

The History of Therapeutic Aerosols: A Chronological Review

Stephen W. Stein, MS¹, and Charles G. Thiel, BA²

Abstract

In 1956, Riker Laboratories, Inc., (now 3 M Drug Delivery Systems) introduced the first pressurized metered dose inhaler (MDI). In many respects, the introduction of the MDI marked the beginning of the modern pharmaceutical aerosol industry. The MDI was the first truly portable and convenient inhaler that effectively delivered drug to the lung and quickly gained widespread acceptance. Since 1956, the pharmaceutical aerosol industry has experienced dramatic growth. The signing of the Montreal Protocol in 1987 led to a surge in innovation that resulted in the diversification of inhaler technologies with significantly enhanced delivery efficiency, including modern MDIs, dry powder inhalers, and nebulizer systems. The innovative inhalers and drugs discovered by the pharmaceutical aerosol industry, particularly since 1956, have improved the quality of life of literally hundreds of millions of people. Yet, the delivery of therapeutic aerosols has a surprisingly rich history dating back more than 3500 years to ancient Egypt. The delivery of atropine and related compounds has been a crucial inhalation therapy throughout this period and the delivery of associated structural analogs remains an important therapy today. Over the centuries, discoveries from many cultures have advanced the delivery of therapeutic aerosols. For thousands of years, therapeutic aerosols were prepared by the patient or a physician with direct oversight of the patient using custom-made delivery systems. However, starting with the Industrial Revolution, advancements in manufacturing resulted in the bulk production of therapeutic aerosol delivery systems produced by people completely disconnected from contact with the patient. This trend continued and accelerated in the 20th century with the mass commercialization of modern pharmaceutical inhaler products. In this article, we will provide a summary of therapeutic aerosol delivery from ancient times to the present along with a look to the future. We hope that you will find this chronological summary intriguing and informative.

Keywords: atropine, dry powder inhaler, inhaler, metered dose inhaler, nebulizer, therapeutic aerosol

The Delivery of Therapeutic Aerosols in Ancient Times

THE DELIVERY OF THERAPEUTIC VAPORS AND AEROSOLS through inhalation has been used for thousands of years in various cultures. The first known reference to therapeutic aerosol delivery is an ancient Egyptian papyrus scroll (Ebers papyrus) dating back to ~1554 BC, which purportedly was discovered between the legs of a mummy in the Assasif district of the Theban necropolis.⁽¹⁾ This papyrus describes having patients struggling to breathe to inhale the vapor formed when black henbane (*Hyoscyamus niger*) plants were placed onto hot bricks. After placing the herbs onto the stone, a jar with a hole was placed over the herbs and the patient

inhaled the fumes through a stalk of reed that was placed into the hole. The instructions as translated by Ebbell⁽²⁾ are “Thou shalt fetch 7 stones and heat them by the fire, thou shalt take one thereof and place (a little) of these remedies on it and cover it with a new vessel whose bottom is perforated and place a stalk of a reed in this hole; thou shalt put thy mouth to this stalk so that thou inhaledst the smoke of it.” Figure 1 shows a representation of the aerosol delivery described in the Ebers papyrus.

Black henbane is a leafy flowering plant native to Europe and northern Africa. The therapeutic properties of the inhaled vapor have been attributed to the tropane alkaloids, including atropine, contained in all parts of the henbane plant.^(3,4) The anticholinergic properties of atropine and

¹3 M Drug Delivery Systems, St. Paul, Minnesota.

²Retired, Tucson, Arizona.

structurally similar alkaloids combined with their prominence in various plants around the world have resulted in this class of compounds playing a critical role in the history of therapeutic aerosol delivery.

