REVIEW

Inhalation therapy: an historical review

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Summary: Inhalation has been employed as a method for delivering medications for more than two thousand years, and the benefits of delivering medication directly to the affected site – the lungs – have been understood for more than two hundred years. At the beginning of the Industrial Revolution, physicians were inventing therapies and experimenting with ideas for devices: it was a time of great creativity. However, by the end of the period the scientist and the regulated pharmaceutical industry had emerged and the role of the physician had been constrained. Few of the devices invented then remain in use today, but many of the principles used are still embodied in modern devices. This review traces the developments produced by the early pioneers who applied their creative thoughts to inhalation therapy, and examines how inhaled drug delivery has progressed. The devices pictured are from www.inhalatorium.com, an online museum of inhalation technologies.

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Introduction

It is tempting to think of inhalation therapy as a modern approach to drug delivery, but this would negate some thousands of years of history and literally hundreds of ingenious devices and hopeful medications. This historical review describes the development of inhalation therapy throughout the ages, from its first recorded use in Ancient Egyptian times through to the numerous different sorts of inhalation device available today.

The 'inhaler'

The word 'inhaler' was first used by the English physician, John Mudge. In his 1778 book, *A Radical and Expeditious Cure for a recent Catarrhus Cough*,¹ he discloses to us his invention of an inhaler adapted from a pewter tankard and the use of opium vapour to treat cough (Figure 1). The engraving in his book is not, however, the first illustration of an inhaler. That honour goes to Christopher Bennet in 1654 in his book *Theatri Tabidorum*,² with an inhaler that bore more than a passing resemblance to a modern Turbohaler ... (see Figure 2). These physicians were not just doctors but they were also inventors and pioneers – there was no regulated pharmaceutical industry to supply patient needs. Indeed, Mudge had to provide his readers with the address of a pewterer in Fleet Street, London who could make the Mudge inhaler.

Inhalation therapy was rationalised by Philip Stern as early as 1764 – “the only possible way of

applying medicines directly to the lung is through the windpipe”. He advocated his own recipe of balsamic vapours in his book, *Medical Advice to the Consumptive and Asthmatic Peoples of England*,³ controversially aimed at the public rather than his peers.

Inhalation therapy in ancient times

Long before Bennet, Stern and Mudge were describing inhalers and advocating inhalation therapy, inhalation was being practised in many parts of the world. The inhalation of the vapour of black henbane is recorded in the ancient Egyptian Ebers papyrus (1,554 BC); Egyptian physicians threw the weed onto hot bricks, causing the alkaloid contents of the plant to vapourise so that the breathless patient could inhale.

In South and Central America, around 2,000 years ago, native populations had discovered the therapeutic and recreational use of tobacco and

Figure 1 John Mudge's pewter tankard inhaler, 1778

Figure 2 Diagram of Christopher Bennet's inhaler, 1654

Figure 3 South American tobacco pipes c. 2000 yrs ago

similar plants. They fashioned pipes which were often ornately crafted – see Figure 3.

In China, opium inhalation has a long history, and ornate metal inhalers and incense burners are associated with its practice. Accounts of asthma predate the earliest accounts of inhalation treatment, with the oldest accounts of asthma going back to the time of the Yellow Emperor of China in 2,600 BC. Huang-Ti, author of the oldest known book on internal medicine, identified the use of Ma Huang, much later shown to contain ephedrine.

Inhalation therapy was also practised in other ancient civilisations: in India, the practice of inhaling the fumes of stramonium and hemp was common, and in Ancient Greece the physician Hippocrates (460-377 BC) advocated the inhalation of vapours of herbs and resins boiled with vinegar and oil which were then drawn into the lungs through a tube. Over a thousand years later, Rhazes (c850 AD-c923 AD), a physician in Baghdad, advocated the inhalation of the vapour of arsenic.

