Research on psychoactive plants at Mexico's National Medical Institute, 1888-1915

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Abstract

The aim of the present essay is to analyze the work performed at the National Medical Institute (NMI) with a group of plants remarkable for containing significant psychoactive principles. The studies on the NMI conducted up to the present time did not analyze in depth the place those substances had in the Institute's research agenda. For that reason we sought to identify the medicinal plants studied at NMI together with their active principles, the diseases to which they were experimentally applied, and the procedures used to study them. To illustrate that process we present two particular cases: peyote (*Lophophora williamsii* (Lem.) J.M. Coult) and white sapote (*Casimiroa edulis* La Llave & Lex.).

Keywords

Medicinal plants; Psychoactive substances; Alkaloids; Materia medica

Pesquisa de plantas psicoativas no Instituto Médico Nacional de México, 1888-1915

Resumo

O objetivo do presente ensaio é analisar os trabalhos realizados no Instituto Médico Nacional (IMN) com um grupo notável de plantas, por conter princípios ativos importantes. Os estudos sobre o IMN realizados até o presente não analisaram profundamente o papel dessas substâncias na agenda de pesquisa do Instituto. Assim, procuramos identificar as plantas medicinais pesquisadas no IMN com seus princípios ativos, as doenças nas quais foram testadas e os procedimentos para o seu estudo. Ilustramos esse processo com dois casos concretos: o peiote (*Lophophora williamsii* (Lem.) J.M. Coult) e sapota branca (*Casimiroa edulis* La Llave & Lex.).

Palavras-chave

Plantas medicinais; Substâncias psicoativas; Alcaloides; Matéria médica

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Introduction

By the end of the 19th century the German company Boeringer & Sons sold *pellotine*.[1] The use of this new hypnotic molecule was soundly supported on 'hundreds' of tests conducted in Europe and the United States. That fact notwithstanding, *pellotine* had a short career, because Bayer soon introduced several synthetic barbiturates in the market like barbital (Veronal®) and phenobarbital (Luminal®), which by being easier to manufacture on large scale made the commercial exploitation of pellotine clearly unviable.[2]

The studies of the alkaloids contained in peyote represent an example of international research networks developed around this plant,[3] which were indispensable to amass the ethnographic, botanic and pharmacological information needed to establish innovative research lines in pharmacological laboratories in several parts of the world. This small cactus endemic to some areas in the south of the United States and north of Mexico acquired botanic and pharmacological relevance as a function of the remarkable action of its alkaloids on the central nervous system, having no parallel but in few among the hitherto known plants.

Mexico contributed largely to the study of peyote and other plants containing psychoactive substances through research conducted at a quite peculiar institution, *Instituto Médico Nacional* (National Medical Institute – NMI).[4] NMI was created in 1889 (to close its doors in 1915) to investigate the so-called *national therapeutics*, namely, the one based on the empirical knowledge preserved in the folk tradition.[5] Originally, the NMI was divided into five sections: Natural History, Experimental Physiology, Analytical Chemistry, Experimental Therapeutics and Medical Geography and Climatology; a few years later a Department of Industrial Chemistry was also established.[6]

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[1] Although mescaline is the main alkaloid, and one of the most important among the currently known psychoactive substances present in *Lophophora williamsii* (Lem.) J.M. Coult, another alkaloid, pellotine, enjoyed global fame by the end of the 19th century. It should be noticed that, as a fact, it was not one, but two different *Lophophora* species that were being studied for botanical identification; as is presently known, pellotine is the main alkaloid of *L. diffusa*. See Daniel M. Perrine, "Visions of the Night: Western Medicine Meets Peyote, 1887-1899," *The Heffter Review of Psychedelic Research*, 2 (2001), 6-52, on 6.

[2] Ibid., 8.

[3] At the end of the 19th century and along part of the 20th century, peyote (*L. williamsii*) was known as *Anhalonium lewinii*; the name was given in honor of Louis Lewin (1850-1929), a toxicologist from Berlin, who was the first to call the attention to the pharmacological activity of peyote alkaloids; Perrini, 7.

[4] See Angélica Morales Sarabia, "El cuerpo y la autoexperimentación en la farmacología y la terapéutica experimental," in *Los contornos del alma, los límites del cuerpo: género, corporalidad y subjetivación*, org. Rodrigo Parrini Roses (México: PUEG/UNAM, 2008), 231-46.

[5] Angélica Morales Sarabia, *El naturalista José Ramírez: Un análisis de su obra científica (1879-1904)* (PhD dissertation, Facultad de Filosofía y Letras, UNAM, México, 2010).

[6] See the article by Liliana Schifter and Patricia Aceves in the present issue of *Circumscribere*.

In the course of its 26 years of existence, NMI published a large amount of information on the classic psychoactive substances - cocaine, opium and its derivatives, as well as the one resulting from research of the native flora conducted in its premises. The latter included species with considerable psychostimulant or depressant actions unknown to or scarcely addressed by the contemporary chemical and pharmacological sciences. In this paper we discuss some of the studies conducted at NMI aiming at placing them within a map of the global circulation of knowledge likely to point to the contribution NMI made to the study of alkaloids.