The most prominent ancient form of respiratory drug delivery was the smoking of opium for therapeutic and recreational purposes using incense burners and pipes. While the earliest known reference of smoking opium dates back to 1100 BC in China,⁽⁵⁾ the practice likely had earlier origins due to the prominence of opium cultivation by that time. It is believed that cultivation of the opium poppy originated among the Sumerian people of lower Mesopotamia and was passed on to the Assyrian and Babylonians who in turn passed the practice on to the Egyptians.⁽⁵⁾ By 1300 BC, opium cultivation had spread to Egypt, Carthage, and Europe. In 1025 AD, the Persian physician, Avicenna (Abū 'Alī al-Husayn ibn Sina), in his influential medical encyclopedia entitled *Canon of Medicine*, described the use of opium for a variety of medical purposes, including analgesia, treatment of diarrhea, and treatment of severe cough. Avicenna described a variety of forms of administration, including smoking and nasal inhalation.⁽⁶⁾ Avicenna extensively described the toxicity of opioids and generally discouraged their use. He recommended, "If you have no other option but to use opioids, closely monitor patient's pulse to avoid overdosing."⁽⁶⁾

The inhalation of therapeutic aerosols for the treatment of asthma is described in the writings of the influential Indian physicians, Charaka and Sushruta, which date back to ~600 BC. These writings provide detailed instructions for preparing herbal compositions, including *Datura* that could be smoked in a pipe or in a cigarette⁽³⁾ to relieve asthma symptoms. Charaka also described the burning of herbal compositions in a bowl fitted with a second bowl on top and a tube fitted to allow inhalation of the fumes.⁽⁷⁾ The therapeutic effects and toxicity described by Sushruta are consistent with atropine, which is a known active ingredient of the *Datura stramonium* species.⁽³⁾ While the oldest existing documents describing smoking of *Datura stramonium* for treatment of asthma come from about 600 BC, Gandevia proposes that the origins of this therapy may date as far back as 2000 BC with early traditional Ayurvedic medicine.⁽⁷⁾

In addition to inhaled *Datura*, Indian physician Charaka Samhita describes in his first century AD medical book a range of asthma therapies that include steam inhalation and smoking cigars made of the paste of turmeric, cassia, cinnamon, the roots of the castor plant, lac, red arsenic, deodar, yellow orpiment, and nardus, smeared with ghee.⁽⁸⁾ The Ayurvedic texts provide instructions on how to modify the strength of the dose, give clear instructions on the optimal inhalation technique, and provide contraindications to this therapy.⁽⁷⁾

The famous Greek physician, Hippocrates (460–377 BC), describes a device for enabling the inhalation of various vapors for the treatment of a number of maladies. This device consisted of a pot with a lid that had a hole through which a reed could be placed to enable the vapors to be inhaled.⁽⁹⁾ Vapors generated from herbs and resins that had been boiled in vinegar and oil were inhaled through the reed.⁽³⁾

In the second century AD, the Greek physician, Galen of Pergamon, described the inhalation of powdered drugs for relief of nasal and chest troubles.⁽¹⁰⁾ In particular, Galen described the inhalation of myrrh and nutgall powders into

the larynx through a bent reed to treat angina and credited the origin of this early practice of powder inhalation to Aesculapius, the God of medicine and healing.⁽¹¹⁾ Around the same time frame, another Greek physician, Aretaeus of Cappadocia, utilized a similar instrument for powder inhalation to treat laryngeal ailments of children.⁽¹²⁾

While not normally delivered through inhalation, ephedra (known in China as Ma Huang) played a key role in the treatment of asthma for thousands of years. The Chinese medical book *Nei Ching* written by Huang-Ti in ~1000 BC describes the use of Ma Huang remedies for the treatment of asthma.⁽¹³⁾ Ma Huang, which was usually delivered orally as a tea or a pill, was later shown to contain the active ingredient ephedrine.⁽³⁾ Ephedra was a mainstay in asthma therapy in the Roman Empire. The noted Roman historian, Pliny the Elder (23–79 AD), recommended ephedra mixed with red wine as a remedy for asthma. Interestingly, Pliny recommended a number of other asthma remedies that probably did not significantly advance the treatment of asthma (e.g., drinking the blood of wild horses, bear's gall mixed with water, or millipedes soaked in honey!), but he made the significant contribution of identifying a link between pollen exposure and respiratory distress [*The Natural History of Pliny*; translated in 1856 by Bostock and Riley⁽¹⁴⁾].

Ephedrine, which would later be isolated from ephedra by Japanese chemist Nagayoshi Nagai in 1885,⁽¹⁵⁾ remained widely used for treatment of cough and respiratory disease until the 1950s when it began to be displaced by other bronchodilators with improved safety profiles.⁽¹⁵⁾ Ephedrine sulfate is still available over the counter in the United States, but with significant restrictions and regulation.

