plant.<sup>1,24</sup>

An article in 1949, buried in a journal of chemical abstracts, reported that a substance related to THC controlled epileptic seizures in a group of children more effectively than diphenylhydantoin (Dilantin®), a most commonly prescribed anticonvulsant.<sup>9</sup>

A number of experimenters, believing that cannabis products might be of value in psychiatry, have investigated the applications of various forms of them in the treatment of mental disorders. Cannabis had been used in the nineteenth century to treat mental illness.<sup>19,25,45,46</sup> However, aside from some rather equivocal clinical studies, primarily in the treatment of depression,<sup>29,30,35,39</sup> and another report of success in treating withdrawal from alcohol and opiate addiction,<sup>42</sup> no significant contemporary psychiatric studies involving cannabis therapy have been reported to date.

Many current “authoritative” publications unequivocally state that there is no legitimate medical use for marijuana. As compared with the 1800s, this century has seen very little medical research on the array of some twenty chemicals that are found in the hemp plant.<sup>37</sup>

Today’s readers may tend to be skeptical about a report of a cure for gonorrhoea published over a century ago.<sup>19,25</sup> Such findings may bear reinvestigation, however, in the light of a report from Czechoslovakia in 1960 that cannabidiolic acid, a product of the unripe hemp plant, has bacteriocidal properties.<sup>7</sup> Some of the therapeutic applications reported in the early medical papers have been corroborated by later investigators, but for the most part the therapeutic aspects of cannabis remain to be re-explored under modern clinical conditions.

In the past twenty years, clinical and basic research on cannabis have dwindled to practically nothing. The record of tax stamps issued by the Federal Bureau of Narcotics for cannabis research, as compared with those for research on narcotic drugs, tells the story of the twenty-year “drought” in the investigation of cannabis products:<sup>43</sup>

*Users for Purposes of Research,  
Instruction, or Analysis*

<i>Year</i>	<i>Narcotic Drugs</i>	<i>Marijuana</i>
<b>1938</b> . . . . .	. . . . .	5
<b>1941</b> . . . . .	<b>94</b>	.
<b>1943</b> . . . . .	. . . . .	<b>43</b>
<b>1946</b> . . . . .	<b>323</b>	.
<b>1948</b> . . . . .	. . . . .	<b>87</b>
<b>1951</b> . . . . .	<b>1078</b>	..
<b>1953</b> . . . . .	. . . . .	<b>18</b>
<b>1956</b> . . . . .	<b>284</b>	.
<b>1958</b> . . . . .	. . . . .	<b>6</b>
<b>1961</b> . . . . .	<b>344</b>	..
<b>1965</b> . . . . .	<b>431</b>	<b>16</b>

The rising non-medical use of marijuana both floated and was buoyed by the “psychedelic revolution” of the mid 1960s. The panicked reaction included a renewed scientific interest in the drug.

Eleven studies funded by the National Institute of Mental Health in 1967 concerning cannabis were either specialized animal experiments, part of an observational sociologic study of a number of drugs, or explorations of chemical detection methods. No human studies were included.

Of the fifty-six projects funded during the next fiscal years 1968-69 only two used humans.<sup>52</sup> The next year was somewhat less cautious with eight out of thirty-five projects devoted to clinical studies.<sup>53</sup>

Some of the preliminary results are in from these studies. Much is still unpublished.

According to Harris, the toxicity factor of marijuana derivatives is over two hundred and that chronic smoking of marijuana is less harmful to the lungs than tobacco cigarettes.<sup>49</sup>

Domino described the cross tolerance of THC and alcohol in pigeons<sup>47</sup> corroborating Jones' clinical observations.<sup>50,51</sup> These rediscoveries demand therapeutic trial.

In August 1971 certain secret Defense Department documents were declassified. While at NIMH as a consulting research psychiatrist in 1967 I had become aware of the existence of clandestine research at Edgewood Arsenal in Maryland.

From 1954-59 Dr. Van M. Sim was in charge of the project. He reported to *Medical World News*: "Marijuana . . . is probably the most potent anti-epileptic known to medicine today."<sup>49</sup>

Dr. Harold F. Hardman, then with the Defense contracting group at the University of Michigan's Department of Pharmacology reported effects of profound hypothermia and felt marijuana derivatives to be potentially quite useful in brain and traumatic surgery.<sup>48</sup>

The principal focus was, however, on the possible use of THC homologs as incapacitating agents. Besides the aforementioned government agency and university, the private sector was represented by the Arthur D. Little Company of Cambridge, Massachusetts."