It is worth to observe that researchers at NMI had the explicit intention to translate the practices of empirical medicine into the language of science. This was not any new enterprise, but had a long history in Mexican pharmaceutics and materia medica. A tradition, it should be said, that was never static. However, differently from the 18th century attempts, NMI's staff had access to the human and material resources and the political support needed to develop a *national therapeutics*. Since the empirical knowledge was at the very center of the Institute's projects, it is not reason for surprise that quite often it served as point of departure for laboratory work.[7]

NMI was deeply committed to the approach proper to medical geography. Such approach was intimately linked to the concepts of medical topography, which although had begun to develop in the 18th century kept strong roots in public health and urbanism along the 19th century.[8] The measurement of climatic characteristics, type of vegetation and altitude, among other factors, served to account for the appearance or absence of particular illnesses. NMI's scientific staff maintained that the local diseases were best treated with endemic therapeutic resources. Therefore the concepts on disease and plant therapeutic resources were formulated within the framework defined by the causal relationship among disease, local flora and geography.

Such approach to the understanding of disease and the therapeutic resources meant to link biological and economic criteria together for the sake of the national

[7] The criterion to select plants for study at NMI was their frequency of use by Mexican herbalists and pharmacists. In all instances, the studies began by an investigation of the therapeutic actions traditionally attributed to the plants. This path to the knowledge of Mexican therapeutics was explicitly recognized by F. Altamirano, upon stating "While performing those studies we noticed that almost all the plants used by the common people were also used by the ancient Mexicans, and that they were first conveyed to as by Dr. Hernández, then by the authors of the Mexican Flora, followed by scientific Societies, the Pharmaceutical one in particular, until the time of the Medical Institute". Within this context, Altamirano points to the need to revise some names, properties and wrong therapeutic applications, because they were exaggerated or unlikely, as well as the amassed information "[…] in the light of the recent advances in science, and to broaden the scope of research"; Fernando Altamirano "Historia y Objeto del Instituto Médico Nacional (1905)," Archivo General de la Nación (AGN)/Gobierno (GD) 125/Instrucción Pública y Bellas Artes (IPBA)/vol. 128/exp. 16, 8 ff.

[8] Federico Fernández Christlieb, "La influencia francesa en el urbanismo de la ciudad de México: 1775-1910," in *México Francia: Memoria de una sensibilidad común, siglos XIX-XX*, coord. Javier Pérez Siller (México: Benemérita Universidad de Puebla; El Colegio de Sal Luis, A.C.; CEMCA, 2000), 227-65, on 258-9.

therapeutics The contemporary physicians and pharmacists assumed that the drugs obtained from the national flora were more accessible and less expensive compared to foreign medications and even more effective in some cases.[9] As in the past, the search for substitutes continued to represent an important part of the study of medicinal plants in general, the alkaloids in particular. As a matter of policy NMI sought to reduce the cost of production of medicines to improve the population's access to them and at the same time rise Mexico to the level of a world power in the field of therapeutics.

It is worth to observe that just as laboratories and medical and pharmaceutical institutions in Germany, England and the United States, also NMI developed interest in the analysis of the much appreciated alkaloids; therefore it reproduced procedures formulated abroad, while developing research lines of its own. This is why we insist on the fact that the local perspective should be considered as a necessary scale of analysis in studies on the history of science, as it allows analyzing the circulation of knowledge across definite geographic-cultural spaces with particular characteristics, which might be quite variable or open new paths of research. While the 19th century was, indeed, the century of the alkaloids, each country or scientific tradition produced unique knowledge as a function of the corresponding availability of natural resources, the configuration of their internal market, the interactions between different social actors and so forth.

While NMI succeeded in enlarging the catalogue of psychoactive substances (analgesics and in lesser degree hypnotics) the number of purgatives, antimalarial and febrifuge drugs, just to mention a few examples, was much larger.

Plants with psychoactive properties at NMI

Among the many plants studied at NMI, we chose for our analysis one particular group of medicinal plants known for containing substances with remarkable action on the central nervous system, presently known as psychoactive compounds. These molecules exhibit analgesic, hypnotic and tonic properties and are known as drugs that alter the sensory perception and state of mind of users, like the aphrodisiacs, or more simply as those that 'enhance drunkenness'.[10] We further included some drugs NMI's pharmacists considered to be highly toxic (for instance, to the animals that ate them) as a

[9] This was the feeling of Mexican pharmacists as a whole, rather than of NMI's staff only. Many students at the National School of Medicine devoted their theses to national substitutes for foreign plants; see Mariana Ortiz Reynoso, *Las tesis de farmacia del siglo XIX mexicano* (México: UAM-X; SQM; Colegio Nacional QFB's, 2002), 297.

[10] Such was the particular case of black nightshade (*Solanum nigrum* L.), which was considered in France to contain an immediate principle with remarkable brain exciting properties and that added to alcohol made drunkenness develop faster. For that reason the species that grew in Mexico was selected for study at NMI; see "Proyecto de Programa de Trabajos del Instituto Médico Nacional durante el primer trimestre de 1907", AGN/GD 125/IPBA/vol. 130/exp. 40/100 ff.

function of their probable action on the central nervous system, or that they judged to be of potential therapeutic interest, e.g., for the treatment of sleep disorders (insomnia), epilepsy and pain.

