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The rise and fall of tobacco as a botanical medicine

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ABSTRACT

A forgotten and valuable chapter in the history of tobacco concerns its role as a botanical medicine. For three hundred years following its importation into Europe, tobacco came to be considered a universal remedy highly prescribed by physicians. In the early history of tobacco, the literature on its medicinal benefits was voluminous. Nonetheless, bitter opposition to its use for non-medicinal purposes began to arise. There was little doubt of its medicinal efficacy at first, but with time, as the concepts and practice of medicine changed, the tide of medical opinion turned against it. Medical support for the therapeutic use of tobacco reached its nadir during the mid-nineteenth century, when it was dropped from most medical pharmacopoeiae. Medical opinion on the health hazards of recreational smoking required another 100 years to arrive at the contemporary opinion that cigarette smoking is the single most important preventable environmental factor contributing to illness, disability and death in the U. S.

1. Introduction

Soon after tobacco was introduced into Europe as an ornamental plant, it came to be regarded as a remarkable medicinal plant. Spanish sailors and the chroniclers of the Indies observed and recorded the widespread use of tobacco. They were impressed by the esteem with which it was held by the natives of the New World. Tobacco played a very important role in the mystical, social and medical rituals of the American natives. Based on the medical applications of the herb by the natives, European herbalists believed that most herbs of the New World possessed some medicinal virtues. By the end of the 16th century, tobacco was in widespread use in Europe to treat a variety of diseases. Some medical authorities popularized tobacco as a panacea for treating over 65 different ailments. Over time, excessive use of tobacco led to the first great well-documented “drug” controversy. Awareness of the inability to give up smoking of tobacco long after recovery from the illness led some to see the habit as sinful, simply because the individual indulged in the practice for “pleasure”. Puritans in England saw non-medical use and dependence on daily tobacco smoking as a sign of a weak and immoral character. A more rational view against the medical use of tobacco argued that a single medication could not possibly cure so many different ailments. It was not till the 20th century that the deleterious health consequences of chronic tobacco smoking became strongly evident and led to efforts to suppress tobacco use.

Identification of nicotine and its physiological effects led to insights into the neurochemistry of the autonomic nervous system. More recently nicotine and the nicotinic receptors in brain are being explored as agents that might enhance cognition. Review of tobacco’s history is relevant to the contemporary problem of differentiating socially or medically-approved use from substance abuse and addiction.

2. Methodology

The methodology used to prepare this review was based on the study of selected publications on the history of tobacco. Many of these books were long out of print but were available at the University of Chicago Regenstein Library. The books selected for study included significant sections on medical use and abuse, as well as the social history of tobacco. Primary documents from the early Spanish chroniclers and physicians were not available and so the author relied on secondary sources, books written in early to mid-1900s. More recent literature on the health dangers of tobacco was obtained by online screening of literature in PubMed, the database of the National Library of Medicine (PubMed, 2020). The results from this review of the literature were organized into the seven sections and within each section, a chronological order was followed:

1 Tobacco as a Substance of Abuse

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- 2 Rationale for the Acceptance of Tobacco as a Medicine
- 3 Medicinal Use of Tobacco by Natives of the New World
- 4 Early Opposition to the Use of Tobacco
- 5 Demonstration of Deleterious Effects of Tobacco
- 6 Resurgence of Nicotine as Medicine
- 7 Newer Medical Applications of Tobacco

2.1. Tobacco as a substance of abuse

From the very outset, tobacco was smoked by the Spanish because it was considered pleasurable, but at the same time it was attributed with exceptional medicinal qualities. The chroniclers of the Indies also noted that once Spaniards began to smoke, it was difficult to give up the practice (Corti, 1932). In 1610, Francis Bacon stated this succinctly:

"Tobacco conquers men with a secret pleasure, so that those who have once become accustomed thereto can later hardly be restrained therefrom (Corti, 1932)

The use of tobacco for pleasure alone would not have been palatable to the Europeans at home, who would have found the habit both primitive and sinful (Ortiz, 1947). Interestingly, tobacco was introduced into Spain as an ornamental medicinal plant.

