

History of Aerosol Therapy: Liquid Nebulization to MDIs to DPIs

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Inhaled therapies have been used since ancient times and may have had their origins with the smoking of datura preparations in India 4,000 years ago. In the late 18th and in the 19th century, earthenware inhalers were popular for the inhalation of air drawn through infusions of plants and other ingredients. Atomizers and nebulizers were developed in the mid-1800s in France and were thought to be an outgrowth of the perfume industry as well as a response to the fashion of inhaling thermal waters at spas. Around the turn of the 20th century, combustible powders and cigarettes containing stramonium were popular for asthma and other lung complaints. Following the discovery of the utility of epinephrine for treating asthma, hand-bulb nebulizers were developed, as well as early compressor nebulizers. The marketing of the first pressurized metered-dose inhaler for epinephrine and isoproterenol, by Riker Laboratories in 1956, was a milestone in the development of inhaled drugs. There have been remarkable advances in the technology of devices and formulations for inhaled drugs in the past 50 years. These have been influenced greatly by scientific developments in several areas: theoretical modeling and indirect measures of lung deposition, particle sizing techniques and in vitro deposition studies, scintigraphic deposition studies, pharmacokinetics and pharmacodynamics, and the 1987 Montreal Protocol, which banned chlorofluorocarbon propellants. We are now in an era of rapid technologic progress in inhaled drug delivery and applications of aerosol science, with the use of the aerosolized route for drugs for systemic therapy and for gene replacement therapy, use of aerosolized antimicrobials and immunosuppressants, and interest in specific targeting of inhaled drugs. *Key words: aerosol, nebulizer, inhaler, metered-dose inhaler, dry powder inhaler, asthma, lung disease, bronchodilator, scintigraphy, drug delivery.* [Respir Care 2005;50(9):1139–1149. © 2005 Daedalus Enterprises]

Introduction: Origins of Inhaled Therapies

Although the term “aerosol” was not coined until around 1920, inhaled therapy for medicinal purposes dates back at least 4,000 years. The origins of inhalation therapy for asthma and other lung complaints may have arisen in the traditional therapies of Ayurvedic medicine in India around 2000 BC.¹ The compounds smoked included herbal preparations, most notably datura species, which contain potent alkaloids with anticholinergic bronchodilating properties. The datura roots were powdered together with other materials such as ginger and pepper, made into a paste for smearing on a reed that could be dried and smoked through a pipe.

Around 1500 BC in Egypt, the vapor of black henbane was inhaled after being thrown onto a hot brick. Henbane is of the genus *Hyoscyamus*, which is in the nightshade family and contains hyoscyamine, another anticholinergic compound. One of the earliest inhaler devices is a design attributed to Hippocrates (Greece, 460–377 BC) that consisted of a simple pot with a reed in the lid, through which vapors could be inhaled. Native cultures from Central and South America also fashioned pipes and devices for inhaling the smoke of tobacco and other plants (Fig. 1).

In 1190 AD, a famous Spanish physician and philosopher Maimonides wrote *Treatise on Asthma* and recommended inhalation of fumes generated from herbs thrown on a fire, in addition to a modest lifestyle, which included chicken soup.² Various ingredients have been documented in these inhaled recipes from antiquity, as evidenced by this quotation from Paulus Aegineta (Greece, 7th century AD): “To be inhaled for a continued cough: storax, pepper, mastick, Macedonian parsley, of each one ounce; sandarach [an arsenical preparation], 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.”³ Commonly used materials for these ancient inhaled remedies included plants with



Fig. 1. Arica inhaler from coastal regions of northern Chile and southern Peru, dating from about 1500 AD. A tobacco-like mixture was prepared on the decorated wooden receptacle and inhaled through the hollow wooden mouthpiece. (Courtesy of Mark Sanders, Inhalatorium.com.)

anticholinergic properties, such as datura, henbane, lobelia, and belladonna, in addition to arsenicals, balsams, and gum resins.

Throughout the ages, many terms have been used to describe inhaled substances. Common terms and definitions are listed in Table 1.