In addition to the explicit relevance of the psychoactive drugs in association with their pharmacological effects, the studies on them performed in the early decades of the 20th century are also worthy of consideration, because it was at that time that the legislation restricting the use of opiates and its derivatives, considered a public health hazard, began to be outlined in Mexico and abroad.[11] The formerly so-called heroic drugs like opium and morphine became *addictive substances that made the race degenerate*.[12] Thus being we sought to establish whether the NMI had special interest in finding, in the early years of the 20th century, substitutes for opiates, marijuana and coca that were less hazardous to health.[13]

The study of medicinal plants performed at NMI was based on the *experimental therapeutics* method, which involved several successive steps corresponding to each of the Institute's sections. The first step consisted in the botanic description and classification of the plant together with the compilation of the historical information on its therapeutic applications. Next chemical analysis was performed and the active principles that would be next used in physiological tests with animals were prepared. Finally, the drugs were used for the treatment of patients admitted to the Clinical-Therapeutic ward of St. Andrew's Hospital. While NMI was allocated a building of its own in the General Hospital in 1905, the therapeutic experiments were also conducted at other public and private hospitals. The prescriptions were made by physicians who voluntarily agreed to participate in the experiments.[14]

A total of 21 plants possibly having psychoactive properties were studied at NMI from 1889 to 1915. Most of them were analyzed at each of the Institute's sections, whereby precise information could be collected on all aspects from botanical

[11] Mexico participated in the 1912 Hague International Opium Convention that discussed limits to the use of opium, morphine, cocaine, heroine and derivatives. It was then agreed to restrict the import, export and preparation of crude opium and its preparations and to impose the need for legal permit to the establishments that manufactured, sold, distributed, imported or exported them. It was further decided that the signatory countries had to enact laws limiting the manufacture, use and sale of morphine, cocaine and their salts for medical purposes.

[12] "This name is used to designate three medicinal substances that moved from the Pharmaceutical Chemical Laboratory on to become a part of the commercial arsenal at bars, cabarets, brothels and dens for addicted people; these are morphine, heroine and cocaine […] which punish users with fast physical and mental degeneration"; anonymous, "Las drogas heroicas," *La Farmacia*, *Nueva Serie*, n. 16: 249-51.

[13] The Dispositions *on the trade of products that might be used to promote vices that degenerate the race, and on the cultivation of plants that might be used for the same purpose* were approved in 1920. These dispositions restricted the cultivation and import of opium, morphine, heroine and cocaine, which were categorized as *dangerous substances*. Twenty years earlier, the Health Code (1902) indicated that substances "with no other use but for vice" were to be confiscated.

[14] See the reports published by NMI in its journal *El Estudio,* later on renamed *Anales del Instituto Médico Nacional*. *Continuación de El estudio*.

classification to clinical effects. However, in some cases the study was interrupted at the stage of physiological experimentation. Data relative to those 21 plants are described in table 1, including: a) common and scientific name; b) type of study; c) therapeutic action to be evaluated (frequently originated in reports by the common people); d) suggested dosage forms; e) outcomes; f) year of publication; and g) additional observations. In this regard it is worth to observe that the performance of a clinical study presupposes previous investigation of the physical action of the drug in animals. Outcomes were categorized as 'confirmed' (the reported common use was corroborated) or 'inconclusive' (the result was controversial).

Many of the studied plants were included in *Datos para la materia médica mexicana* (Data for the Mexican materia medica – DMM, 1894-1908),[15] which NMI published from 1894 to 1908 to divulgate the research performed in its premises. Among such plants the following stand out: añil (anil indigo, *Indigofera suffrutiocosa* Mill.), *zapote blanco* (white sapote, *Casimiroa edulis* La Llave & Lex.), *cicutilla* (famine weed, *Parthenium hysterophorus* L.) and *tepozán* (butterfly bush, *Buddleja americana* L.). Also satisfactory results were achieved in the case of *chicalote*, (Mexican poppy, *Argemone mexicana* L.), *palillo* (*Croton morifolius* Willd.) and tatalencho (*Gymnosperma multiflorum* DC.). The fact that these plants were studied over long periods of time suggests that NMI had particular interest in them or in the diseases they were able to heal. Some evidences further indicate that also some commercial establishments in Mexico and abroad manifested interest in these plants.

Table 1. Plants with actions on the central nervous system studied at National Medical Institute, 1889-1915

Plant and part used	Study type	Assessed action	Dosage form	Outcomes	Additional observations	Study date
Anil indigo *Indigofera suffrutiocosa* Mill. (leaves)	-	Antiepileptic; purgative	Packets (leaves)	Confirmed	Too violent purgative action	1891 1894 1912
Madroño borracho/Summer-blooming manzanita *Arctostaphylos arguta* Zucc. (seeds, dry and fresh fruit, leaves)	-	For insomnia or weakness caused by alcohol abuse	HAE (hypnotic)/ petrolic extract (purgative)	Confirmed mild hypnotic action (dry fruit) Confirmed mild purgative action (dry fruit)	Narcotic action in animals not confirmed. Confirmed sleep induction without side effects (nausea, headache). Effects similar to white sapote.	1891 1894 1907

[15] The first part of DMM was published in 1894 and contained the monographs of white sapote, *palillo*, *coca de Motzorongo*, Mexican poppy, famine weed, summer-blooming manzanita and *tabaquillo*, among others; "Lista de las plantas que formarán la primera parte de la Materia Médica Nacional" *Anales del Instituto Médico Nacional. Continuación de El Estudio* 1, no. 5 (1894): 218.

