

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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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.

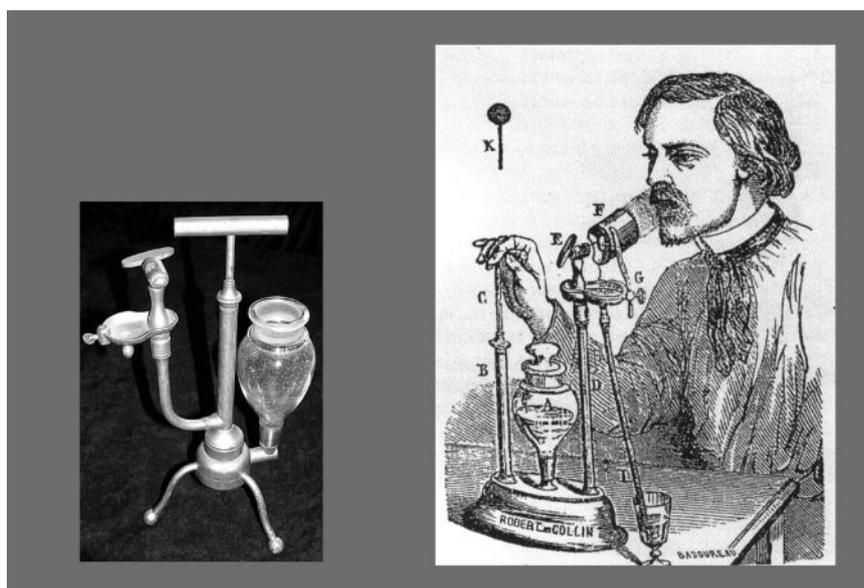


Fig. 4. The Sales-Girons "pulverisateur," which won the 1858 silver prize of the Paris Academy of Science. The pump handle draws liquid from the reservoir and forces it through an atomizer. (Courtesy of Mark Sanders, Inhalatorium.com.)

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

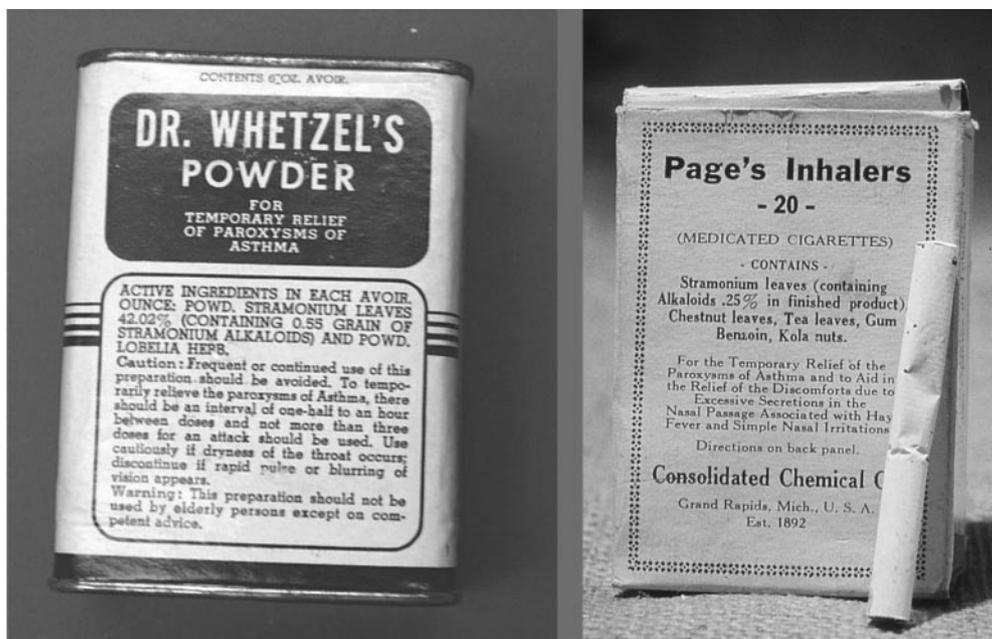


Fig. 5. Asthma powder and asthma cigarettes were popular around the turn of the 20th century. One of the active ingredients was stramonium, which has anticholinergic bronchodilating properties.