By the first century AD, the smoking of tobacco and other plants in Central and South American cultures using ornate pipes had become common.⁽³⁾ It is believed that these cultures also had identified the smoking of *Datura* as a therapeutic remedy for the treatment of asthma⁽⁷⁾ and had used the inhalation of cannabis for recreational and therapeutic purposes, including the use as a sedative.⁽¹⁰⁾

In the fourth or fifth century AD, the Roman physician, Caelius Aurelianus, provided a clear description of the symptoms of bronchial asthma and proposed the inhalation of steam as a technique to treat asthmatic episodes. He also proposed inhaling sea air as a technique for preventing episodes.⁽⁸⁾ The warm steamy air in Roman public bath systems that were widely developed at that time in major cities was recommended by Roman physicians for treatment of various ailments, including asthma.⁽¹⁰⁾

Delivery of Therapeutic Aerosols from the Middle Ages to the Industrial Revolution (476–1760 AD)

There were relatively few major innovations in the delivery of therapeutic aerosols during the period between the fall of Rome (476 AD) and the start of the Industrial Revolution (c. 1760 AD). The recorded examples of the delivery of therapeutic vapors and aerosols through inhalation during this period relied heavily on practices developed before the fifth century AD, such as the smoking of *Datura* or opium and directing the fumes and vapors of burning herbs into the lung of the patient.

The seventh century AD Greek physician, Paulus Aegineta, catalogued a host of ingredients to be inhaled for the

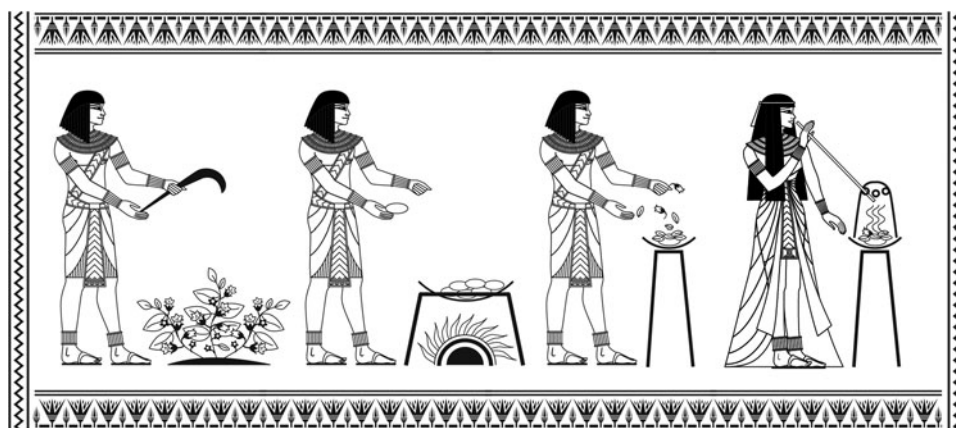


FIG. 1. A schematic representation of the oldest known reference (c. 1554 BC) of therapeutic aerosol delivery in which smoke of henbane plants was inhaled through the stalk of a reed.

treatment of persistent cough. His recommended treatment consisted of placing a complex herbal remedy onto coals and inhaling the fumes through a funnel. Aegineta's instructions are recorded as, "To be inhaled for a continued cough: storax, pepper, mastic, Macedonian parsley, of each one ounce; sandarach, 6 scruples; 2 bayberries; mix with honey; and fumigate by throwing them upon coals so that the person affected with the cough may inhale the vapor through a funnel."^(9,16) The resultant vapor contained arsenic since sandarach is the Greek and Roman name for red arsenic sulfide.^(9,16)

Rhazes, the Arab physician who lived in Baghdad from 850 to 932 AD, proposed some of the more innovative approaches for pulmonary delivery during the Middle Ages. He utilized sponges that had been soaked in a solution of narcotic plants (opium, hyoscyamus, mandrake, and henbane) and then allowed to dry. Then, just before the surgery, the sponge was moistened and placed over the mouth and nose of patient in order that the vapors be inhaled as anesthesia during surgery.⁽¹⁰⁾ Rhazes also advocated for the inhalation of arsenic for the treatment of respiratory conditions.⁽³⁾