Iguande (Llora sangre) *Bocconia arborea* S. Watson	-	Local anesthetic and hypnotic, mainly anesthetic	Alkaloid bocconine is soluble in ether, water and chloroform. Bocconine chlorhydrate, acetate, citrate per hypodermic injection.	Confirmed	Local anesthetic and hypnotic effect, mainly anesthetic. Confirmed effect attended with irritation (bocconine is soluble in ether)	1891 1894 1907 1913
Coca cultivada; coca de Motzorongo Erythroxylum macrophyllum Cav. (leaves)	ChA	Tonic; analgesic	-	Inconclusive; 0.4% of impure alkaloids and traces of cocaine	Although suggested, it was not included in DMM (1898) due to inconclusive results. According to Ramírez it should be called Peruvian coca.[16]	1890 1903
Yerba loca/Purple locoweed *Astragalus amphyoxis* Humb	Phys (rabbits)	Poisonous (intoxication and death in herd after eating it)	-	Inconclusive; doubts on botanical identification	Not confirmed	1891 1903
Yerba de la cucaracha Aplophyton cimicidum A.DC.	Phys (dogs) Clinical	Parasiticide; sedative	Packets; tincture; fluid extract; syrup	Confirmed insecticide and parasiticide actions. Kills dog fleas and human *Pediculi capitis* and *pubis*	Two species have the same scientific name. No purgative effect. Toxic to lower, but not to higher animals	1901 1903 1907
White sapote *Casimiroa edulis* La Llave & Lex (dry pit)	Phys Clin (cases of nephritis; WIA)	Sedative; diuretic	Dry extract (distilled ground pits in the presence of an alkali). Extract capsules (clinical use)	Confirmed. In dogs: epileptic-like seizures, vomiting, stools, urination, narcosis, loss of sensitivity, paralysis and death (in high dose)	Glycoside was named casimirose. Sedative effects stronger when prepared with bromide	1894 1896 1897 1900 1902 1903 1905 1906 1912
Peyote *Anhalonium lewinii, Anaholonium williamsii*	Clinical Phys (doves and rabbits)	Cardiotonic; aphrodisiac	Clinical: fluid extract; tincture (pellotine chlorhydrate). Phys: fluid extract	Clinical: confirmed. Phys inconclusive.	Undesirable effects include auditory and visual hallucinations. Hallucinogenic. Studies sought to establish similarity between its alkaloid and apomorphine	1900 1901 1902 1905 1912 1913
Famine weed *Parthenium hysterophorus* L.	Clinical	Analgesic	Dry and HAE; tincture	Confirmed.	Satisfactory results in rheumatism, otitis media and headache. Considered a substitute for salicylate of soda	1896 1901 1902 1905 1907

[16] Leopoldo Flores, "Junta mensual del 31 de octubre de 1902," *Anales del Instituto Médico Nacional. Continuación de "El Estudio"* 5 (1903): 374-5, on 374.

Butterfly bush *Buddleja americana* L.	Clinical (TEW; WIA)	Hypnotic; diuretic	HAE; tincture	Both actions confirmed		1894 1896 1897 1900 1901 1902 1903 1907
Iguande/Plume poppy *Bocconia arborea* S. Watson	-	Local anesthetic; analgesic; hypnotic.	Hypodermic injection (bocconine chlorhydrate)	Inconclusive, albeit promising	Action similar to morphine, but predominantly analgesic (opposite to morphine)	1890 1894
Palillo *Croton morifolius* Willd. (seeds)	Phys (dogs) Clin (TB cases)	Analgesic (stomachache; facial neuralgia); drastic purgative	Oil; fluid extract; *horchata* (rice-based beverage); tincture	Confirmed.	A resinous active principle was isolated on ChA	1891 1894 1901 1902 1907 1912 1913
Tatalencho *Gymnosperma multiflorum* DC.	Clinical	Analgesic; wound-healing; antidiarrheal	HAE; tincture; infusion; brewing	Confirmed	Cases with muscle and joint rheumatic pain. Cases with alcohol- or TB-related and membranous enterocolitis (to demonstrate the antidiarrheal action).	1891 1894 1900 1902 1905 1907 1913
Mexican poppy *Argemone mexicana* L. (seeds, stem, flowers)	Clinical (insomnia in alcoholics; cough in TB; pain by womb gangrene; scabies, pemphigus and ichthyosis)	Antipruritic; emetic-cathartic; hypnotic; antitussive	Flower extract (womb pain); extract in tablets (alcoholism and TB); latex; seed oil (skin indications)	Confirmed	Successfully employed in patients with insomnia and delirium by epilepsy or alcoholism; dyspnea and cough in TB (flowers). Useful in scabies, pemphigus and ichthyosis (seed oil). Recommended as substitute for Helmerich ointment (sulfur-based).	1891 1894 1902 1903 1907 1912 1913
Black nightshade *Solanum nigrum* L. (root, berries)	Clinical (cases of chronic rheumatism)	Quickens and enhances drunkenness	Tincture; powdered root; extract	Confirmed	Suggested as substitute for the European variety. Emetic-cathartic and purgative. Poisonous in high dose	1902 1913
Ololluhqui/Morning glory *Ipomoea sidaefolia* (Kunth) Sweet. (whole plant and root)	Phys (toads) Clinical	Induces nervous and gastrointestinal disorders	HAE and active principle	Confirmed	Confirmed clinical effects: nervous and gastrointestinal disorders (headache; sleepiness; numbness; muscle pain; cryostasis; paresthesia; excessive thirst; nausea; vomiting; stomachache; feeling of weight	1900 1912