"Pleasure sought tobacco, but medicine justified it for reasons of its own, and sensuality was able to hide behind the cloak of curative science" (Ortiz, 1947)

In England, smoking became fashionable at a time when Puritanism was taking hold. The Puritans did not deny tobacco's medicinal qualities but objected when smoking was indulged in for non-medical reasons. They noted that tobacco "drinking" (as smoking was then termed) was not confined to specific doses at certain times of the day like other medicines, and therefore might be harmful, especially to the young (Apperson, 1914). The Puritans in the colony of Connecticut, in attempting to set controls on the consumption of tobacco, passed laws (around 1650) prohibiting persons under the age of 21 from smoking, and ordering that no smoker could enjoy his pipe unless he obtained a doctor's certificate (Apperson, 1914). Even with a doctor's permission, smokers of the colony at that time were not allowed to take tobacco publicly in the "street, highways, or any barnyards" (Apperson, 1914). During the 17th century many writers and physicians condemned the use of tobacco for non-medicinal purposes and attempted to differentiate legitimate use from "licentious" abuse. Tobias Venner in his "Brief And Accurate Treatise Concerning The Taking Of The Fume Of Tobacco, Which Very Many In These Days Do Too Licentiously Use" (London, 1637) denounced the common mode of smoking tobacco which most men took "like tinkers drank ale" (Apperson, 1914). He listed 10 precepts for the correct use of tobacco. For example, that "you drink not between taking of fumes, as our idle and smoakie Tobacconists are wont" and "that you goe not abroad into the aire immediately upon taking of the fume, but rather refrain therefrom the space of half an hour, or more, especially if the season be cold or moist" (Apperson, 1914).

Many people associated recreational smoking with idling. In the rules of the grammar school at Essex, England, founded in 1629, it was prescribed that "the Master must be a man of sound religion, of grave behavior, of sober and honest conversation, no tippler or haunter of alehouses, no puffer of tobacco" (Apperson, 1914).

In spite of condemnation of recreational use, the smoking of tobacco was practised more for pleasure than for its medicinal value in Western Europe and the American colonies. Tobacco did continue to be employed as medicine, especially in forms other than smoke, until mid-nineteenth century. From the American Civil War to the present, tobacco has been used almost exclusively as a recreational substance. The attacks on its abuse in the late 19th and early 20th centuries were linked to temperance movements and based on moral arguments. Only in the last 50 years has the opposition to smoking been based on strong medicinal arguments. The last attacks on the use of tobacco re-introduced a moral component to the medical argument: non-smokers are

subject to some deleterious health consequences of smoke pollution generated by smokers. The point is made that it is immoral to smoke since innocent non-smoking victims (including children) may be hurt.

2.2. Rationale for the acceptance of tobacco as a medicine

It has been suggested that the tobacco epidemic was due to a lack of prior restraints on grounds of convention, religion, morality or law simply because neither the substance nor the technique of smoking was previously known (Laufer, 1924). It was up to medical profession to provide "restraints" in the form of a set of rules for appropriate consumption of tobacco. It should be emphasized, however, that there undoubtedly was a real belief in the medicinal efficacy of tobacco, especially within the context of the fifteenth and sixteenth century notions of health and disease. For example, certain diseases were seen as a disturbance in the balance of four qualities: hot, dry, cold, wet. Catarrh (the common cold), particularly prevalent in the northern countries, was believed to be due to excess of cold and wet, so that applications of hot and dry tobacco smoke was seen as beneficial. Purgation of the head by nasal irrigations and fumigations, or by provoking sneezing, was commonly practiced. "Caput pungia" or clearing of the head was the Latin term applied to this practice (Ortiz, 1947). Purgation of the gastrointestinal tract by eliciting vomiting or promoting bowel movements were popular medical remedies for which tobacco in one form or another was efficacious (Ortiz, 1947).

The practice of medicine from antiquity to the Renaissance was based therapeutically on plant-derived substances. During the Renaissance, prior to the discovery of tobacco, there was great interest in identifying the lost panacea of antiquity, the sylphium, described in great detail by the ancient physicians, Hippocrates, Galen and Celsus. This plant, indigenous to desert regions of North Africa, had been reported to be useful in treating fever, bronchitis, scrofula, tumors, toothache, bites of rabid animals, wounds from poisonous weapons, sore throats, pertussis, pleurisy, icterus and epilepsy (Castiglione, 1943a). This wondrous plant, still not unequivocally identified, had disappeared, so that the introduction of tobacco was hailed as a substitute for the long-lost panacea of legend.

Two other factors helped perpetuate the notion that tobacco was a panacea. Spanish sailors and the chroniclers of the Indies observed and recorded the widespread use of tobacco and were impressed by the esteem with which it was held by the natives of the New World. Tobacco played a very important role in the mystical, social and medical rituals of the American natives. Based on the medical applications of the herb by the natives, European herbalists believed that most herbs of the New World possessed some medicinal virtues.

A few influential books on the medical benefits derived from tobacco generated a host of literature on the san sancta (holy cure), the panacea of panaceas (Castiglione, 1943b).