The figure with the greatest influence on the inhalation of therapeutic aerosols during the Middle Ages was the Spanish-born physician, Maimonides (1138–1204 AD), who fled Spain and eventually became the personal physician to Saladin, the sultan of Egypt (1137 or 1138–1193 AD). Maimonides was responsible to care for the king's asthmatic son and wrote the first known book on asthma (*A Treatise on Asthma*) in 1190. His recommendations for management of asthma included inhaling herbs burned on a fire, abstaining from sex, and eating chicken soup.⁽³⁾ Maimonides provided numerous other dietary recommendations for the management of asthma and recognized the link between air pollution and asthma.⁽¹³⁾ Maimonides reasoned, "Town air is stagnant, turbid, and thick... Air winds carry stealthily inside the houses and many become ill with asthma without noticing. Concern for clean air is a foremost rule in preserving the health of one's body and soul" [quoted in Brenner⁽¹³⁾].

There were limited advancements in the understanding of asthma and the delivery of therapeutic aerosols between the time of Maimonides and the start of the Industrial Revolution. The most notable contributions came from the Indian physician, Yogaratnakara, who in the 17th century provided

further description and modification of *Datura* smoking therapy for treatment of asthma⁽⁷⁾ and English physician, Christopher Bennet, whose 1654 drawing (Fig. 2) is the oldest known illustration of an inhalation device.⁽³⁾

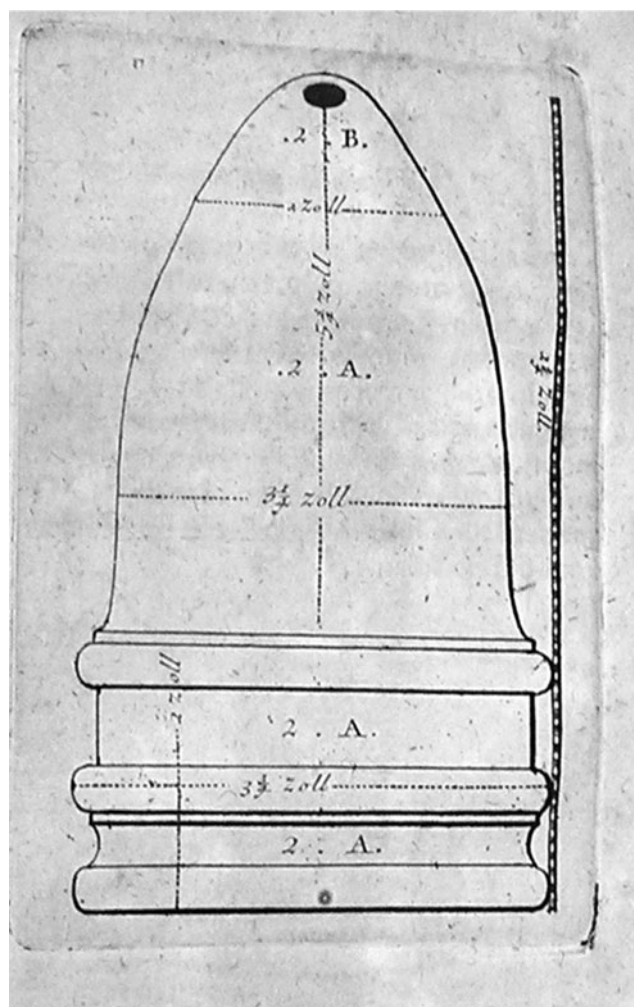


FIG. 2. The oldest known drawing of a therapeutic inhaler device developed in 1654 by the English physician Christopher Bennet. Image courtesy of Mark Sanders

The Delivery of Therapeutic Aerosols from 1760 to 1955

With the dawn of the industrial revolution in 1760, new manufacturing capabilities and technical discoveries paved the way for significant advances in the delivery of therapeutic aerosols. Before this time frame, therapeutic aerosols were primarily prepared directly by the physician or patient, but during this era, devices and therapeutic aerosol preparations began to be mass produced by individuals completely removed from the treatment of the patient. In addition, this was an era where new therapeutic entities were identified and techniques were developed for enhancing the potency and safety of these therapeutic entities by isolating the active ingredient. New delivery systems such as nebulizers and early dry powder inhalers (DPIs) were also introduced during this period. These advances set the stage for the beginning of the modern era of pharmaceutical aerosols, which began in 1956.