					and adynamic stomach; diarrhea; reduction of heart and respiratory rate). In toads: reported paralysis and death	
Tabaquillo *Calamintha macrostema* (Moc. & Sessé ex Benth.) Benth	Phys (Guinea pigs)	Essence	Poison	Inconclusive	Confirmed toxicity	1890 1896 1902 1907 1912 1913
Axocopaque *Gaultheria acuminata* Schtdl. & Cham (leaves)	Clinical	Essence in unguent; fluid extract	Analgesic	Confirmed	Unguent in rheumatism. The efficacy of the essence is comparable to methyl salicylate	1889 1902 1913
Chapuz *Helenium mexicanum* Kunth	Clinical (tabes dorsalis; polyneuritis)	HAE; dry HAE; tincture (*chapuz* resin)	Analgesic	Inconclusive		1894 1907 1912 1913
Peyote *Echinocactus williamsii* Lemaire ex Salm-Dyck[17]	Clinical (one case of mitral insufficiency; one case of enteritis)	HAE	Cardiotonic	Confirmed cardiotonic effect	Remarkable increase of urine output, reduction of edema, dyspnea, insomnia and cough. Increased the blood pressure and made the pulse rate regular. In the case recovering from enteritis it caused severe headache, mild vertigo, increased the blood pressure and made the pulse rate regular	1912

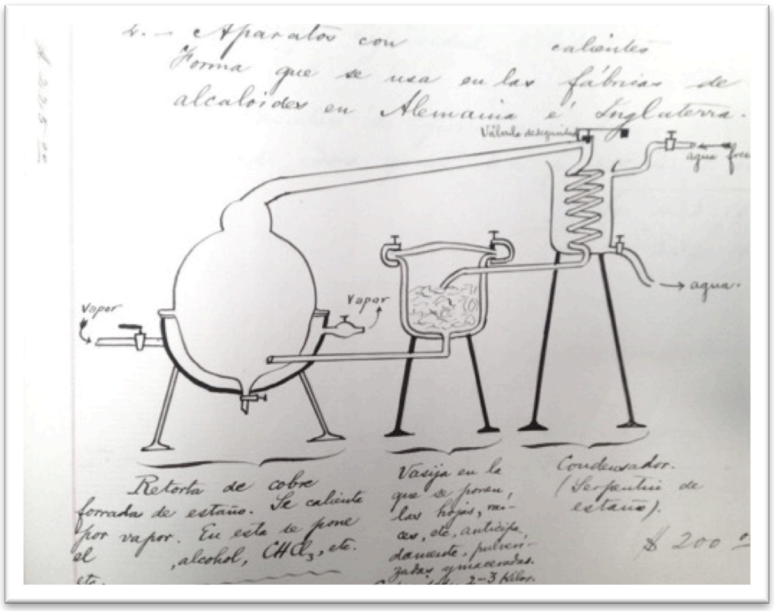
NMI's Section Two (Analytical Chemistry) was highly productive. Active principles were isolated for most plants, and also their components could be quantified, although in a smaller number of species. The quantitative and qualitative chemical analytic techniques used were based on solubility assay and the method for identification of alkaloids developed by Johann G.N. Draggendorff (1836-1898), which was the most widely used at that time. According to Eduardo Armendáris, chair of the Experimental Physiology section, that was the most efficient method for the study of the active principles of medicinal plants.[18] It required a retort, a condenser and a closed

[17] Currently *E. williamsii* Lemaire ex Salm-Dyck and *L. williamsii* (Lem.) J.M. Coult) are considered synonyms, but they appear as different species in earlier records, see e.g., El Peyote," *Anales del Instituto Médico Nacional* 12, no. 6 (1914): 183-243.

[18] Eduardo Armendáris, "Análisis de las semilla del Yoloxochitl," *El Estudio* 4 (September 1892): 248-9, on 249.

receiver flask with drain. It is worth to notice that NMI requested the same equipment for manufacture of alkaloids as the one used in German and English laboratories, as Figure 1 shows.