Ceramic Inhalers (19th Century)

Variations on Hippocrates’s pot-and-reed design were used in the late 18th and early 19th century. The English physician John Mudge described his invention of an inhaler based on a pewter tankard, in his 1778 book *A Radical and Expeditious Cure for a Recent Catarrhus Cough* (Fig. 2). Dr Mudge is thought to be the first person to use the term “inhaler,” and describes using his device for inhaling opium vapor for the treatment of cough.⁴ Numerous models of ceramic inhalers followed this design and were popular from the 19th century onward (Fig. 3). The design caused air to be drawn through warm water or an infusion prior to inhalation; one of the most popular models, the Nelson’s inhaler, manufactured by S Maw and Sons in London, was described in a *Lancet* article in 1863. Dr Scudding, in his 1895 treatise on inhalation therapy, related that “the most efficient apparatus for the inhalation either of simple steam or of medicated vapors is that which is known by the name of Nelson’s Inhaler: it is constructed of earthenware, and, in addition to its complete adaptation to the purpose for which it is intended, possesses the triple recommendation of cleanliness, portability, and cheapness.”⁵ Those are certainly qualities that are valued in modern inhalation devices.

The earliest use of inhaled datura for asthma in Britain was recorded in 1802 by Dr Sims, who had learned of this treatment from General Gent, an asthmatic posted to Madras, who had adopted the practice for his own use.^{1,6}

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HISTORY OF AEROSOL THERAPY: LIQUID NEBULIZATION TO MDIs TO DPIS

Table 1. Definitions of Common Terms Applied to Inhaled Therapies

Aerosol	Solid or liquid particles suspended in a gas
Atomizer	Device used to form a mist of fine droplets from a liquid. A high-velocity air jet passes over a liquid feed tube and draws liquid to the surface by the Bernoulli effect. The liquid is then propelled forward as a thin sheet, from which it breaks up into droplets by shear-induced instability.
Nebulizer	An atomizer modified with a baffle or impactor in front of the jet to remove large particles from the air stream
Fume	Solid-particle aerosol produced by the condensation of vapors or gaseous combustion products
Vapor	The gaseous state of substances that are normally in the liquid or solid state (at normal room temperature and pressure)
Smoke	Visible aerosol resulting from incomplete combustion; the particles can be solid or liquid
Dust	Solid-particle aerosol formed by mechanical disintegration of a parent material, such as by crushing or grinding
Powder	A solid substance in the form of tiny, loose particles
Suspension	Mixture in which particles are suspended in a fluid and the particles are large enough that gravity causes the particles to settle
Solution	Homogeneous mixture of 2 or more substances; frequently a liquid solution
Gas	State of matter distinguished from the solid and liquid states by (1) relatively low density and viscosity, (2) relatively great expansion and contraction with changes in pressure and temperature, (3) the ability to diffuse readily, and (4) the spontaneous tendency to distribute uniformly throughout any container.
Mist	Liquid-particle aerosol formed by condensation or atomization



Fig. 2. The Mudge inhaler, invented by Dr John Mudge in 1778, was a pewter tankard with a mouthpiece covering the top and an air passage drilled through the handle. As the patient breathed through the mouthpiece, air was drawn through the holes in the handle and passed through the liquid at the bottom of the vessel. (Courtesy of Mark Sanders, Inhalatorium.com.)

Reportedly, General Gent may have become a victim of his own inhaled therapy, with toxic manifestations leading to his untimely demise. There are other reports of datura use being brought back to Britain from the Far East, and the drug may have been used for its hallucinatory effects as well. The drug entered orthodox pharmacopoeias in Europe during the first part of the 19th century; its alkaloid component was identified as atropine in 1833.

Early Atomizers and Nebulizers (Mid-to-Late 19th Century)