2.3. Medicinal use of tobacco by natives of the New World

Tobacco was mentioned for the first time in the very first book written about the discovery of the New World, the diary of Columbus. An entry in his diary, dated October 15, 1492, mentions dry leaves carried by an "Indian" in a canoe, who valued the leaves for their healthfulness (Corti, 1932). Columbus later wrote, in November 1492, that 2 members of his crew, sent out to explore the island of Cuba, saw many people who carried a burning torch to kindle fire and to perfume themselves with a certain herb. Later it was learned that the herb was smoked in a rolled cylindrical form (cigar) and employed to lessen fatigue and as a disinfectant (Corti, 1932). On the second voyage, Columbus left Father Ramon Pané on the island of Hispaniola to convert the Taino Indians. Pané described the use of a snuff, cohoba, derived from an intoxicating plant, by a medicine man in a healing ritual. The "doctor" followed the same diet and assumed the same aspect of a sick person. Both doctor and patient would purge themselves by inhaling

the snuff intranasally. The use of cohoba was also referred to by many chroniclers, including Oviedo, Las Casas and Columbus himself (Corti, 1932). The identity of cohoba has been disputed, but most agree that the effects of the powder might not be due to tobacco alone, but to the addition of powder derived from grinding products of the hallucinogenic plant *Piptadenia peregrina* (Ortiz, 1947).

In 1500, the Portuguese explorer Cabral reported the use by Brazilian natives of a medicinal herb called betum (later identified as tobacco) for a variety of ailments including abscesses, fistulas, sores, and polyps (Corti, 1932). In 1535, the first official chronicler of the Indies, Oviedo y Valdes, published "The General History of the Indies" in which he described the use of tobacco as a medicine by the Indians, and also that some Spaniards on the island used it for treating the disease of syphilis, unknown to Europeans until this time (Corti, 1932). Oviedo was the first to use the word tabaco correctly in print. Tabaco was the word for the instrument with which the natives of Hispaniola inhaled the smoke or powder of the herb. The word tabaco (or the anglicized tobacco) came later to mean the plant itself (Corti, 1932).

The actual amount of tobacco introduced into Europe between 1500 and 1600 is not recorded, but the growing importance of tobacco is reflected in the literature of the period. Between 1503 and 1600, the number of books published in Europe which referred to the medicinal use of tobacco increased markedly (see Table 1).

The two most influential books on the medicinal use of tobacco were by Nicolas Monardes, a prominent physician and medical advisor to the Archbishop of Sevilla, and by Jean Liebault and Charles Estienne of France. Monardes published his work in Spanish in 1565 in Sevilla -"Primera, Segunda y Tercera Partes de la Historia Medicinal de las Cosas que se traen de Neustras Indias Occidentales que Sirven en Medicina". This book which was frequently quoted and translated into many languages (into English in 1577) became the chief source of information on tobacco. Monardes recommended tobacco in many different forms against a wide range of ailments -a total of 65 different diseases or conditions. (Castiglione, 1943c)

"This plant, which is commonly called tobacco, is a very ancient herb and known among the Indians, especially those of New Spain. After these lands were conquered by our Spaniards, they, being taught by the Indians, made use of it in wounds suffered in war, healing themselves with it, to the great benefit of all. It was brought to Spain a few years ago more to adorn gardens with its beautiful appearance than for the marvelous medical virtues which it has; now we use it more for these virtues than for its beauty, for they are certainly such as to attract admiration its quality is hot and dry in the second degree. It has the virtue of heating and dissolving, with some astringency and invigoration. It glues together and closes up fresh wounds, so they say, at the first application. It cleans and purifies infected sores, and brings them to perfect health, as we shall describe later. And now I shall speak of the virtues of this plant and the things which it is useful for, one after another"

Monardes then systematically listed all the ailments which can be cured by either smoking, chewing, or drinking tobacco, or applying hot leaves or tobacco ointments onto skin (Ortiz, 1947). For-example, ailments of the breast are alleviated by tobacco syrup; smoke taken by mouth expels the causes of most complaints. The use of warmed leaves,

salves, clysters (enemas) is prescribed for internal congestion, stomach aches, constipation, kidney stones, and flatulence. For ailments of pregnancy and labor pains a leaf of the plant, very hot, is applied to the navel. To expel worms, tobacco is invaluable. Tobacco is also recommended for rheumatism, abscesses, toothache, and venomous wounds; furthermore, application of tobacco is sufficient to restrain any flux of blood. Monardes advertised tobacco as a household remedy and it was due primarily to his authority that the new herb was accepted by physicians and laymen alike as one of the most popular remedies (Castiglione, 1943a).

The book on horticulture "Maison Rustique" by Liebault and Estienne published in 1567 (Paris) included a chapter entitled "Nicotiane" which says that tobacco was introduced into France by Jean Nicot and was called by some the "Queens Herb". Nicot sent seeds of tobacco to Queen Catherine de Medici, who later became a great advocate of tobacco, and was supposedly the first promoter of medicinal snuff. Catherine treated her ill young son, Francois II with an unction of tobacco. The young prince died with symptoms of poisoning and it was generally believed to be a consequence of the tobacco ointment (Castiglione, 1943b).