Figure 1. System for extraction of alkaloids from medicinal plants[19]



Among the reagents used, the following acids and inorganic salts stand out: hydrochloric acid, nitric acid, sulfuric acid, ammoniac and lead subacetate; relative to the organic solvents, the ones frequently used were chloroform, petroleum ether and sulfuric ether. In turn, the preferred dosage forms were liquid or semisolid, mainly liquid or dry extracts, tinctures, packets and unguents; tablets were seldom recommended.[20]

[19] Nineteenth-century chemistry and pharmacy were signaled by the study of alkaloids. In Mexico, the work in this regard was limited to the isolation of alkaloids from local plant species and investigation of their possible therapeutic applications. While NMI requested the same equipment as the one used by German manufacturers of alkaloids, the Europeans did not only seek to extract, but also to produce artificial (synthetic) alkaloids. So, for instance, in the reports of the Cavendish Society it says: "It is more tan probable that by studying the mode of their formation, we may in course of time be led to prepare artificially, and at little experience, morphine, quinine, strychnine, &c. […]," M.E. Kopp, "VII Report on the Artificial Formation of Alkaloids," In: *Chemical Reports and Memoirs, Cavendish Society* (London: T.R. Harrison, 1848), 297-322, on 297.

[20] These dosage forms might seem poorly innovative. The innovative aspect introduced by the Mexican scientists is not related with pharmaceutical technology, but consists in the use of active principles extracted from the national flora. This characteristic is also found in the pharmaceutical dissertations presented at the National School of Medicine and the various Mexican pharmacopeias, published from 1846 until well after the Mexican Revolution (ca. 1910-1920); see Liliana Schifter Aceves, "La farmacopea: guardiana de un patrimonio nacional viviente," *Casa del Tiempo* 4th series 3, no. 29 (2010): (29) 63-7.

As mentioned above, the isolated active principles were tested in animals to establish some pharmacokinetic parameters, such as the route and speed of elimination, and visible pharmacological responses, like vomiting, sleepiness, paralysis, or even death. The animals employed included doves, Guinea pigs, dogs, toads and rabbits, seemingly indistinctly and without any particular preference. In some specific instances, as, e.g., in the study of *yerba de la cucaracha*, the tests were performed with flies, small crustaceans and mollusks, fish, arachnids, worms and several insects. The reports do not make mention of the rationale underlying the choice of experimental animals nor of their greater or lesser closeness to humans. Once the physiological studies were completed, the most adequate dosage forms and doses were selected for the clinical trials with human beings.

The clinical studies were conducted at few hospitals that granted access to NMI staff. For this reason the tests were often performed in patients with conditions other than the ones for which the drugs were allegedly useful. However, even in those cases measurement of response parameters, such as perspiration, body temperature, urine output and dizziness, was attempted, as well as of any other phenomenon likely to represent a pharmacological or toxic effect.

Among the classes of compounds of greatest interest, the glycosides and alkaloids found in white sapote and peyote stand out. The active principle of the former was rated an excellent hypnotic, and the one of the latter a cardiotonic and aphrodisiac. Interestingly, although manufacture on industrial scale was suggested for both, it did not come to be. The reason is that although white sapote was thoroughly analyzed at NMI, it failed to arouse interest abroad, and in the case of peyote, German pharmacists had been the first to call the attention to its alkaloids and their potential medicinal use. Relative to white sapote, the time devoted to its study and the setting for the clinical trials, namely, the asylum for insane women, are worthy of mention, and peyote arose interest among businessmen and research institutions abroad. For those reasons we discuss them in more detail in the following sections.

White sapote (Casimiroa edulis)

White sapote was one of the first hypnotics to yield promising results. Research at NMI allowed detecting a glycoside, which was named *casimirosa*. Pharmaceutical preparations of casimirosa suggested by NMI's Section Four (Experimental Therapeutics) were successfully administered to 125 patients admitted to the asylum for insane women, this being one of the few records of tests with psychoactive substances conducted in the psychiatric setting. The reports made by the asylum doctors indicate that combination of casimirose with bromide was extraordinary as a sedative, "because success was achieved in 371 out to the 411 times it was used to reduce excitation in

alienated women"[21]. The list with more than 20 pharmaceutical preparations made by professor Juan Manuel Noriega (1869-1958) in 1896 includes casimirose tincture and extracts (hydroalcoholic, petroleum ether and sulfuric ether). It is worth to observe that NMI elaborated pharmaceutical preparations for external doctors who expressed interest in some of them, like, e.g. *tatalencho* tincture and sapote extract.[22] Therefore, the fact that New York-based company Parke Davis & Son manifested interest in industrial scale production of casimirose extract is no reason for surprise.[23]

Peyote (Lophophora williamsii)

Peyote was officially included in NMI's work plan for 1899, however, the results were inconclusive. In 1902, the Institute's director informed the Secretary of Development that Dr. Miguel Zuñiga had sent a tube of anhalonium chlorhydrate extracted by Mr. Merck, from the Merck company, Germany.[24] According to a previous agreement, Merck was in charge of the isolation of alkaloids from peyote and NMI of the physiological experiments.[25] One year earlier, the NMI had sent 2 kg of peyote (*Anhaloniun lewinii*) to the Merck laboratories, which was a rather considerable amount as a function of the difficulties to obtain the plant and the ongoing confusion between two species of peyote, *Anhalonium lewinii* (also known as *L. williamsii* (Lem.) J.M. Coult.) and *L. diffusa* (Croizat) Bravo.[26-27] Merck also requested NMI to send him "the substantial part of that root", for which he would pay 8 marks per kg, so that he could continue his laboratory experimental research.