More recently, at the end of the 12th century, Maimonides (1135-1204 AD), the Spanish-born physician to the Arab King Saladin, wrote the first book on asthma (*A Treatise on Asthma*) in 1190, and recommended numerous treatments (including chicken soup and sexual abstinence) for the king's son who was asthmatic.⁴ Among those treatments was the inhalation of vapour generated from herbs thrown onto a fire.

Inhalation therapy: the 1800s

Twenty years after the appearance of Mudge's book,¹ Cavallo pointed out that, rather than using a purpose-made inhaler, the patient could simply

use a common teapot and inhale through the spout⁵ – though the subsequent tea may have had an oddly balsamic flavour! Perhaps this suggestion was the original inspiration for the later Nelson's inhaler which indeed resembles a teapot ...

In 1802 Gent publicised and advocated the ancient Indian practice of inhaling the vapours generated by burning the leaves of *Datura Stramonium*, and the inhalation of various such mixtures became very popular throughout the 1800s. Stramonium produces the anticholinergic agent atropine.

The celebrated physician Thomas Beddoes (1760-1808) founded the Pneumatic Institute at Clifton, Bristol, for the treatment of disease by inhalation. Beddoes' work⁶ was the catalyst which fostered the genius of his assistant, Humphrey Davy.

In 1811 François-Joseph Double, a notable French physician, wrote *Traité du Croup*,⁷ a dissertation on croup, stating, "The inhalation of vapour, medicated with æther, opium, or cicuta, and pediluvia rendered a little irritating by the addition of mustard, are also said to be serviceable." It remains unclear by what means he preferred the inhalations to be administered.

The treatment of consumption

A key driver for inhaler development during this period was the treatment of consumption. Asthma was a relatively uncommon condition. All the medications depended on heat to be volatilised or vapour to be aerosolised.

Sir Charles Scudamore in his "*Cases illustrating and confirming the remedial power of the inhalation of iodine and conium in tubercular phthisis and various disordered states of the lungs and air-passages*" published in 1834,⁸ describes the use of inhaling the vapour of hot water medicated with iodine and conium (hemlock). The treatment was given three times a day for 15-20 minutes each time using water at 120°F. He refers back to Galen's use of arsenic fumes or orpiment. Doctors Percival and Withering are mentioned for their use of inhaling carbonic acid gas generated by the reaction of chalk and vinegar and Sir Alexander Crichton is credited with the practice of inhaling the vapour of boiling tar. Scudamore also refers to two French doctors; M. Gannell for his use of chlorine inhalation, and Laennec for his endeavours to create an artificial marine atmosphere by use of seaweed (after having observed improvement in patients taking sea voyages). Scudamore advocated iodine and conium after having experimented with inhalations of stramonium, belladonna, lobelia, ipecacuanha, digitalis, hydrocyanic acid and sulphuric ether.

Figure 4 The first pressurised inhaler, 1858

In 1834 Francis Ramadge developed an inhaler for treating consumption.⁹ This was a long tube through which the patient would inhale slowly. He records the inhalation of vapours, including tar, iodine, chlorine, hemlock, turpentine and others.

Inhalational anaesthesia

On October 16th 1846, the first demonstration of inhaled anaesthesia took place. John Collins Warren performed the operation and William Morton delivered the anaesthetic. The surgeon Henry Bigelow witnessed the operation and left an excellent account and received much of the credit. Within three weeks, on November 9, Bigelow had written and presented his paper to the Boston Society of Medical Improvement;¹⁰ an abstract was presented at the American Academy of Arts and Sciences on November 3. The following month inhaled anaesthesia was being tried in London. Anaesthesia demanded special inhalation devices and there were numerous ones which were rapidly developed.

The first pressurised inhaler

The first 'powered' or pressurised inhaler was invented in France by Sales-Girons and was presented at the Medical Academy, Paris in 1858.¹¹

Figure 5 Hyde Salter's account of burning nitre papers, 1860

It used pressure to atomise the liquid medication — see Figure 4.