Atomizers (also known as nebulizers) were developed in the mid-1800s in France and were thought to be an outgrowth of the perfume industry as well as a response to the fashion of inhaling thermal waters at spas. Dr Auphon Euget-Les Bain invented the atomizer in 1849, and in 1858 Jean Sales-Girons introduced a portable nebulizer (Fig. 4). Dr Sales-Girons won the silver prize of the Paris Academy of Science in 1858 for his invention, which used a pump handle to draw liquid from the reservoir and force it through a nozzle against a plate.⁷ At that time, spa therapy was very popular in France, and the Sales-Girons “pulverisateur” was invented to allow those patients who could not attend the thermal baths to benefit from treatment. The thermal spas in France and elsewhere in Europe had long been used for therapeutic purposes, and the waters were inhaled as aerosols as well as ingested.^{6,8} These waters contained minerals, bicarbonate, and arsenicals, and occasionally substances were added that were harmful to the lungs, such as turpentine and petroleum. An improvement on the Sales-Girons device has been attributed to Bergsen, of Berlin, “whose apparatus consists of 2 glass tubes, having capillary openings at one end—these 2 ends being placed almost at a right angle with each other. The more open end of the perpendicular tube is immersed in the medicated fluid, and, as the compressed air is forced through the horizontal tube, the air in the perpendicular one becomes exhausted, and the medicated solution then rises in it, and, when it arrives at the capillary opening, is dispersed in very fine spray by the force of the compressed air passing along the other tube.”⁹ This is an early but accurate description of the Venturi system employed by today’s jet nebulizer.



Fig. 3. Examples of earthenware inhalers from the late 19th century for inhalation of infusions. Left: The Alexandra inhaler, which has a vertical air channel at the back, through which air is drawn; a cover with a mouthpiece would complete the item. (Courtesy of Mark Sanders, Inhalatorium.com.) Right: The Maw's (or Nelson) inhaler, which would have had a stopper with a tube extending down into the liquid infusion.

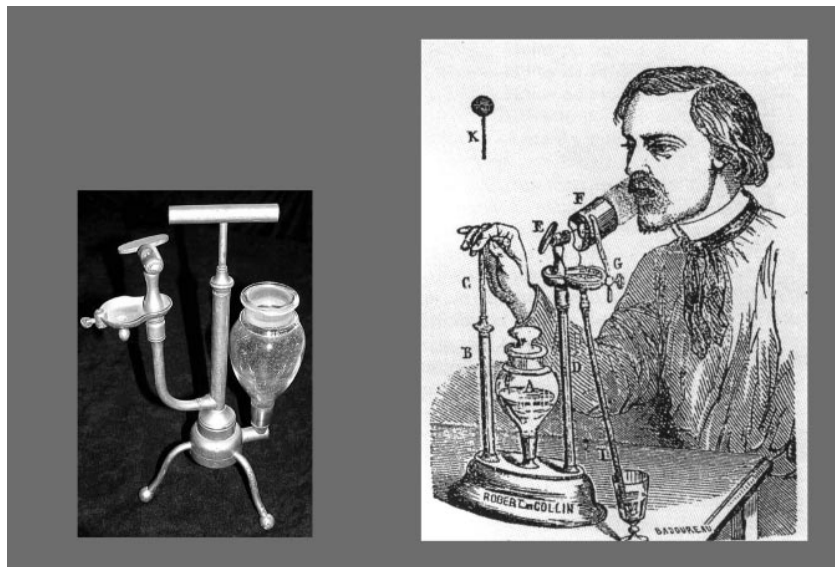


Fig. 4. The Sales-Girons "pulverisateur," which won the 1858 silver prize of the Paris Academy of Science. The pump handle draws liquid from the reservoir and forces it through an atomizer. (Courtesy of Mark Sanders, Inhalatorium.com.)

Siegle's steam spray inhaler, developed in Germany in the 1860s, was based on the same principle, but it used steam rather than compressed air to disperse the medicated liquid. During that period, there were some authorities

who doubted that spray solutions actually reached the lungs. In what might have been one of the first deposition experiments, Demarquay studied a woman with a tracheal fistula and demonstrated by doing chemical tests at the