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 Carboloc 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 Carboloc 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



Fig. 6. AsthmaNefrin hand-bulb nebulizer from the 1940s. The nebulizer was constructed of a plastic-like material and used for the inhalation of epinephrine.

which, when burned, are inhaled for the relief of the paroxysm. These fumes seem to be antispasmodic in action and following their inhalation thick sputum is raised and temporary relief results.”¹⁴

Adrenalin chloride solution was supplied in the 1930s as a bronchodilator and was nebulized via glass-bulb nebulizers such as the Parke-Davis Glaseptic, and in the 1940s, via plastic-bulb nebulizers such as the AsthmaNefrin (Fig. 6). The AsthmaNefrin instructions state that “the appliance reduces the solution to a mist so fine it actually floats in air. You breathe it as easily as you would a moist sea breeze, and the inhalant accomplishes its work because it can really be inhaled.”

In the early 1930s, a compressor nebulizer, the Pneu-mostat, was manufactured in Germany.¹⁵ This piece of equipment had a rheostat for the power supply, allowing adjustment of the electrical voltage powering the compressor. Also around that time, the London Inhalatorium offered a treatment room that utilized a nebulizer powered by a cylinder of compressed oxygen, for inhalation of adrenalin, menthol, eucalyptus, turpentine, and other ingredients.¹⁶

Early DPIS and MDIS (1940s–1950s)

Abbot Laboratories developed the Aerohaler for inhaled penicillin G powder and launched this device in 1948. Each small sifter cartridge contained 100,000 units of penicillin powder, which was inserted in the inhaler; the inhalation air intake caused a metal ball to strike the cartridge and shake out powder into the airstream. The device could also be used for nasal inhalation, and the instructions strongly exhort against exhaling into the device. This de-

vice was also used in the 1950s by Abbot for administration of norisodrine powder for treatment of asthma.

The development of the pressurized MDI (pMDI) was a revolution in inhaler design. In 1955, Dr George Maisson, the president of Riker Labs (now 3M Pharmaceuticals, St Paul, Minnesota), stimulated the development of the pMDI at the suggestion of his asthmatic teenage daughter, who got the idea from perfume spray devices.^{10,17} Researchers at Riker Labs developed a metered-dose valve and worked with DuPont, which manufactured propellants to produce an alcohol-based solution MDI. In March 1956, new drug applications were approved for Medihaler-Epi (epinephrine) and Medihaler-Iso (isoproterenol). Three months later, these products were packaged for marketing. In 1957 the first oral suspension pMDIs of epinephrine and isoproterenol were produced.

There have been remarkable advances in the technology of devices and formulations for inhaled drugs in the 50 years since the development of the first pMDI (Fig. 7). Jet and ultrasonic nebulizers have advanced, with devices that are breath-enhanced, breath-actuated, and dosimetric. Several new devices use vibrating-mesh technology in portable, efficient nebulizers. MDI development has proceeded in several directions to address the problems posed by improper inhalation technique and coordination, high oropharyngeal deposition, and the need to replace chlorofluorocarbon (CFC) propellants. This has resulted in marketing of accessory devices, breath-actuated MDIs, DPIS, non-CFC MDIs, and metered-dose liquid inhalers. Some early developments warrant mention, such as the first breath-actuated inhaler, the Duo-Haler, manufactured by 3M in 1970.¹¹ This device did not gain clinical acceptance because of its large size and the fact that it made a loud click on actuation.

Early DPIS included the Spinhaler for cromolyn, introduced by Fisons in 1971, and the Rotahaler for albuterol, introduced by Glaxo in 1977. Also, the ultrasonic nebulizer, which uses a transducer made from a piezoelectric crystal, was put into production in the 1960s, but was never as commercially successful as the jet nebulizer.