The treatment of asthma

In 1860, Henry Hyde Salter published his famous text, *On Asthma its Pathology and Treatment*.¹² He systematically reviewed the treatment options of the period, including inhaled therapies, and distinguished between depressants (ipecacuanha, tobacco, tartar-emetic), stimulants (coffee, alcohol), and sedatives (tobacco, chloroform, opium, Stramonium, Lobelia and Indian Hemp). The inhalation of the fumes of burning nitre papers was also discussed by Salter. Salter was unsure of the origin of this practice, but estimates that it began around 1860. He described its efficacy as being beyond question and gave detailed accounts of four treated cases — see Figure 5. The activity of nitre papers is attributable to ammonia which is formed during the combustion process. However, vapours, in general, did not form a significant part of his armamentarium. Salter was very negative about the value of opium in asthma, and regarded it as being more a cause than a cure, although he did accept its role in bronchitic cough.

In the USA in 1862, Charles Broadbent wrote "*A Medical Treatise on the Causes and Curability of Consumption, Laryngitis, Chronic Catarrh and*

Diseases of the Air Passages – Combining the Treatment by Inhalation by Medicated Vapours".¹³

He eloquently makes the case for treatment by vapour inhalation; "The soothing and quieting effects of these vapors is brought immediately to act upon the parts locally irritated and diseased, by the gentle inhalation of the vapor from a bottle arranged expressly for the purpose ..." He justifies delivery of the drugs directly to the lungs; "We contend that no remedy, or combination of remedies, however potent, whether allopathically or homeopathically administered through the medium of the stomach has ever nor can ever cure a single case of asthma. For the reason that they do not reach the seat of the disease, their principal force is spent upon the general system, and long before they find their way to the lungs, their power is lost." His reasoning was very similar to that of Stern and Mudge many years earlier. Broadbent describes a rich list of inhalants familiar to him, explaining that each was made to the requirements of the individual patient; "Iodine, Conium, Oxygen, Hydrogen, Nitrogen, Nitrous gas, a great variety of Gums and Balsamic Resins, Vapor of boiling Tar, Hydrocyanic Acid, Camphor, Ammonia, Balsam Tolu, Naphtha, Chlorine, Hyoscyamus, Lactuca, Belladonna, Digitalis, Colchicum a great variety of Balsamic Herbs, Galbanum, Vapor of Vinegar, Nitre, Stramonium, Lobelia, Inflata, Ipecacuanha, Alcohol, Hydriodate of Potassa, Storax, Marshmallows, Rose Water, a great variety of Emollient and Narcotic Herbs, &c." Broadbent was clearly a remarkable experimenter in terms of the range of substances that he employed to medicate his vapours.

The first dry powder inhaler

In London in 1864, Newton patented an inhaling apparatus for the delivery of dry powder medications.¹⁴ He observed that the powder needed to be finely pulverised and that it had to be kept dry – principles that still apply to dry powder inhalers today. His use of potassium chlorate as a therapy was probably unfortunate because this is now considered to be a lung irritant. However, this device is probably the earliest recorded dry powder inhaler.

The Nelson inhaler

In 1865, a new invention was reported in *The Lancet*¹⁵ – the Improved Nelson Inhaler from the well-known pharmacy supplier S.Maw & Sons in London (see Figure 6). The Nelson inhaler is still

Figure 6 The Improved Nelson inhaler, 1865

manufactured to this day, with very few modifications. A vast number, many of them quite ornate, have been produced under different names and to different designs. Maw's catalogue¹⁶ of 1869 shows two ceramic inhalers together with Mudge inhalers, a Ramadge inhaler and others.

The formal recognition of inhalation therapy

The 1867 edition of the British Pharmacopoeia¹⁷ was the first to formalise inhalation therapies. It listed five medications;

- a) vapor acidi hydrocyanici
- b) vapor chlori
- c) vapor coniae
- d) vapor creasoti
- e) vapor iodi

For any medical therapy, listing within a major pharmacopoeia marks the medical acceptance of that therapy. In this sense, inhalation therapy had won its spurs and had been formally accepted as a means of medical treatment. Nevertheless, most of the substances listed above would now be considered unsuitable for inhalation.