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[21] "El zapote blanco: *Casimisora eduli*. Rutáceas," in *Datos para la materia médica mexicana, Segunda parte, (México:* Oficina Tip. de la Secretaría de Fomento, 1898): 110-37 on 133.

[22] At the end of his report, Noriega asserts the need for adequate supply of the necessary material so as to deliver the substances requested to NMI and expounds on the obstacles to the manufacture of medicines on large scale and that naturally hindered their possible commercialization. In his own words: "Similarly I report that once again it was difficult for me to deliver the preparations with their desirable power for lack of adequate equipment for evaporation, for which reason a I beg you to try and find me a water bath," *Anales del Instituto Médico Nacional. Continuación de El Estudio* 2 (1896): 185-6.

[23] Leopoldo Flores, "Reseña Histórica acerca del objetivo, fundación, desarrollo y estado actual del Instituto Médico Nacional, leído en la sesión del 25 de abril de 1902," *Anales del Instituto Médico Nacional. Continuación de El Estudio* 5 (1903): 262-74 on 272-3.

[24] Arthur C.W. Heffter (1859-1925) isolated for the first time two alkaloids from *Lophophera* plants in 1894, pellotine and anhaline (hordenine). At that time they were described as pure crystalline substances, and the discovery was published in 1894; see Perrine, 7.

[25] Leopoldo Flores, "Junta mensual del 25 de abril de 1902," *Anales del Instituto Médico Nacional. Continuación de El estudio* 5 (1903): 245-6, on 245.

[26] While the main alkaloid of *L. williamsii* is mescaline, it also contains other important active molecules. According to Perrine, 7, the most active are (in decreasing order): "pellonitne nahalonidine, anhalamine, hordenine (anhaline), lophophorine, 3-demethylmescaline, anhalonine, N-methylmescaline, anhalidine, N,N-dimethyl-4-hydroxy-3-methoxyphenethylamine, anhalinine, O-methylanhalonidine, isopellotine, and peyophorine".

[27] Fernando Altamirano, "Sección tercera," *Anales del Instituto Médico Nacional. Continuación de El estudio* 5 (1903): 294-5, on 294.

The results communicated by Merck led NMI staff to think their research over, as they had been working with fluid extract of peyote rather than with the isolated alkaloid. In addition, they sought to corroborate that anhalanine was, indeed, the active principle of peyote.[28] For that purpose, Armendáris prepared two extracts, one with and the other without anhalanine. One month later, he reported to have isolated the alkaloid in peyote as a sulfate, which salt he used in the following physiological experiments.[29] Later on MNI communicated that the fluid extract was only active when the alkaloids of peyote were present, and that its action all but disappeared when the alkaloids were separated. More than 40 active alkaloids were identified in peyote up to the present day.

According to Armendáris:

> "Peyote (*Anhalonium lewinii*) is also undergoing general analysis, and the following principles have been isolated up to the present time: fat and essential oil (0.225), vegetable wax (0.087), rubber (traces), yellow dye matter, acid resin and a body with alkaloid reaction. This body is doubtlessly the most interesting one; it could be isolated by means of the following procedure: a hydroalcoholic extract is prepared, which is exhausted using boiling water, the liquid is alkalinized and agitated with ether; by separating the ethereal solution and evaporating it, an amorphous extract with resinous appearance is obtained, which is treated with water acidulated with hydrochloric [acid]; that solution is evaporated until it becomes dry and [then] treated with absolute alcohol, which by [inducing] spontaneous evaporation leaves abundant crystals of alkaloid chlorhydrate as residue."[30]

Another example of the relevance of the local and global levels of study of cactuses is provided by the correspondence exchanged between NMI and Dr. J.N. Rose, from the Smithsonian Institute, Washington, which dealt with the collection and botanical classification of Mexican cactuses. The letters describe the stipulations for Alberto McDowell, hired special commissioner of the Mexican Department of Horticulture to the St Louis Exhibition of 1904, to be appointed collector of cactuses in the states of Morelos and Guerrero; the NMI was promised duplicates of all the specimens thus collected. Within this context, Fernando Altamirano observed:

> "[…] the study of the Cactaceae, in my opinion, is of much interest to our country, because it is a very special family of Mexican plants, many of which have medicinal and industrial applications, and others will also be found to have useful applications. Finally, I believe that if this botanical study

[28] Ibid., 306.