Another device that was in widespread use in the 1970s and 1980s was the intermittent positive-pressure breathing machine for delivery of bronchodilator solutions. Reports suggested that this device was not an improvement over the nebulizer or pMDI, and, in fact, it was associated at times with worsening asthma, worsening gas exchange, and barotrauma, so use of this device declined.^{18,19}

A milestone in the clinical use of inhaled drug therapy that deserves mention took place in 1974: the Conference on the Scientific Basis of Respiratory Therapy, also known as the “Sugarloaf Conference,”²⁰ at which many experts in pulmonary medicine and respiratory care came together to examine the scientific basis for respiratory care and specifically address aerosol therapy.

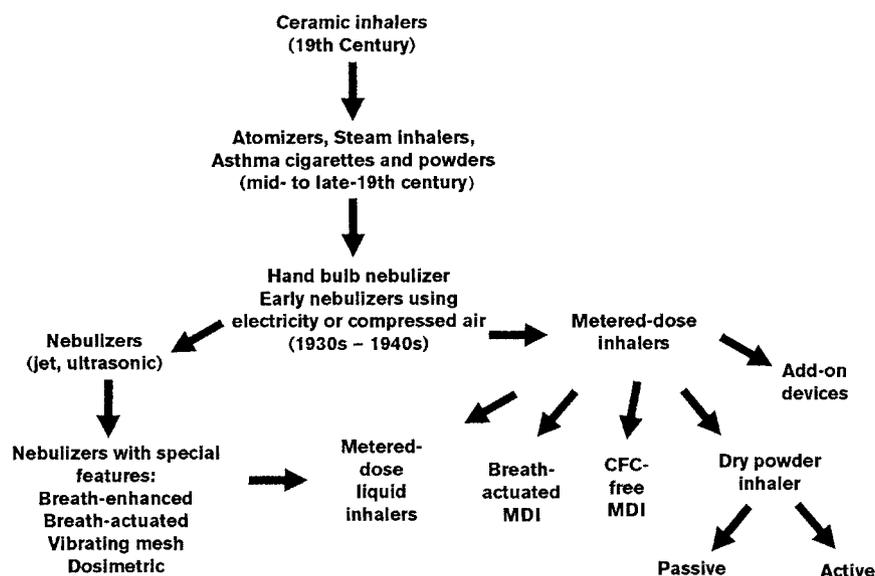


Fig. 7. The evolution of inhaler devices.

Advances in Aerosol Science

Theoretical Models

During the 20th century several scientific advances had major impacts on inhaled-drug delivery. These include (1) theoretical models and predictions, (2) indirect measures of lung deposition, (3) particle sizing techniques and in vitro measurements, (4) scintigraphic measurement of lung deposition, (5) pharmacokinetics and pharmacodynamics, and (6) the 1987 Montreal Protocol, which banned CFC propellants. In the early part of the 20th century it was not the medical field that stimulated investigations into measurements of respiratory-tract particle deposition, but chemists working on toxic aerosols used in warfare during and after World War I and industrial hygienists concerned with environmental and occupational particle exposure. The first mathematical model of respiratory deposition of aerosols was presented by Findeisen in 1935.^{21,22} He used a simple 9-generation lung model, excluding the upper airway, and using 7 different particle diameters (from 0.03 μm to 30 μm), and assumed deposition from the mechanisms of impaction, sedimentation, and Brownian diffusion. He found that as particle size increased, the site of deposition moved proximally, toward the trachea. Landahl modified Findeisen's model by adding a mouth and pharynx, an alveolar duct generation, and several different breathing conditions.²³ There were subsequent refinements of these models in the years that followed, but one of the most widely used models was developed and reported^{24,25} by the Task Group on Lung Dynamics to the International Commission on Radiation Protection (Fig. 8). The model divided respiratory tract deposition into 3 zones, the na-

sopharyngeal, tracheobronchial, and pulmonary zones, and performed calculations for particles from 0.01 μm to 100 μm , with several breathing patterns. Although the task group's model was intended for radiation-protection purposes, it was widely applied to other situations. For all of the models, the particles were assumed to be spherical and of unit density (1 g/cm^3), and the concept of aerodynamic particle diameter was established. In 1963, Weibel published lung anatomical schemes with 23 generations, based on detailed anatomic examination of several excised normal adult human lungs, which were used in many of the subsequent theoretical models.²⁶