In 1867, Armand Trousseau, one of France's most famous doctors, published a series of lectures which were given in Paris.¹⁸ He reviewed asthma in detail, referring to the inhalation of stramonium, tobacco, hyoscyamus and belladonna. He also cited the use of opium, arsenical cigarettes, nitre papers, and described how to prepare these products. Trousseau refers to Dr Faure's method of inhaling ammonia vapour for 15 minutes (four times a day) from a vase at a distance of about one foot, the nostrils needing to be occluded to avoid unpleasant effects. He observed that some patients respond better to one medication while others respond better to another.

In 1869 the German doctor Louis Waldenburg, writing about tuberculosis,¹⁹ claims to have completely cured asthma through the continued use of inhalations. He employed the use of sodium chloride inhalations to soften the viscid mucus, and oil of turpentine to stimulate the mucus glands. Waldenburg also devised an apparatus for delivering medicinal gases which he used alongside the other inhalations.

The first nebulisation devices

Da Costa published a fine account of inhalation medications and devices in 1867.²⁰ Among the devices described are the hand-ball spray and the Siegle's steam spray inhaler – a German invention from the early 1860's (see Figure 7). Siegle's steam spray used the Venturi principle to atomise liquid medication, and this was, in effect, the beginning of nebuliser therapy.

Writing in 1878, Berkart identified the use of turpentine and assafoetida as a mucolytic,²¹ and commented how they were best administered as inhalations. He also describes a "spray-producing apparatus" about which he expressed some disappointment, which he rationalised as being due to the spray not always helping the deeper structures of the lung. The importance of droplet size is now much more thoroughly understood and controlled in modern nebulisers.

The age of advertising and the entrepreneur

Frederick Roe patented the Carbolie Smoke Ball in 1889 as a 'device to facilitate the distribution, inhalation, and application of medicated powders'.²² The patent describes a hollow rubber ball with a sieve across the orifice to de-agglomerate the powder inside. When squeezed, a cloud of powder was produced. A glass version was

Fig. 23.—SIEGLE'S APPARATUS.

Figure 7 Siegle's steam spray inhaler, early 1860's

also marketed. The ball contained a mixture of glycyrrhiza and white hellebore (*Veratrum videri*) together with a tarry residue smelling of carbolic acid. The device cost ten shillings and was refillable for five shillings – see Figure 8.

The Carbolic Smoke Ball occupies an important place in history, not only in terms of the evolution of dry powder inhalers but also in law. It was advertised as being a positive cure for a range of respiratory conditions including influenza, asthma, bronchitis, croup, whooping cough and many others. Testimonials from many notable people were also published. The advertisement offered a £100 reward to anyone who contracted influenza having used the Carbolic Smoke Ball according to the directions. Mrs Calill, despite using her Carbolic Smoke Ball in accordance with the directions, contracted influenza. Her claim for £100 compensation was ignored by the manufacturer and so her husband, a solicitor, sued. When the case came to trial in 1892, the defence vigorously argued that the advertisement did not constitute a binding obligation, but the judge found for Mrs Calill, a decision that was supported in the Court of Appeal. This established the legal principle that offers made through advertising constitute a legal contract, and consequently the Carbolic Smoke Ball Company modified its advertising, focussing instead on the testimonials of famous users. Mrs Calill lived to the age of 96, eventually dying of influenza in 1942 ...