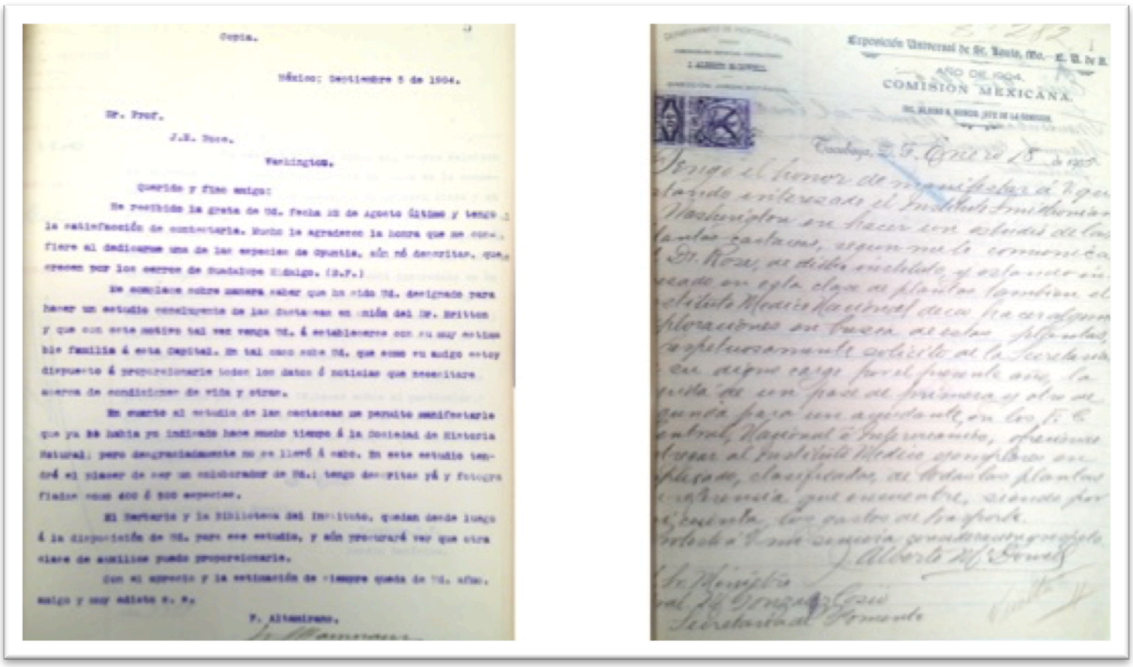
[29] Armendáris made a detailed description of the preparation of various substances contained in peyote, in "Sección Tercera" *Anales del Instituto Médico Nacional. Continuación de El estudio* 5 (1903): 306-8; 322-4.

[30] Federico Villaseñor, "Segunda Sección," *Anales del Instituto Médico Nacional. Continuación de El estudio* 5 (1903): 377-9.

of one family could be combined with all the other [studies] performed at the Institute, to wit, chemical, physiological, therapeutic, etc. the study of the Cactaceae might be indicated as the work program for next year."[31]

Figure 2 illustrates two of the letters exchanged between NMI and the Smithsonian Institute.

Figure 2. Letters exchanged between NMI and the Smithsonian Institute[32]



Final remarks

Research at NMI had to cope with some limitations that made the working conditions less than ideal. First, constant lack of whole specimens of the plants to be tested and in adequate state of conservation and amount for analysis and use. NMI staff admitted on several occasions that studies had to be interrupted or delayed due to the lack of material in adequate amount or quality. Second, poor selection of the animals species used in the physiological tests. No document discusses the closeness of the selected species to humans, nor explains the preference for doves or toads, for instance,

[31] Letter of Fernando Altamirano to the Secretary of Development, communiqué no. 21, México, January 28 1905, AGN/GD 125/IPBA/vol. 128/exp. 13, 14 ff.

[32] Left: Letter of Fernando Altamirano to professor J.N. Rose from the Smithsonian Institute of Washington dated September 5 1904; Right: Letter of the hired special commissioner of the Mexican Department of Horticulture to the St Louis Exhibition of 1904, Alberto McDowell, to the Secretary of Development, Manuel González Cosío, dated January 18 1905;. AGN/GD 125/IPBA/vol. 128/exp. 13, 14 ff.

over Guinea pigs or dogs. This fact suggests that the researchers used whatever was available to them rather than the most adequate species, or simply did not take the pharmacological and pharmacokinetic variations among species into consideration. Third, poor relationship between investigated drug and targeted disease or clinical condition. For instance, the effectiveness of peyote as an aphrodisiac was tested (and naturally, not corroborated) in a patient "weakened by his alcohol dependence". Fourth, constant lack of the number of patients needed to replicate research. And fifth, lack of clarity in the expression and justification of the methods used.

The protocol exhibits several methodological and institutional weak points that nonetheless do not reduce NMI's merit, but lead us to put forward some hypothesis for the closure of NMI in 1915. Shortage of raw materials in adequate amount and quality, inadequate selection of experimental animals and impossibility to select patients with the right clinical profile and subject them to proper clinical follow up, in addition to the excessive pressure exerted by the ministries of Development and Public Education are elements to consider when assessing NMI's results.

Those shortcomings notwithstanding, the results obtained by Sections One and Two might be rated successful. Those sections developed rigorous methods that yielded indisputable results that were taken on by scientists abroad. As a fact, the work performed in all the Institute's sections largely served as a link between the autochthonous, colonial and modern pharmaceutical practices and set the grounds for the modern scientific production.

Research at NMI sought to elaborate a 'national' catalogue of medicinal products, in which the psychoactive substances played if not the central, a considerable role. The formulations that included them were meant for several diseases that represented a public health concern, for being chronic conditions that affected a large part of the population (somniferous, analgesics) or emergent illnesses like the ones associated with abuse of alcohol or narcotics. The therapeutic effects reported by common people were confirmed in 14 out of the 21 studied plants (66%). This fact points to the relevance of preserving the knowledge gathered by the Mexican traditional medicine, as well as NMI's effectiveness in recovering and reinterpreting in scientific terms the medical-pharmaceutical knowledge originated many centuries earlier.