Much more sophisticated models are now available, use more accurate lung anatomy and 3-dimensional simulations, and incorporate factors such as airway narrowing and hygroscopic particle growth. In contrast to the original stimulus of modeling in toxicology and occupational hygiene, there is much more interest at present in modeling delivery of therapeutic aerosols. Therapeutic aerosols present many more challenges for modeling, in that they take different physical forms and can be generated in many different ways. The physical form may be liquid drops, solutions, micronized drug in suspension, or dry particles. Some are physically unstable and may be subject to evaporation, growth, agglomeration, or repulsion as they pass from the delivery device into the humid respiratory tract. Models are currently evolving to account for these variables.^{27,28}

Indirect Measures of Lung Deposition

During the period of theoretical model development, experimental studies of aerosol deposition in humans were also taking place. These studies utilized laboratory-gener-

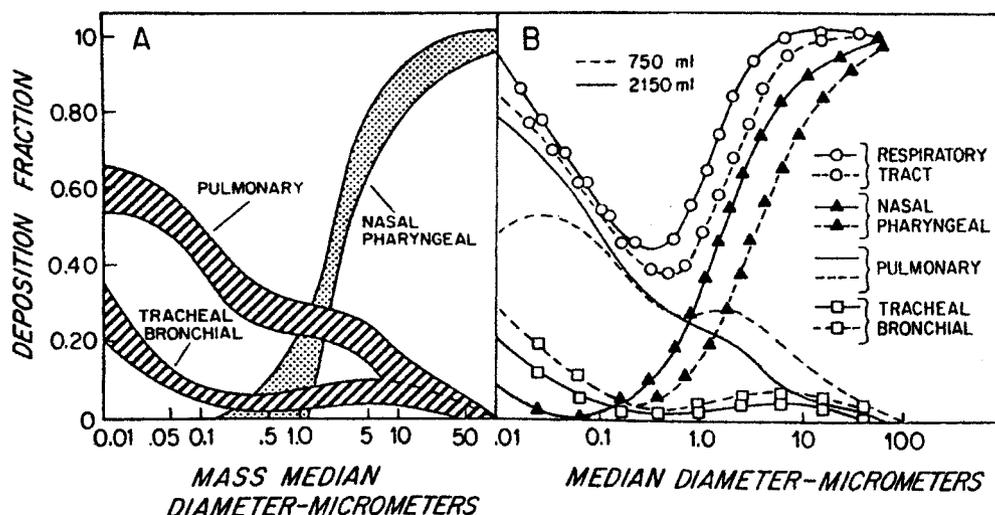


Fig. 8. Task Group on Lung Dynamics theoretical model. The model divided respiratory-tract deposition into 3 zones: the nasopharyngeal, tracheobronchial, and pulmonary zones. (From Reference 25, with permission.)

ated monodisperse aerosols, normal subjects, and techniques that compared fractions of inhaled and exhaled air to estimate particle retention.^{29,30} Techniques for aerosol analysis included light scattering measurements and chemical analysis of inhaled and exhaled air. Several different aerosols were used, including triphenyl phosphate, CaCO_3 , ZnO , sebacate, and NaCl particles. In general, these early measurements were in reasonable agreement with the available theoretical models. Over the next 20–30 years, the technology and experimental data improved as theoretical models improved and the effect of particle size and breathing pattern on the deposition of inhaled aerosols became more clear.^{31,32}

Particle Sizing Techniques and in Vitro Measurements

During the period of development of theoretical deposition models and early deposition experiments, advancements were also made in respirable mass sampling of aerosols and particle sizing. The concept of respirable mass was developed for industrial hygiene purposes, to indicate what portion of a harmful dust could penetrate deep into the lung and cause lung disease. Several definitions were put forth in the 1950s and 1960s and the decades that followed.²² Early sizing of harmful mineral dusts was via microscopy, but mechanical samplers were developed that divided particles that were nonrespirable from those that were respirable.³³ These fractions can be gravimetrically measured, and this technology is still used today in the workplace.