During the 1880's through to the early 1900's there was a proliferation of inhalers and inhalants produced both in the USA and in Europe. The age of the 'quack cure' had truly begun and the entrepreneurial spirit was applied to curing asthma. New plastic materials such as Gutta Percha and Bakelite became available. Distribution systems for supplying drugs further afield improved and advertising of medicines became commonplace. All these aspects contributed to feed the expanding demand for such 'cures'. Inhalers were not the only

FEB. 25, 1893 THE ILLUSTRATED LONDON NEWS 253

£100 REWARD
WAS RECENTLY OFFERED BY THE
CARBOLIC SMOKE BALL CO.

To any person who contracted Influenza, Coughs, Colds, Catarrh, Asthma, Bronchitis, Sore Throat, Hoarseness, Loss of Voice, Throat Deafness, Croup, Whooping Cough, or any Disease caused by taking Cold, after having used the Carbolic Smoke Ball according to the printed directions.

Many thousand Carbolic Smoke Balls were sold on these advertisements, but only three persons claimed the reward of £100, thus proving conclusively that this invaluable remedy will prevent and cure the above-mentioned diseases.

THE CARBOLIC SMOKE BALL CO., Ltd.,
NOW OFFER
£200 REWARD

to the person who purchases a Carbolic Smoke Ball and afterwards contracts any of the following diseases, viz—

INFLUENZA	CATARRH	THROAT DEAFNESS	DIPHTHERIA
COUGHS	ASTHMA	LOSS OF VOICE	CROUP
COLD IN THE HEAD	BRONCHITIS	LARYNGITIS	WHOOPIING COUGH
COLD ON THE CHEST	SORE THROAT	SNORING	NEURALGIA
	HOARSENESS	SORE EYES	HEADACHE

or any disease caused by taking cold while using the Carbolic Smoke Ball. This offer is made to those who have purchased a Carbolic Smoke Ball since Jan. 1, 1893, and is subject to conditions to be obtained on application, a duplicate of which must be signed and deposited with the Company in London by the applicant before commencing the treatment specified in the conditions. This offer will remain open only till March 31, 1893.

As all the diseases mentioned above arise from one cause, they can therefore be cured by the remedy which stops the cause, viz—
THE CARBOLIC SMOKE BALL.

One **CARBOLIC SMOKE BALL** will last a family for several months, making it the cheapest remedy in the world at the price—10s. post free.

The **CARBOLIC SMOKE BALL** will be refilled and returned, post free, the same day, on receipt of Money or Postal Order for 5s.

ADDRESS—
CARBOLIC SMOKE BALL CO., Ltd.,
27, PRINCES STREET, HANOVER SQUARE, LONDON, W.
PARIS DEPOT—14, Rue de la Paix. AMERICAN DEPOT—196, Broadway, New York. CANADIAN DEPOT—71 & 73, Front Street, Toronto, Ontario.

FREE TRIALS AT OUR CONSULTING ROOMS
FOR INHALATION ONLY.

Figure 8 An advertisement for the Carbolic Smoke Ball, 1889

MUNSEY'S MAGAZINE.

Booth's Pocket Inhaler Outfit, by mail, \$1.00.

BY INHALATION ONLY, THE **Australian "Dry-Air" Treatment**

of Catarrh, Asthma, Bronchitis, Hay Fever, and Whooping Cough.

BOOTH'S HYOMEI "DRY-AIR" TREATMENT.

Restores a person's natural condition, and cures the most stubborn cases of Catarrh, Asthma, Bronchitis, Hay Fever, and Whooping Cough.

Price by mail, **CIGAR, 65 cents; CIGARETTE, 50 cents.**

For Catarrh, Sore Throat, Hoarseness, Etc.

The **Cigar Inhaler**

In the simplest and most effective manner, this inhaler delivers a fine stream of medicated vapor into the throat, lungs, and chest, relieving all the above-mentioned ailments.

THE INHALER.

It is a simple, portable, and effective device, and is recommended by the best physicians of France, Germany, and America.

COMENOL.

It is a simple, portable, and effective device, and is recommended by the best physicians of France, Germany, and America.

THE UNITED STATES COMPOUND OXYGEN CO.

