The early evolution of nebulizers

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Inhaled treatments of respiratory diseases have a long history, and these treatment modalities seem to have emerged independently in different cultures. The earliest references to inhalation devices that we have found are from the Ebers papyrus in Egypt (~1554 BC). The inhalation of chromones was practiced in Assyria at an early stage (~650 BC) and somewhat later in Greece, Hippocrates (460-377 BC) described an inhalation apparatus [1]. In India the Ayurvedic practice of inhaling the smoke of burning stramonium and hemp by pipe, and in China the inhalation of the smoke from burning opium had been developed. In South and Central America natives developed the practice of smoking tobacco and similar plants.

Throughout the evolution of inhalers, drugs available for treatment of respiratory diseases seem to have been the drivers behind the development of new inhalation systems like pipes, straws, vaporizers and atomizers.

In the following text we have picked examples of atomizers and nebulizers to highlight the evolution of the nebulizer from the 1850's to the 1950's. Due to the limited space available in a single article we have focused on major developments and inventions, and used these as examples. As both authors collect old inhalers and old published material in this field, the examples are somewhat selective, based on availability in our collections. One of these is available on the web [2].

Atomization of liquids

The technology used for atomization of liquids – that is the reduction of the liquid into a fine spray – in the early atomizers was based on the Bernoulli principle described by the Dutch-Swiss mathematician D. Bernoulli in 1738, in his work Hydrodynamica [3]. The theorem stated that when a liquid or a gas is forced through a tube with a constriction, the speed of the liquid or gas is greatest at the constriction and the pressure on the sides of the tube is least at that point. The total energy, which is the sum of kinetic energy of flow and pressure energy, is constant in the tube. The Italian physicist G.B. Venturi used this principle some decades later to provide suction by forcing water through a constriction [3]. The same principle was later applied to air jet streams providing the basis for the design of air jet atomizers and nebulizers (Figure 1).

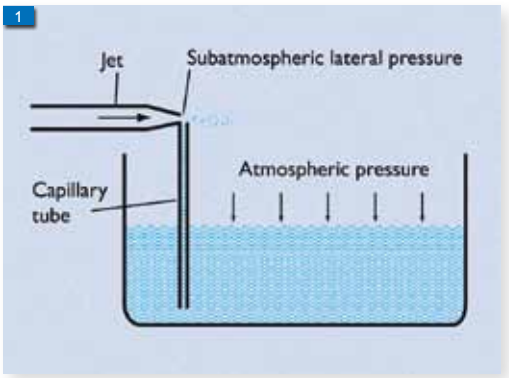

Figure 1. Atomization of a liquid (reduction of the liquid into a fine spray) in jet nebulizers is based on Venturi's application of the Bernoulli principle, i.e., to create lateral negative pressure at the jet. Atmospheric pressure, pushing down on the surface of the water, forces water up the capillary tube. As water leaves the capillary tube, it hits the gas stream and is broken up into an aerosol by the force of gas flow from the jet. (Adapted from Glover DW. Respiratory Therapy. St. Louis, 1978, The C.V. Mosby Co.)

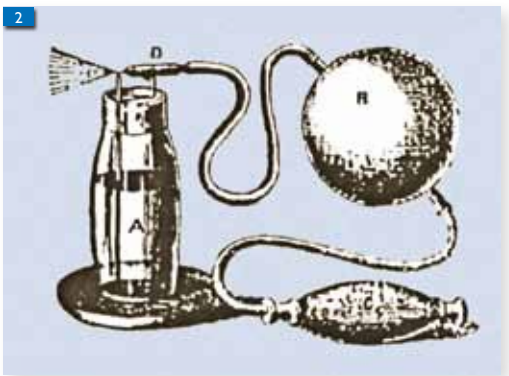

Figure 2. The Hydrokonium atomizer based on the Bergson tube design. Observe the adaptation of the Bergson tubes.
From *www.inhalatorium.com*.

An early example of the Venturi principle is the atomizer developed by the German physician Bergson in 1862. The design was known as the "Bergson tubes" and was embodied in a device he called the "Hydrokonium" (Figure 2). It consisted of two tubes that interfaced at right angles, with one tube taking a feed from a reservoir of liquid drug while the other had a jet of air passed through it. The air jet was generated

Figure 3. The Siegle Steam Spray Producer atomizer from 1864. Another example of how the Bergson tubes were built to create a spray. From *www.inhalatorium.com*.