More sophisticated methods for determination of particle size distribution were developed using inertial impaction and optical devices, which have become the standard for pharmaceutical aerosols.³⁴ The cascade impactor draws

the aerosol through a series of stages, each containing a plate or filter upon which the particles deposit according to their sizes. Optical methods use light scattering, diffraction, phase Doppler, and time-of-flight measurements to derive particle size distribution. From these measurements a mean aerodynamic diameter and the variability around that mean (geometric standard deviation) can be determined. These measurements are important for quality control and comparison of devices, and they can be used to estimate the amount of deposition in the respiratory tract. Characteristically, cascade impactors or multistage impingers are used to quantitate the respirable fraction or fine-particle dose (usually the percentage of particles $< 5\text{--}6\ \mu\text{m}$ diameter) as an estimate of lung delivery.

Cascade impactor measurement with drug-specific assay is the method of choice in the United States, and a standard inlet manifold should be used. Recommendations are available for assessment of particle size distributions and mass output of nebulizers, MDIs, and DPIS.^{35,36} In vitro systems have been added to particle sizing devices in ways that more closely simulate the clinical scenario. Anatomic throats have been used with impactors or impingers instead of standard inlet manifolds. Radiolabeled aerosols have been delivered to anatomic lung models using simulated breathing patterns. Other measurements of “inhaled mass” from a nebulizer have used a patient or patient surrogate (piston pump) breathing from a nebulizer through filters.

Scintigraphy

The gamma camera was invented and reported by Anger in 1958,³⁷ and radionuclide imaging of the human body was initially done in hospitals for diagnostic pur-

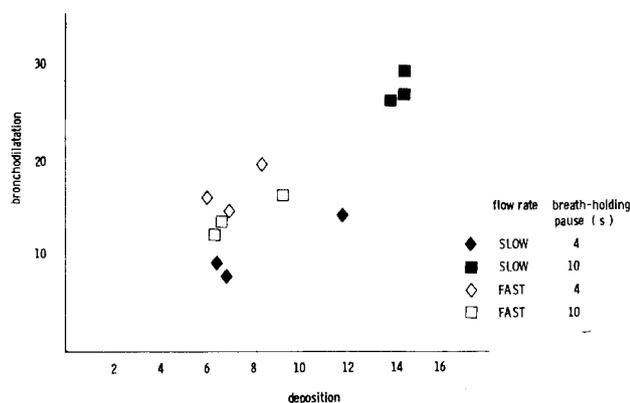


Fig. 9. Early scintigraphy study showing the relationships between breathing pattern and the lung deposition and lung function response with bronchodilator from a pressurized metered-dose inhaler. (From Reference 38, with permission.)

poses. In the late 1970s it was recognized that scintigraphy could be used to assess drug delivery to various organs, including the lungs.³⁸ Total and regional deposition and clearance of therapeutic aerosols can be measured noninvasively by the use of inhaled radiolabeled particles and scintigraphic scanning techniques. The distribution as well as quantity of label in the oropharynx, lungs, and gastrointestinal tract can be assessed, most often as 2-dimensional images obtained with a gamma camera. More recently, pulmonary drug delivery has been assessed with the 3-dimensional imaging methods of single-photon-emission computed tomography and positron emission tomography. Information about the site and extent of deposition of particles in the air spaces is invaluable and difficult to obtain by any other means. Scintigraphic studies^{38,39} have added basic information about the effects of variables such as breathing pattern, add-on devices, spray characteristics, particle size distribution, and lung disease on the amount and distribution of particle deposition (Fig. 9). These studies can also be correlated with drug efficacy and toxicity outcomes.