BOSTON, WORCESTER, PROVIDENCE, R.I.,

MAW'S EARTHENWARE INHALERS

For Hot Water, Infusions, &c.

Fig. 6.—Double-Valved, 60/- per dozen; with Elastic Tubes, 75/- per dozen.
Fig. 8.—Marbled, 25/- per dozen.
Fig. 8a.—White, 25/- per dozen.
Fig. 8a.—White, half size, 15/- per dozen.

ELASTIC TUBES, with Mouthpieces, to fit Fig. 8 and 8a, 7 inches long, 4/- per dozen; 9 inches long, 12/- per dozen.

SPECIAL QUOTATIONS TO WHOLESALE BUYERS.

MANUFACTURED BY
S. MAW, SON & THOMPSON, LONDON.

Dr. Worst's INHALER

Sent Free on Trial.

A Scientific Cure for Catarrh, Asthma, Bronchitis, Colds, and all Throat and Lung Diseases.

THE GREATEST DISCOVERY OF THE AGE.

Dr. E. J. Worst, of Berlin, has made a discovery which will revolutionize the treatment of all the above-mentioned ailments.

SPECIAL OFFER.

Send for a short time trial order of "Dr. Worst's Inhaler" free of charge.

Dr. E. J. Worst, DEPT. 22, ABERLAND, O.

Vapo-Cresolene

(Established 1870.)

"Cures While You Sleep"

Whooping-Cough, Croup, Bronchitis, Coughs, Diphtheria, Catarrh.

Confidence can be placed in a remedy which for a quarter of a century has earned unqualified praise. Restful nights are assured at once.

Cresolene is a Balm to Asthmatics.

ALL DRUGGISTS
Send Postal for Description, Circulars.

Cresolene Antiseptic Throat Tablets for the irritated throat, of your druggist or from us, 10c. in stamps.

The Vapo-Cresolene Co.
180 Fulton St., N. Y.
Lewing-Niles Bldg., Montreal, Canada.

Figure 9 Collage of adverts of various inhalers from around 100 years ago

advertised cures for asthma though – magnetism, ultra-violet rays and numerous pills, creams and potions were also promoted.

Notable inhalers and inhaled therapies from a hundred years ago

Antiseptic inhalation. Following Lister's hugely important discovery of antiseptic surgery the notion of inhaled antiseptics was promulgated. Coal tar derivatives such as Vapocresolene were promoted. Booth's Hyomei was another heavily promoted medication that provided 'dry air' from a small bakelite inhaler. The Cigar Inhaler was a clever discreet design for discreet inhalation of the antiseptic substance Gomenol. Dr Worst's inhaler, a beautifully crafted nickel plated device was patented in 1901. Compound Oxygen was another heavily promoted cure that relied heavily on testimonial advertising. A collage of adverts is shown in Figure 9.

Ceramic inhalers. Numerous versions of the Nelson inhaler and other ceramic inhalers appeared to deliver medicinal products. In Europe the enamel inhalers fulfilled a similar purpose.

Pillow inhaler. This clever approach involved the use of a small shallow pot in a specially made pillow. Volatile inhalants were put into the pot and these were vapourised through the night, delivering medication to the sleeping patient – see Figure 10.

Combustible powders. These were to be burnt and the arising vapour inhaled. Most contained stramonium plus other alkaloids such as belladonna and lobelia. Well known examples include Braters Powder, Kinsman Powder, Green Mountain Powder, Kellogg's Powder, Schiffmann's Powder, and Himrod's – see Figure 11. Many were also produced as asthma cigarettes (see Figure 12) and as a pipe mixture.

Menthol inhalers. Menthol and eucalyptus oil are well known today as over-the-counter therapies for cough and cold relief. Since Gaubius in 1774 first extracted crystals from peppermint oil, later to be known as menthol, inventors have been finding ways of delivering its cooling vapours to the respiratory tract.