In any case, the book by Liebault and Estienne became very popular among physicians and laymen, containing information about tobacco and its various applications in disease.

"Tobacco will heal all old sores and cancerous ulcers, ringworms, great scabies, and what evil so ever may be, by stamping the leaves in a clean mortar and applying the herb and juice together upon the sore" (Castiglione, 1943c)

The book also mentions a host of other virtues of the plant including its efficacy in treating dropsy (Castiglione, 1943a). As early as 1565, the plant was called Nicotiane in honour of Jean Nicot, who as was mentioned, introduced the plant into France, but also performed medicinal experiments with the herb, demonstrating its effectiveness in shrinking a cancerous growth on the face (Castiglione, 1943b).

The bubonic plague was endemic almost every year of the 16th century in some part of Europe. A number of serious outbreaks in Great Britain popularized the use of tobacco as a disinfectant, documented in 1572 in the book by Dr. Antoine Sarracin "De Peste Commentarius" published in Geneva and Lyons (Castiglione, 1943c). In addition to all of the books by physicians attesting to the wondrous cures produced by tobacco, a great number of poets, historians and botanists bolstered the panacea image of tobacco. Of the total of 254 diseases and other conditions reported as treated with tobacco between the years 1492 and 1860, 71 were reported as treated with tobacco between the years 1586 and 1600 (Castiglione, 1943a). In these 15 years, physicians invented new formulae using tobacco and also found new uses for it, since they also applied it to patients' eyes and ears.

2.4. Early opposition to the use of tobacco

Before the year 1600, there were only four medical authorities who warned of possible harmful effects of the herb (Stewart, 1967). By 1600 tobacco was at the height of its fame as a medicinal herb, but the first book published about medicinal tobacco in London in 1602 (Work for chimney-sweepers) emphasized its harmful effects. The author, writing under a pseudonym, "Philartes", probably found it expedient to avoid using his real name since his book was exposing the harmful effects of tobacco. He argued that no one remedy could be applied to all maladies any more than one shoe could fit all men's feet. Tobacco purged its users too violently and dried up the sperm of a man so that if used too long, "the propagation and continuation of mankind will be abridged". Moreover, Philartes declared tobacco had a stupefying effect, not unlike opium, and it increased melancholy greatly and wasted the liquid part of the blood and much more (Stewart, 1967). This book elicited 3 more books in defense of tobacco, setting the stage for the London tobacco controversy which lasted 65 years (Stewart, 1967).

Table 1

Books published in Europe referring to medicinal tobacco^a.

20-year blocks	Number of books
1501-1520	7
1521-1540	3
1541-1560	16
1561-1580	48
1581-1600	59

^a Contents of Table adapted from (Stewart, 1967).

In England, as opposed to the Continent, tobacco was seen less as a medicinal herb than as a recreational social habit (Apperson, 1914). Sir Walter Raleigh is generally credited with introducing tobacco smoking to Queen Elizabeth and the English court, thereby making it the latest fashion in London. By the end of Elizabeth's reign (1603) smoking was popular among all classes of society: but it was especially the mark of the young man of fashion:

"At the end of the 16th century, London was infested with strutting, affected dandies, and these gallants adopted smoking as something especially devised for them. Their extravagances in this art, the elaborate smoking equipment they carried about with them, and their insolent claim that only they knew the correct method of smoking made them the butt of many literateurs." (Dickson, 1954)

On the continent the use of tobacco by smoking was hardly known. A German visitor to England in 1598 could scarcely believe his eyes when he saw everyone smoking even in the theatres (Apperson, 1914). In 1604, James I, King of England, published anonymously "A Counterblaste to Tobacco" (London). This book was the first to strongly condemn the habit of smoking in a printed work with a wide distribution. James opposed tobacco smoking from motives of racial and national pride, he refuted its medicinal virtues, he castigated smoking as morally sinful, and a waste of national wealth.

"What honour or policie can move us to imitate the barbarous and beastly manners of the wild, godlesse, and slavish Indians, especially in so vile and stinking a custom? ... And what greater absurditie can there bee, than to say that one cure shall serve for divers, nay contrarious sortes of diseases? (smoking) is a custome loathsome to the eye, hatefull to the nose, harmfull to the braine, dangerous to the lungs, and in the black stinking fume thereof, nearest resembling the horrible stigious smoke of the pit that is bottomless" (Austin, 1978).