Pharmacokinetics and Pharmacodynamics

Another approach to assessing respiratory drug delivery is to measure plasma levels of drug after absorption (pharmacokinetics) and to relate those levels to clinical efficacy and toxicity (pharmacodynamics).⁴⁰ Determination of pharmacokinetic profiles is difficult for inhaled drugs, because the low plasma levels require a sensitive assay and may be altered by drug absorbed from the gastrointestinal tract. In many cases it is important to distinguish the relative contributions of lung and gastrointestinal tract absorption, as drug absorbed from the lung can be used as a surrogate for deposition. Pharmacokinetic/pharmacodynamic assess-

ments can be made from plasma or urinary levels. These measurements can provide confirmation of *in vitro* and scintigraphic assessments and can often add insights into the relationship between drug delivery and clinical efficacy and toxicity. Borgström et al used scintigraphy and urinary drug levels to measure differences in terbutaline lung deposition between an MDI and a DPI in asthmatics.⁴¹ Spirometry showed that at the lower dose of terbutaline, improvement in forced expiratory volume in the first second was significantly greater with the device that had greater lung deposition, but that at the higher dose there was no difference in forced expiratory volume in the first second, despite higher deposition. This is an example of how pharmacokinetics/pharmacodynamics data can clarify that higher deposition may not improve the clinical outcome and may cause toxicity. These types of measurements are used to assess new formulations and devices, to determine the most clinically appropriate dose of drug, and to improve the therapeutic ratio of the drug/device combination.

1987 Montreal Protocol

MDIs were initially developed with CFC propellant systems. Because of CFC's deleterious effects on the ozone layer, the Montreal Protocol was developed by the United Nations in 1987, which banned substances that deplete the ozone layer.⁴² This ban phased out the use of CFCs by 1996, although pharmaceutical companies had exemptions. While the contribution of CFC inhaler propellants has a minute environmental impact, this ban had a large effect on the development of inhaler technology. Hydrofluoroalkane (HFA) propellants were found to be effective substitutes, and HFA134a was developed as an alternative to CFC. The substitution of HFA propellants has changed the properties of the aerosols produced by pMDIs, and HFA-propelled aerosol is, in general, a "softer" spray that exits the pMDI at a lower velocity. Also, the spray temperature from a HFA-propellant pMDI is above freezing—much warmer than that of a CFC-propellant pMDI.

HFA-propelled beclomethasone required reformulation as a solution rather than as a suspension, and the resulting aerosol contains a much higher fraction of fine particles, which exit the inhaler at a lower velocity.⁴³ This results in higher lung deposition and lower oropharyngeal deposition. The improved drug deposition is of sufficient magnitude that pharmacokinetic studies found that the label dose could be cut in half and achieve results similar to that of the CFC formulation. The phasing-out of CFC propellants has stimulated the development of CFC-free MDIs, DPIS, and MDI liquid inhalers. The United States Food and Drug Administration recently issued a final rule that, as of December 31, 2008, all CFC devices will be phased out.

There have also been great technologic advances in nebulizers, with development of breath-enhanced, breath, actuated, vibrating-mesh, and dosimetric nebulizers.

Summary

Inhalation therapy is one of the oldest approaches to the therapy of respiratory-tract disease, and it is well recognized today that the most effective and safe means of treating the lungs is to deliver drugs directly to the airways. We are approaching the 50-year anniversary of the introduction of the pMDI and are in an era of rapid technologic progress in inhaled drug delivery and applications of aerosol science, with the use of the aerosolized route for vaccines, systemic therapy and gene-replacement therapy, the use of aerosolized antimicrobials to treat or prevent lung infections, and the use of aerosolized immunosuppressants for lung-transplantation recipients. There is also great interest in tailoring particle size and delivery to treat specific areas in the respiratory tract, and in developing new, safer inhaled corticosteroids. One challenge that has been present since antiquity still exists, however, and that is ensuring that the patient has access to the medication and understands how to use it effectively and faithfully.