Oxygen bars. These were first developed in the 1890s and were reported in Scientific American (Supplement 999 Feb 23 1895). Just like today, customers would inhale purified oxygen at a bar. In France, an establishment was set up in 1891 by Doctors Labbé, Oudin & Desnos for treating patients with anaemia and tuberculosis; it was located in Saint Raphael, France, beneath a casino. Ozone was generated on the premises by ozonizers and was available in two concentrations – see Figure 13.

PILLOW-INHALER IN USE.

(OVER.)

Figure 10 The pillow inhaler

Figure 11 Various powders used in combustible inhalers

Figure 12 Asthma cigarettes

Figure 13 Depiction of an Oxygen Bar, 1890's

Figure 14 The Maxim inhaler, 1909

Maxim inhaler. Sir Hiram Maxim, an American living in London, was an inveterate inventor. Most famous for the Maxim machine gun, he also invented a steam driven flying machine! In August 1909, plagued by the effects of the London atmosphere, he developed and patented his own inhaler. It resembled a glass retort and delivered a combination of menthol and pine essence (*dirigo*), and was known as the Pipe of Peace. The pack included a separate bulbous glass inhaler for nasal delivery of menthol – see Figure 14.

The end of the entrepreneur and the age of the scientist

Controls on advertising and promotion imposed by the FDA in 1906 sounded a death knell for the entrepreneurial quack cures, and the scientist took over. The general trend was that nationally produced and licensed products superseded locally produced devices.

In 1900 Solis-Cohen first used adrenal extracts to treat asthma considered to be due to vasomotor ataxia.²³ The following year Bartlett advised the use of 2 grains of dessicated adrenal extract three times a day. In 1904, Kaplin and Bullove identified the value of adrenalin in asthma and it went on to become the foundation of what we can consider to be modern pharmaceutical inhalation therapy. From 1910 onwards experiments into the delivery of adrenalin began. Pick, in 1911, reported successful nebulisation of adrenalin in two patients. In 1929 Camps reported on the

Figure 15 The Abbott Aerohaler, 1948

successful use of nebulised adrenalin in an oxygen stream. Adrenalin Chloride (epinephrine) solution 1:100 was supplied in the 1930's as a bronchial muscle relaxant, to reverse constriction; it was vapourised through electrical compressors such as the Pneumostat or by hand nebulisers such as the Parke-Davis Glaseptic. Adrenalin was a life-saving drug but had significant associated problems.

The use of atropine for the treatment of asthma was also being explored at this time. Von Terray claimed that atropine given hypodermically was a specific treatment for asthma. Weiss found good results from spraying it through the mouth.

Throughout the early 20th century there were some notable inhaler inventions:

- In the 1920s, the first mention of the inhalation of atropine from an atomizer was made by Hurst.
- In 1924, Schmid and Chen, whilst investigating Ma Huang, identified ephedrine²⁴ – a substance similar to adrenaline. This alkaloid was subsequently used by inhalation.
- In the 1930s, early compressor nebulisers (such as the Pneumstat) were used to deliver adrenal extracts and papaverin (Bronchovydin).
- In 1940, isoprenaline was first described by Konzett, and it rapidly became available for inhalation.
- In 1948, Abbott launched the Aerohaler with a preparation of penicillin for inhalation. Additionally a further presentation of the bronchodilator Norethisderone was also made available. The Abbott Aerohaler, a dry powder inhaler, used a lactose-based formulation to deliver penicillin from small capsules known as 'sifters' – see Figure 15.
- In 1950, Reeder and Mackay treated pneumonia with inhaled corticosteroid, leading to intensive investigation into the use of inhaled anti-inflammatories. Gelfrand, in 1951, reported on five patients who were treated with nebulised

cortisone. In 1955, Foulds used hydrocortisone in powder form. This work was ultimately to lead to the discovery of beclomethasone nearly 20 years later.