Aside from the attacks on the abuse of tobacco, there was another reason for condemning its use. The tobacco trade was largely in the hands of the Spanish, the enemies of England, and represented great economic loss for the country. King James raised the duty on tobacco in an attempt to diminish importation. Despite the king's opposition in words and deeds, the use of tobacco increased rapidly during his reign. The increased duty imposed by the king suppressed the regular trade and developed a great traffic in smuggling from Spain and the colonies and also promoted the cultivation of tobacco in England. The outbreak of the plague again in 1614 in London helped overcome the king's opposition. Doctors declared that steady smokers were less subject to infection than others and recommended tobacco as a disinfectant, with the result that smoking increased enormously in spite of the king's antipathy (Corti, 1932). By 1615, there were upward of 7,000 apothecaries, grocers, chandlers and inn-keepers living by the trade of selling tobacco in and near London (MacInnes, 1926). From 1620 to 1758, the production of tobacco in the English American colonies increased exponentially from 20,000 lbs. per year to 22,050,000 per year (Jacobstein, 1907).

The spread of tobacco to Japan, China, Turkey and Russia is beyond the scope of this essay. It should be noted that the most severe penalties in the form of torture and death failed to suppress the use of tobacco in those countries, and eventually tobacco use became worldwide (Brooks, 1952; Austin, 1978).

By the beginning of the 18th century, tobacco was being used more for pleasure than for its medicinal value both in Western Europe and the American colonies. Before tobacco was to become abandoned as a medicine altogether another twist of fashion propelled it, in the form of snuff, as the primary medicinal form. In 1655, a book had been published in France dealing with the preparation and use of snuff for medicinal purposes (Brooks, 1952). Snuff-taking became fashionable among the upper classes in France and rapidly disseminated among the upper classes of Western Europe. The habit took such a hold of the governing classes, the nobility, and clergy in France and England, that it almost supplanted smoking. Smoking "was relegated to the middle and lower classes during this period (Corti, 1932).

One of the books of the time, "Grundlicher Unterricht" (Ulm) by Frederick Hoffman, physician to the king of Prussia, devoted a chapter to the correct use of snuff. He believed that snuff was particularly advantageous in curing head ailments caused by "moist humours" and in the treatment of certain conditions of the eyes and ear. He prescribed snuff powders mixed with balsams and different herbs, which were able to "relieve the nose of germs and offensive odors and also have a beneficial effect in gout" (Castiglione, 1943b). He also warned that constant, careless use of snuff affected the sense of smell and produced throat ailments and its abuse resulted in deafness, insanity and fatal illness (Castiglione, 1943c). While Hoffman's assertions of the therapeutic value of tobacco was weak, the arguments against its abuse were no better founded (Castiglione, 1943a). A pupil of Hoffman, Frederick Camel, also published a dissertation in which he analyzed the different qualities of snuff and attempted to explain the action of the different constituents of tobacco. A small controversy arose in Europe over snuff, which was used as much for pleasure as for medicine. Proponents presented case histories to prove snuff had cured bronchitis, consumption, apoplexy and other diseases. Opponents to the use of snuff called snuffers snivellers and snorters, and that they were digging an early grave with their noses. The controversy which ended around 1750 did have the effect of reducing snuff taking for both medicine and social purposes, but the habit did not entirely disappear from medical practice until more than a century later (Stewart, 1967).

In 1753, Linnaeus published his "Species Plantarum" in which tobacco was classified as a member of the nightshade family (Solanaceae) and the modern scientific terms for the chief species of the genus *Nicotiana*, *tabacum* and *rustica* were first included (Castiglione, 1943b).

Physicians who continued to use tobacco as a medicine found two new applications. Dr. Tissot suggested introducing tobacco smoke into a patient's lungs to resuscitate the apparently drowned (Stewart, 1967). A second new application was the procedure for giving tobacco smoke clysters, again for resuscitating drowning victims (Stewart, 1967).

By 1799, medicinal tobacco was being abandoned and deleted from some but not all materia medica. Several pharmacopoeiae continued to include tobacco leaves up until the beginning of the 20th century. The Swiss pharmacopoeia still mentioned "Folium Nicotianae" in 1893. The German pharmacopoeia mentioned tobacco for the last time in 1901 (vanProosdy, 1960v).

2.5. Demonstration of deleterious effects of tobacco

As early as the 17th century, experiments were carried out with extracts of tobacco "essential oils of tobacco"; its poisonous effects were demonstrated by showing that one drop of tobacco oil would kill a dog or cat (Castiglione, 1943c). By 1809, Louis Laugelien, a French chemist discovered, but was unable to completely isolate the active principal of tobacco, which he called "Nicotianine". Other chemists continued the work until 1828 when Posselt and Reimann, at Lille, France, isolated the constituent of tobacco now called nicotine (Volle and Koelle, 1970). With the discovery of this potent poisonous alkaloid, the attacks on the medicinal and recreational use of tobacco were intensified. In 1851, a summation of the effects of tobacco was published by L. B. Coles, in the United States. He emphasized the dependence liability of tobacco, noting that tobacco was never taken like other medicines and then lain aside. "A man takes this so-called medicine for forty years perhaps, but gets no cure." (Stewart, 1967) He also cited many, many case histories to prove tobacco never cured diseases for which it was prescribed and noted the harmful effects of nicotine.