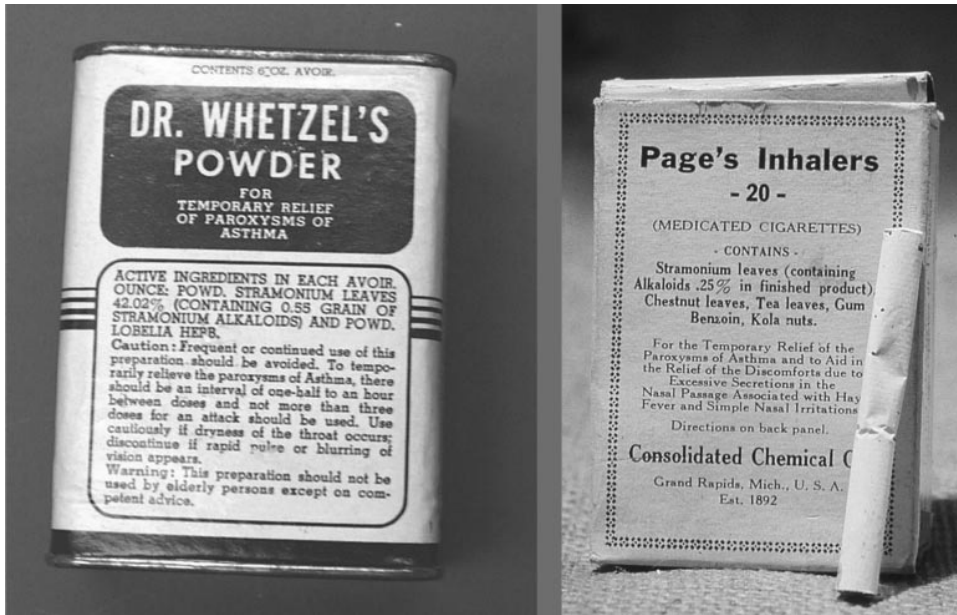


Fig. 5. Asthma powder and asthma cigarettes were popular around the turn of the 20th century. One of the active ingredients was stramonium, which has anticholinergic bronchodilating properties.

tracheal opening that the inhaled substances had at least penetrated as far as the trachea.⁹

Asthma Cigarettes and Powders

Around the turn of the 20th century, combustible powders and cigarettes for the treatment of asthma and other lung complaints were popular (Fig. 5).^{6,10} These cigarettes contained stramonium (from *Datura stramonium*) as well as other ingredients, such as tea leaves, belladonna, kola nuts, and lobelia. A spoonful of powder was placed in a saucer and burned, and the smoke was inhaled through the mouth or with a funnel. The instructions for the asthma cigarette were to “exhaust the lungs of air, then fill the mouth with smoke and take a deep breath, drawing the smoke down into the lungs. Hold for a few seconds and then exhale through the mouth and nostrils,” which are similar to instructions given in modern clinics for metered-dose inhalers (MDIs) and dry powder inhalers (DPIS). During that period, inhaled treatments were very popular and many of dubious benefit. Some devices employed the inhalation of vapors of menthol, creosote, turpentine, camphor, eucalyptus, balsam, pine, or mustard. A few inhaler advertisements even claimed great benefit from the regular inhalation of dry air.

Of note is the Carbolice Smoke Ball, patented in 1889, for the inhalation of medicated powders.¹¹ This device was a hollow rubber ball with a sieve across the orifice to deaggregate the powder inside. The ball was squeezed to produce a powder aerosol of *Glycyrrhiza*, hellebore, and

carbolic acid, and a £100 reward was offered to anyone who contracted influenza while using the Carbolice Smoke Ball according to directions. This may have been one of the first examples of a DPI. Throughout history, and especially in the 19th and early 20th centuries, much of the popularity and advertisements for inhalation therapies and devices were driven by the current lung conditions. Many of these devices were advertised as treatment for consumption, catarrh, croup, bronchitis, pertussis, diphtheria, or influenza, as asthma was less commonly diagnosed.

Hand-Bulb Nebulizer and Early Electric and Compressor Nebulizers (1930s–1940s)

Although the herb ma-huang had been used since 3000 BC in Chinese medicine for the treatment of bronchospasm, advances were made around the turn of the 20th century, with the recognition of adrenal extract as a bronchodilator. In 1899, epinephrine was named by Abel, and this was followed by its synthesis by Stolz and Dakin.^{12,13} Solis-Cohen reported the use of adrenal extract to treat asthma patients in 1900, and the first use of epinephrine as an aerosol was reported in 1910 by Barger and Dale. It’s of interest that the 1932 edition of the *Oxford Medicine* does not mention inhaled adrenalin as a treatment for asthma, but states “. . . if the patient himself cannot use hypodermic medication he tends to rely upon patent medicines and so-called asthma cures. The most serviceable among these seem to be the ones that contain stramonium leaves and saltpeter in the form of a powder, the fumes of

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