Modern times

Undoubtedly the most significant event of the 1950's was the development in 1955 of the pressurised metered dose inhaler (pMDI).²⁵ Charles Thiel working at Riker (3M) was one of the key workers in the team that developed cold-fill pMDIs using special valves developed by Philip Maschberg. The products were shown to be effective in studies conducted by Dr Carr at the Veterans Administration Hospital (Long Beach, California) in June 1955 and new drug applications (NDAs) filed in January 1956 were approved in March the same year. Medihaler-iso (isoprenaline) and Medihaler-epi (adrenalin) were launched in late March 1956. Nowadays, pMDIs have become a very important inhalation technology with annual sales currently in excess of 400 million units. The drugs, of course, have been updated and the propellant technology improved through the use of less environmentally-damaging HFAs. The use of pMDIs has, however, been limited by several drawbacks: the need to co-ordinate the inhalation and the actuation can prove difficult for patients; the inhalers have lacked dose-counters; and their ability to deliver large doses of drug is limited.

Bengers Laboratories (subsequently acquired by Fison's Pharmaceuticals) were engaged in testing the anti-allergic properties of synthetic cromone derivatives of khellin (an Egyptian plant) during the early 1960's. Dr Roger Altounyan, the real-life 'Roger' of Swallows and Amazons fame, himself an asthmatic, personally tested the compounds. A former Spitfire pilot who was very familiar with aerodynamics, he invented the Spinhaler, a capsule inhaler that used a small propeller to create turbulence. It was necessary to find alternatives to the standard pMDI technology because the dose to be delivered exceeded the capability of pMDI metering valves. Intal (sodium cromoglycate) was launched in 1967 as a Spinhaler device. Some years later a pMDI version was created, using a lower dose.

The following year, 1968, the remarkable bronchodilator actions of salbutamol were described by Lunts, working at Allen and Hanbury's. Having been first synthesised in 1966, it was marketed in 1969 as Ventolin, and rapidly became the most prescribed bronchodilator globally. Salbutamol was the first of the selective

bronchodilators, relatively free from secondary effects on other systems. Salbutamol was formulated in a pMDI, as a dry powder inhaler in the Rotahaler and the Diskhaler, and was also produced as nebulised, tablet and syrup formulations.

The Rotahaler, a dry powder capsule inhaler, simply required twisting for a loaded capsule to be pulled apart and the powder to be inhaled through a mesh. The Diskhaler represented an important step forward because it did not require reloading for every dose, so it was the first multi-unit dose dry powder inhaler. This inhaler used a cartridge with foiled sealed pre-measured doses that were perforated at the time of use to permit the drug to be inhaled.

In 1972 Allen & Hanbury's marketed the first inhaled steroid, beclomethasone, in the same inhalers as salbutamol. Numerous steroids have subsequently been developed, and some have led to new inhaler developments.

The Allen & Hanbury's technology was refined and substantially improved in the Diskus (Accuhaler) which has proved outstandingly popular and which is used to administer bronchodilator and anti-inflammatory drugs and also combinations of the two.

In 1987, Astra Zeneca launched a novel steroid, budesonide, in a new multi-dose dry powder inhaler that did not depend on each dose being isolated; rather, the drug substance was kept in a reservoir from which individual doses were taken at administration. This device, the Turbuhaler, has also proved very popular and in a similar way is now used to administer bronchodilators, inhaled steroid, and combinations of the two.

Subsequent development of dry powder inhalers has followed the three themes described above: capsule inhalers; the multiple-unit dose inhalers; and the reservoir devices.

Conclusion

There is a rich history of ingenuity and inventiveness that has accompanied the development of inhalation therapy throughout the ages. Our understanding of the engineering, pharmacological, and medical science involved has improved vastly. At the same time we have now lifted our sights higher, aiming to use inhalation therapy to treat diseases that involve systems other than the lungs. New inventions await.

Conflict of interest declaration

The author is employed by Pharmaxis Ltd, holds

shares in Innovata plc, and is the creator of www.inhalatorium.com

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