The first pharmacological studies of nicotine were initiated by Orfila in 1843, and Langley and Dickinson described the actions of nicotine on autonomic ganglia in 1889. Using nicotine as a pharmacological tool, they studied the sites of ganglionic synapses of autonomic efferent fibers and greatly enlarged our knowledge of the physiology of the nervous system (Volle and Koelle, 1970).

Nevertheless, the tobacco industry continued to grow, purely on the basis of recreational use. From 1880–1979, the per capita tobacco consumption in the U.S. increased almost three-fold, but with changes in the form of use. Prior to World War I, tobacco chewing was the principle mode of use in the U.S., but the 1920s saw cigarette consumption, particularly of prefabricated cigarettes, increase astronomically, as the use of chewing and other smoking tobacco decreased. A cigarette consumption plateau in the 1930s was followed by a sharp increase during World War II when widespread adaptation of the cigarette by women was added to large-scale consumption by American troops (Surgeon-General's, 1979). It has been noted that since the introduction of tobacco in Europe, any major war has invariably been associated with an enormous increase in the prevalence of smoking (Corti, 1932).

The deleterious effects of tobacco on health had been suspected, and alluded to, for centuries before appropriate tools for scientific investigation were developed. The relationship between cancer of the lip and tobacco use was noted as early as the 18th century, but it was not until 1920 that the first systematic approach to that association was made (Surgeon-General's, 1979).

In 1900 statisticians began to note increases in the incidence of lung cancer.

In the 1930s, trends in diseases such as lung cancer became evident, promoting the start of intensive inquiries and animal experiments into disease relationships and into the chemical composition and pathogenic effects of tobacco smoke. The end of the 1930s marked the beginning of 40 years of retrospective studies on selected diseases suspected of association with tobacco use (primarily lung cancer, chronic bronchitis, emphysema and coronary heart disease) and prospective studies of diseases and mortality among cohorts of smokers and non-smokers. By the 1950s, there were reports of many significant epidemiologic studies; tobacco was increasingly being identified as a most serious health hazard (Surgeon-General's, 1979). In 1962, an expert committee was formed by the Public Health Service to review all data on smoking and health. Representatives of the American Cancer Society, American College of Chest Physicians, American Heart Association, the Tobacco Institute, Inc., The Food and Drug Administration, National Tuberculosis Association, Federal

Trade Commission, and the President's Office of Science and Technology met with the Surgeon General to establish the work of the expert committee and to agree on a list of 150 scientists and physicians qualified to evaluate data on relationships between tobacco and health. In 1964, the historic Report of the Surgeon General on Smoking and Health was released and reflected the most informed medical opinion on the use of tobacco (Surgeon-General, 1964). Cigarette-smoking was judged to be causally related to lung cancer in men. Included as evidence in the judgment of causality were the findings of a dose-response relationship: the risk of death from lung cancer increased directly with duration of smoking, number of cigarettes smoked per day, inhalation and indirectly, with age when smoking began; discontinuation of smoking lowered the risk. Cigarette smoking was judged to be the most important of the causes of chronic bronchitis in both men and women in the U.S. Male smokers were found to have a significantly higher death rates from coronary artery disease than non-smoking males. A causal relationship was not established at that time for coronary artery disease (and a number of other cardiovascular diseases). Significant associations between several other cancer sites and tobacco use were judged to be causal, including pipe-smoking and lip cancer, and cigarette smoking and laryngeal cancer. A number of other diseases or conditions suggested to be associated with smoking by clinical impressions or by showing excess mortalities in the prospective studies were also scrutinized: tobacco use and esophageal cancer, urinary bladder cancer, peptic ulcer, tobacco amblyopia, cirrhosis of the liver, accidents, influenza and pneumonia, and low infant birth weight. The committee concluded "cigarette smoking is a health hazard of sufficient importance to warrant appropriate remedial action (Surgeon-General,

1964).