Advances in the delivery of medicated vapors

In the late 1700s, respiratory drug delivery continued to rely on inhaling medicated vapors. It should be noted that the phrase “medicated vapor” is probably simplistic since some of the techniques described below that were utilized during this period undoubtedly resulted in some aerosol droplets being formed either through condensation of saturated water vapor in the system or through atomization of the medicated solution (e.g., when air is bubbled through the solution or the solution is boiled). As a result, the therapeutic benefit of these techniques was likely a result of both the vapor and aerosolized droplets. Nevertheless, these therapeutic aerosols were commonly referred to as medicated vapors and are similarly described in this article.

In his 1764 book, *Medical Advice to the Consumptive and Asthmatic Peoples of England*, English physician Philip Stern prescribed his personal recipe for inhalation of bal-

samic vapors for the treatment of asthma. Stern’s book was groundbreaking in that it was intended to provide instruction for the general public rather than physicians.⁽³⁾ English physician John Mudge advocated for inhaling the aerosol from heated water containing opium for the treatment of catarrhal cough.^(3,9) In his book, *A Radical and Expeditious Cure for a Recent Catarrhus Cough*, he coined the term inhaler to describe a clever inhalation device for generating and delivering steam-based aerosols.⁽¹⁷⁾ The inhaler device, first introduced in 1778, consisted of a pewter tankard having a volume of approximately one pint with a lid that had a cover on the top with an adapter that could be coupled to a 5- or 6-inch-long flexible tube through which the patient inhaled for the 20–30-minute duration of the dosing (Fig. 3). The device had holes in the handle through which air was drawn in and bubbled through the warm liquid.⁽¹⁷⁾ Through use of a clever valve design, the patients were able to keep their lips surrounding the mouthpiece tube and breathe in and out through the tube in a way similar to many modern nebulizers. The Mudge inhaler marked the first known commercialization of an inhaler device with Mudge detailing in his book the name of a local pewterer that he partnered with and from whom the inhaler could be obtained.

Throughout the 1800s, the inhalation of medicated vapor from aqueous solutions continued to be a primary mode of treatment of respiratory ailments. Various ceramic inhalers with similar functionality to the Mudge inhaler were commercialized for generated medicated vapors and gained popularity in England in the 19th century. Prominent among these ceramic inhalers was the Nelson inhaler, which was commercialized by S Maw and Sons in London.⁽⁹⁾ Other approaches were used to generate medicated vapors, such as pouring the medicated solution over a sponge.⁽¹⁸⁾

As devices for generating medicated vapors proliferated, so too did the recommended therapies. In 1834, Sir Charles Scudamore proposed heating iodine and hemlock (conium)



FIG. 3. A drawing (a) and photo (b) of the Mudge Inhaler.⁽¹⁷⁾ As the patient inhaled through the flexible mouthpiece, air was drawn through the three holes on the handle and the air was bubbled through the medicated liquid before exiting the mouthpiece. The right side of the drawing shows the valve configuration, which utilized a small cork that moved and allowed the exhaled breath of the patient to exit the tankard. Images courtesy of Mark Sanders.

in water to 120 F and having the patient inhale the vapor for 15–20 minutes three times per day for the treatment of tuberculosis or other lung diseases.⁽³⁾ The 1867 British Pharmacopoeia listed detailed instructions for the generation of various medicated solutions to be inhaled, including hydrocyanic acid for the treatment of cough, chlorine for treatment of tuberculosis, hemlock for the treatment of cough, creasote for the treatment of tuberculosis and bronchitis, and iodine for the treatment of tuberculosis, pharyngitis, and laryngitis. The inclusion of these therapies in the British Pharmacopoeia demonstrates that these therapies had received widespread acceptance by that time.⁽¹⁹⁾