Recently in the course of a study of effects on driving, it was incidentally discovered that cannabis lowers intraocular pressure, thus being possibly useful in the treatment of glaucoma.<sup>56</sup>

Thus, a helix is made. Modern technologic methods confirm O'Shaughnessy's observations 130 years ago. After swinging away from the knowledge of marijuana's properties through the worship of new synthetics, an unrelated rise of marijuana use socially, illegalization and removal from availability for clinical use, medicine rediscovers marijuana.

The flame of knowledge is at a low ebb, kept alive by isolated scientists and clinicians; it is now being rekindled by these recent circumscribed revelations.

Unless existing restrictive state and federal laws governing marijuana are changed, there will be no future for either modern scientific investigation or controlled clinical trial by present-day methods.

The tide is turning. The Federal Bureau of Narcotic and Dangerous Drugs, National Institute of Mental Health and The Food and Drug Administration Joint Committee recently authorized human therapeutic trial of cannabis products. We may now look forward to reinvestigation of the numerous possible medical uses of marijuana.<sup>54</sup>

A concerted effort is indicated for full-scale investigations where knowledge is lacking. Acute and chronic effects of cannabis should be restudied by modern methods. Metabolic pathways of action and detoxification need exploration by the pharmaceutical means of today. Chronic toxicity studies must be undertaken to examine possible long-term effects of cannabis use. \*

Medical science must again confront the problems of cannabis' insolubility in water and its variable strength. Since human and animal responses vary a great deal, individual doses must be titrated. The popular "double blind" type of study methods will require revision. The reporting of personal drug experience was once acceptable to the scientific community. <sup>15,22,25,29,34,39,44</sup> Humans who are drug "sophisticates" will again become indispensable to psychoactive drug research, as wine tasters are to the wine industry, for only humans can verbally report the subtle and complex effects 'of these substances.

\* Cunningham in 1893 found no gross central nervous system changes with chronic administration of hemp drugs to primates over several months.'

Government agencies having stimulated little significant clinical research in this field, the pharmaceutical industry should take the initiative in starting basic research and clinical studies into the purified **congeners** of cannabis for their chemical properties, pharmacologic qualities and therapeutic applications.

***Possible Therapeutic Applications of  
Tetrahydrocannabinols and Like Products***

- Analgesic-hypnotic<sup>16, 18, 19, 23, 25, 27, 33, 45</sup>
- Appetite stimulant<sup>18, 25, 27</sup>
- Antiepileptic-antispasmodic<sup>9, 18, 27, 33, 40, 45, 49</sup>
- Prophylactic and treatment of the neuralgias, including migraine and tic douloureux<sup>3, 16, 17, 18, 19, 23, 25, 28, 31, 33, 38, 40, 45</sup>
- Antidepressant-tranquilizer<sup>6, 16, 18, 19, 23, 25, 31, 33, 40, 45</sup>
- Antiasthmatic<sup>18, 25, 45</sup>
- Oxytocic<sup>25, 45</sup>
- Antitussive<sup>3, 16, 25, 38, 45</sup>
- Topical anesthetic<sup>8</sup>
- Withdrawal agent for opiate and alcohol addiction<sup>5, 23, 24, 38, 42, 45, 47, 50, 51</sup>
- Childbirth analgesic<sup>12</sup>
- Antibiotic<sup>7</sup>
- Intraocular hypotensive<sup>56</sup>
- Hypothermogenic<sup>48</sup>

Medicine, being an empiric art, has not hesitated in the past to utilize a substance first used for recreational purposes, \* in the pursuit of the more noble purposes of healing, relieving pain and teaching us more of the workings of the human mind and body. The active constituents of cannabis appear to have remarkably low acute and chronic toxicity factors and might be quite useful in the management of many chronic disease conditions. More reasonable laws and regulations controlling psychoactive drug research are required to permit significant medical inquiry to begin so that we can fill the large gaps in our knowledge of cannabis.

\* Morton "discovered" ether for anesthetic purposes after observing medical students at "ether frolics" in 1846. (Howard W. Haggard: ***Devils, Drugs and Doctors***, Harper and Row, New York, 1929, p. 99.)

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