The 1979 report of the Surgeon General strengthened earlier conclusions regarding the relationship between smoking and mortality, and in addition pointed out the increased dangers of passive smoking, that is the effects of environmental smoke on non-smokers. Additional findings of the 1979 report included:

"Women who smoke and use oral contraceptives are at a significantly elevated risk for fatal and nonfatal myocardial infarctions ... A synergistic role of cigarette smoking and oral contraceptive use is suggested for subarachnoid hemorrhage ... Lung cancer mortality rates in women are increasing more rapidly than in men, and if the present trend continues, will be the leading cause of cancer death in women in the next decade ... According to studies of long-term-growth and development, smoking during pregnancy may affect physical growth, mental development, and behavioral characteristics of children at least up to the age of eleven ... The risk of perinatal mortality attributable to smoking is highly significant and is dose-related ... Smoking by pregnant women contributes to the risk of their infants being victims of the " sudden infant death syndrome." (Surgeon-General, 1964)

The dangers of involuntary (passive) smoking was described:

"Levels of carbon monoxide which can be reached in cigarette smoke-filled rooms have been shown to decrease the exercise duration required to induce angina pectoris in patients with coronary artery disease. Side-stream smoke, which comes from the lighted tip of the cigarette between puffs, has higher concentrations of some of the irritating and hazardous substances than does mainstream smoke (that smoke inhaled by the smoker)." (Surgeon-General, 1964)

The most recent opinion on passive smoking appeared in a prestigious journal of medicine, reporting that chronic exposure to tobacco smoke is deleterious even to the non-smoker, significantly reducing small-airway resistance (White and Froeb, 1980).

Over the last 40 years, the health hazards associated with cigarette smoking have been communicated to the public by the mass media. According to the 1979 report of the Surgeon General, the increased awareness by the individual smoker of the deleterious effects of tobacco smoke has resulted in a decrease in the prevalence of smoking in the general population. However, the percentage of teenagers who smoke has not declined in the last 2 decades, and the number of teenage females who regularly smoke has increased (Surgeon-General's 1979) The historical record on tobacco has demonstrated that establishment of the most severe penalties for smoking in the past, including torture and death, failed to suppress smoking in the long run in Turkey, Russia and Japan (Brooks 1952). It is no surprise, then, to see that the threat of delayed physical harm, in the form of disease, has failed to suppress smoking among the youth of the U.S. today.

It is clear that tobacco has reinforcing properties that motivate its user to continue smoking even when aware of the possible health consequences. Nicotine appears to be the compound in tobacco which is most likely responsible for these effects. When the nicotine and tar content were varied independently, it was the nicotine content that correlated with ratings of strength and satisfaction (Surgeon-General's, 1979). Moreover, laboratory research has demonstrated that animals will self-administer nicotine (Surgeon-General's, 1979).

An approach to this problem has been suggested recently by an English physician(s), an approach that has a ring of familiarity. They argue that tobacco snuff would be an acceptable and less harmful substitute for cigarette smoking. They note that in the 400 years of tobacco history, during which time tobacco has been chewed, snuffed or smoked, no population gave up one form of tobacco use without replacing it with another. The only time that the British decreased the frequency of smoking was in the 18th century when they switched to snuff. Snuff, they report, produces peak blood levels of nicotine comparable to those produced by smoking tobacco. In addition, there are no products of combustion such as tar carbon monoxide and oxides of nitrogen. The pollutant effects of tobacco smoke would be eliminated by the use of snuff. These physicians postulate a new age for snuff is

ahead, predicting that snuff could save more lives and avoid ill-health more than any other rational preventative measure likely to be available well into the 21st century (Russel, Jarvis et al. 1980).

In the last few years, a new way to inhale nicotine (e-cigarettes or e-pens) is growing in popularity especially among youth. E-cigarettes are electronic devices that heat a liquid and produce an aerosol or mix of small particles in the air. E-cigarettes can deliver a high level of nicotine. According to one manufacturer, a single refillable cartridge in an e-pen contains as much nicotine as a pack of 20 regular cigarettes. A National Health Interview Survey reported:

“Overall, 15.3 % of adults aged ≥ 18 years had ever used an e-cigarette, and 3.2 % currently used e-cigarettes in 2016. Adults aged 18–24 years were the most likely to have ever used an e-cigarette (23.8 %); the percentage declined steadily to 4.4 % among adults aged ≥ 65 years. Adults aged 18–24 years (4.7%) and 25–44 years (4.2 %) were more likely to be current e-cigarette users than adults aged 45–64 years (2.8 %) and those aged ≥ 65 years (1.0 %). Across all age groups, fewer than one fourth of adults who had ever used an e-cigarette reported being a current user.” (MMWR, 2017)

An e-cigarette aerosol is not harmless, but it generally contains fewer toxic chemicals than smoke from burned tobacco products, like regular cigarettes.

2.6. Resurgence of nicotine as medicine

Nicotine interacts with a group of receptors that are normally targeted by the neurotransmitter acetylcholine. Nicotinic acetylcholine receptors (nAChRs) are transmembrane ion channels. When activated, either by acetylcholine or by nicotine, they allow selected ions to flow across the cell membrane. nAChRs are distributed in the autonomic and central nervous systems and at the neuromuscular junction. Acetylcholine and nicotine act at these receptors to alter electrochemical properties at a variety of synapses, which can in turn affect the release of several other neurotransmitters.