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Discussion

Leach: You mentioned a timeline that Charlie Thiel referenced for the first filing of a new drug application for an MDI. I believe it involved filing the application in January 1956, approval in June 1956, and marketing in July 1956. I'm sure a lot of us here are eager to get the slide he has of the Qvar regulatory package. In the picture, Charlie holds up the 35-page application filed in 1956 and he's standing behind a sea of boxes with 450,000 pages for a new drug application filing for an existing product. Are regulatory filings too complicated?

Newman: Many of the earliest inhalation delivery systems, going back hundreds and even thousands of years, were based on gases and vapors. I guess some of those vapors would have condensed into particles. At some point we must have made the transition from inhalation therapy being primarily gaseous to primarily particulate. At what point did that transition occur?

Anderson: That's a very good observation, because the infusions used in the early earthenware inhalers created vapors. In the 1800s inhalers used menthol and aromatic compounds and oils in water. I would put the transition to inhalation of aerosolized particles around 1850, with the development of the atomizer in the perfume industry. It was a very simple device

that forced the fluid through a nozzle in the Sales-Girons apparatus, and Venturi type systems were available by the late 1800s.

MacIntyre: Smoke particles technically could be considered an inhaled powder, so in fact the world started with DPIS, and now DPIS are the wave of the future.

Dhand: It strikes me that we are discounting the role of warming to some extent. With previously employed devices, warmed air (smoke, steam) was delivered to the respiratory tract. We know that cold is not good for asthmatics, especially cold air. Do you think there may be a role for warming or heating the aerosols prior to administration?

Anderson: It's worth investigation. A lot of the old earthenware inhalers used just warm water and may not even have had any drugs or herbs in them.

MacIntyre: The asthma cigarette must have had quite a bit of heat in it.

Anderson: I would think so.

Hickey: I just want to add something to Neil's comment. Smoke, basically, is nanoparticles, and we haven't quite got there in terms of nanotechnology with dry powders yet. Maybe in 20 years we will be where we were 4,000 years ago.

Anderson: We've come full circle.

MacIntyre: When does a nanoparticulate become a gas?

Hickey: When the particle size approaches the size of a gas molecule. I don't know what that would be exactly, perhaps in the range of 0.1–10 nm, depending on the gas.

Laube: I'm interested in the idea of the "bong." When I get out my spacer devices for demonstration purposes, I often hear "oh, that's a variation on the bong."

Anderson: That type of inhalation device is still very popular, especially in the Middle East. And it is used in the United States. It's called a narghile, and the tobacco is in a container. They put a burning coal on top of it, and the smoke is inhaled through water, but it is also called a bong. It's a way of filtering the aerosol, and you lose some of the compounds in the water. I suspect that technology has been around for thousands of years.

Ahrens: Anticholinergics were used in many of the devices you described. Others used epinephrine. Were there any other classes of drugs used, and did any of them actually make some pharmacologic sense by current standards?

Anderson: An herb called ma-huang, which has an epinephrine-like or ephedrine-like substance, has been used in China for asthma since 3,000 BC, but it was always taken orally.

There is the whole category of inhaled steroids, but that was in relatively modern times. That would cover the main classes of anticholinergic, adrenergic, and anti-inflammatory agents.

Dhand: The hookah is another device used for tobacco smoking in the Indian subcontinent. Tobacco is

burned in an earthen pot, bubbled through water, and inhaled through a long tube. People smoke the hookah in a community setting.

Jim Fink performed an experiment with a standard ventilator circuit, in which he placed a nebulizer between the ventilator and humidifier and found that passing the aerosol through water

increased drug delivery to the end of the endotracheal tube by almost 50%, compared to placing the nebulizer between the humidifier and endotracheal tube. We jokingly referred to that experiment as being based on the “Hookah Principle,” although we are not sure what changes were produced in the aerosol by passing it through water.



Robison's Powder Blower from *The American Armamentarium Chirurgicum*.
New York: George Tiemann & Co; 1879.
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