The inhalation of anesthetic gases through makeshift face masks emerged in the 1840s.⁽¹⁰⁾ There is a debate over whether the use of inhaled ether as surgical anesthetic was introduced by American physicians Crawford Long in 1842 or William Morton and John Collin Warren in 1846, but the practice gained rapid acceptance.^(3,20,21) Due to the side effect of nausea associated with ether, physician James Young Simpson introduced inhaled chloroform as a surgical anesthetic in 1847.⁽¹⁰⁾ The use of nitrous oxide for dental anesthesia was first demonstrated by American dentist Horace Wales in several dental operations in 1844⁽¹⁰⁾ and then gained widespread acceptance due to the influence of New York dentist Gardner Quinicy Colton.⁽²²⁾

The diversification of technologies for inhalation delivery in the last half of the 19th century

The last half of the 19th century saw unprecedented innovation in the area of pharmaceutical aerosol delivery technologies. The introduction of nebulizers, DPIs, advances in the commercialization of asthma cigarettes, and a number of other delivery technologies dramatically reshaped the practice of delivering drugs to the respiratory tract. Other innovations, although less influential, are worthy of mention. One innovation was direct spraying of medicated solutions into the respiratory tract. By 1852, Ira Warren (the inventor of the first DPI) was selling a kit consisting of a laryngeal, pharyngeal, and nasal shower syringe for applying an aqueous solution of silver nitrate for treatment of various respiratory conditions such as nasal catarrh and diseases of the throat.⁽²³⁾ At the 1890 Annual Meeting of the American Medical Association, J. Mount Bleyer published an article describing a similar approach that he claimed was capable of administering medications such as silver nitrate, iodine, tannic acid, and hydrogen peroxide deeper into the bronchia.⁽²⁴⁾

Inhaling the fumes of burning niter paper (which generates ammonia as it burns) was recommended by Henry Hyde Salter in his famous 1860 book, *On Asthma its Pathology and Treatment*, as a form of inhalation therapy.⁽³⁾ In the 1890s, the Wyeth Pencil Inhaler was commercialized as a portable and convenient treatment of various ailments, including catarrh, bronchitis, and croup. This inhaler contained menthol crystals and a rotatable cap with holes, which when in the proper orientation allowed air to penetrate through the holes and over the crystals to vaporize the menthol (which has a vapor pressure of 8.5 Pa at 25°C) so as to allow the vapor to be inhaled by the patient.⁽²⁵⁾

Another interesting innovation during this period was a patent by Helbing and Pertch⁽²⁶⁾ in 1899 of a propellant-based liquid aerosol generator that used ethyl or methyl

chloride (now considered toxic via inhalation) as the propellant to atomize the liquid. The invention utilized heat of the hand to increase the vapor pressure of these liquids (135 and 506 kPa at 20°C, respectively) and provided sufficient pressure to atomize the formulation through a small orifice. Clark⁽²⁷⁾ points out that the Helbing and Pertch inhaler was in many respects a precursor to the pressurized metered dose inhaler (MDI) that would reshape the treatment of lung diseases when introduced in 1956. However, Helbing and Pertch did not recognize the value of this invention for inhalation therapy and instead targeted applications requiring a medicated spray to be applied during surgery.

Asthma cigarettes

Smoke therapies for the treatment of respiratory ailments originated in India and date back to at least 600 BC. After being introduced in the United States by Philadelphia physician Samuel Cooper in 1797 and in Great Britain in 1802 by General Gent upon his return from India,⁽²⁸⁾ smoked stramonium rapidly became a popular asthma therapy in the 1800s in Europe and the United States. Traditionally, these therapies were individually assembled for the specific patient (either by the patient or a physician). However, at the turn of the 20th century, there was a change to large-scale commercial manufacturing of cigarettes to be sold to unknown patients. A number of commercially available asthma cigarettes with stramonium were widely used in Europe, the United States, and China^(28,29) (Fig. 4). Some of the cigarettes included other herbs such as tea leaves, kola nuts, lobelia, and atropine-containing atropa belladonna leaves.⁽⁹⁾

Given the abundance of data demonstrating health risks associated with cigarette smoking, it may seem surprising to the 21st century reader that cigarettes would be a preferred therapeutic option for patients with lung ailments. Clearly, the smoke from asthma cigarettes contained tar and a number of other toxic substances that would prove detrimental to lung function. However, the detrimental impact on lung function of



FIG. 4. Page's asthma cigarettes containing stramonium, tea leaves, chestnut leaves, and gum benzoin. Image courtesy of Mark Sanders

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