Nicotine has been shown to enhance attention, the ability to concentrate on particular stimuli and screen out the rest. Researchers at the National Institute on Drug Abuse have shown, using neuroimaging methods, that nicotine activates specific brain areas in subjects performing tasks that demand attention (Powledge, 2004).

Researchers are beginning to study the efficacy and safety of nicotine patches for treating mild cognitive impairment, thought to be a precursor of Alzheimer disease (Powledge, 2004). Interestingly, smokers have lower rates of neurodegenerative disorders, and nicotine improves cognitive and motor functioning in people with Alzheimer's disease and Parkinson's disease (Newhouse, Potter et al. 2004). The mechanism is not clear, but it is hypothesized that nicotine modulates release of neurotransmitters depleted in those diseases.

Nicotine is also being studied for its analgesic actions and for treating obesity.

Development of synthetic drugs by pharmaceutical companies that mimic nicotine actions at selective receptors may lead to novel therapeutics to enhance cognition, alleviate pain and to promote weight loss. However, there are those who advocate for less expensive nicotine products like a transdermal patch, chewing gum, or nasal spray. These formulations are generally intended for smoking cessation but are widely available, usually without prescription (Powledge, 2004).

2.7. Newer medical applications of tobacco

Since the late 1980s, the tobacco plant has been used as a natural living laboratory to generate bio-pharmaceutical agents. Plant molecular “pharming” or farming (PMP or PMF) is the practice of using plants to produce human therapeutic agents. Many therapeutic proteins have been produced in plants, and some of them have are close to commercialization (Yao, Weng et al. 2015; Dirisala, Nair et al. 2017). The tobacco plant has the potential to mass-produce pharmaceutical

products with less cost than traditional methods. The first application of plant pharming was for the generation of human growth factor in tobacco (Barta, Sommergruber et al. 1986). Tobacco-derived proteins have been tested and used to combat the Ebola outbreak in Africa. Plant Biotechnology Inc. (Hayward, CA, USA) produced an immunoadhesin (DPP4-Fc) in transgenic tobacco. Purified DPP4-Fc exhibits strong binding to MERS-CoV and prevents the virus from infecting lung cells (Yao, Weng et al. 2015). Other examples of therapeutic agents produced in tobacco include a number of vaccines directed against malaria, anthrax, hepatitis and influenza.

In addition to harnessing the power of the plant to produce useful bio-pharmaceuticals, the tobacco plant continues to reveal new molecules that had not previously been identified as biologically active. Recently, a plant defensin (NaD1), a cationic antimicrobial peptide, was isolated from the flowers of the ornamental tobacco plant (*Nicotiana glauca*) (Poon, Baxter et al. 2014). NaD1 exhibits potent antifungal activity against pathogenic fungi. The potential of the tobacco plant to yield novel therapeutic agents or facilitate production of antigens and antibodies is an expanding frontier for this versatile plant.

3. Conclusions

From the time of the introduction of tobacco into Europe, the medical profession rationalized the use of tobacco as a medicine and facilitated its incorporation into the fabric of society. This period of medical approval legitimized the widespread use of tobacco for “therapeutic” reasons, but the excessive use of this substance elicited a body of opposition based primarily on moral arguments. Eventually medical opinion was brought to bear against the use of tobacco as a medicine. However, the recreational use of tobacco continued unabated to the present time. For the last 40 years medical opinion has opposed the recreational use of tobacco for health reasons alone. Most recently, ethical arguments against the smoking of tobacco have been raised, stressing the deleterious effects of tobacco smoke on innocent non-smokers.

An historical review of this nature underscores the difficulty in suppressing the use of tobacco. For over 400 years, no population of tobacco users has given up the habit, but instead has replaced one form of tobacco for another. Severe opposition to smoking by imposition of fines, prison sentences or death penalties had little effect on overall consumption of tobacco. Similarly, the present pronouncement of a shortened life span for tobacco users by the Surgeon General's reports has been found to have little effect on the incidence of smoking by the youth of this country.

In tracing the gradual transformation of medical opinion on the use of tobacco, it is clear that medical opinion evolves with increasing information and technology, but it is also molded by contemporaneous social, economic and political circumstances. Although most of the concepts of medicine from before the 19th century are no longer tenable or valid in modern times, man himself has not changed from a biological point of view. The propensity to ingest plant or chemical substances has been a characteristic of man since before recorded history and will remain with him as long as he lives.

Social attitudes and medical opinion are subject to relatively rapid change. Future decisions on the regulation of tobacco and of newer synthetic substances with abuse potential must be approached with this in mind. Man will continue to self-administer psychoactive substances. The responses of society and of the medical profession will most likely undergo the transformations described for tobacco.

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Declaration of Competing Interest

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