Figure 4. The Sales-Girons nebulizer. From *www.inhalatorium.com*.

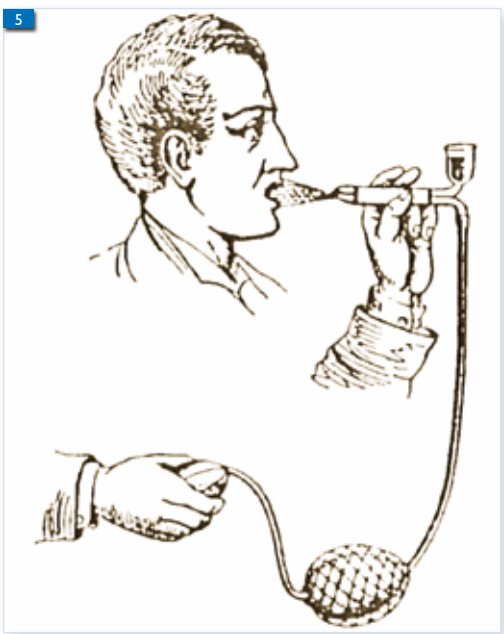

Figure 5. The nebulizer with baffle designed by Dr Lewin. From AAM Moeller [11].

by a double rubber squeeze-bulb arrangement made of an early form of rubber [4].

Bergson's approach was further improved by the German physician E. Siegle who applied for a patent in 1864 for a Steam Spray Producer (Figure 3). Instead of using a squeeze-bulb arrangement the jet was created using steam from a small boiler [5]. The atomizer design based on the Bergson tubes with a double rubber squeeze-bulb arrangement was further improved and popularized by a number of inventors. Atomizer designs based on the Siegle atomizer were popular throughout the nineteenth century in Europe, USA and Japan.

The evolution of the modern nebulizer developed for aerosolization of liquids can be traced through

available published sources to the mid-nineteenth century and the evolution of the atomizers. The early nebulizers were often referred to as "apparatus for the pulverization of liquids" and were in essence atomizers. In the literature the terms "nebulizer" and "atomizer" seem to have been used synonymously during the nineteenth century. In the Oxford English Dictionary the term "nebulizer" was included in 1872, and both terms have the same definition and are attributed to the late nineteenth century [6]. We agree with May in his definition of a nebulizer as a "baffled spray cloud-producing device" [6]. The early atomizers – for example perfume atomizers - lacked a baffle system which would have created an aerosol with small droplets (<5 µm in diameter), and therefore a respirable aerosol.

From atomizers to nebulizers

An early example of the use of a baffle to create aerosol was described by the American physician G. Evans (1891) who claimed that "the first direct attempt to convert liquids into spray, however, was made in 1849 by Auphan, at Euzet-les-Bains in France, who forcibly projected a fine stream of mineral water against the wall of a small room, filling the space with mist or spray, which he caused his patients to inhale" [7].

Auphan's ideas were further developed by another French physician, J. Sales-Girons, who developed a series of portable inhalation devices that applied the same principles to achieve atomization (Figure 4). He presented his device – a reservoir for the medication solution, an air pump, a small jet nozzle and an impaction plate – at the Paris Academy of Medicine in 1858 [8]. The pump forced the liquid through the nozzle where it was atomized against the plate. The Academy considered whether the fine spray was capable of reaching the bronchial tubes and, after due deliberation, they confirmed that it would and A. Trousseau stated that "Sales-Girons has rendered a great service to the world at large by his invention of the treatment by pulverization." The nebulizer went through several iterations but was manufactured and marketed [8].

Somewhat later, descriptions and drawings of nebulizers designed with baffles were presented in the books by the German physician L. Waldenburg (1862), the American physician S. Solis-Cohen (1867), and the French physician A.A.M. Moeller (1882) [9-11]. Common for these early nebulizers was the use of compressed air to exert pressure on the liquid, and the liquid spray was directed against a tube-shaped surface (baffle) to create a respirable aerosol. The compressed air was usually created by a manually operated pump. In his book Moeller presents a nebulizer with an early tube shaped baffle designed by his colleague Dr Lewin (Figure 5). The nebulizer developed by Solis-Cohen incorporated a gravity-fed adaptation to the Bergson tubes. The use of baffles was discussed in detail in his book [10].

▲ Figure 6. An advertisement for the Globe Multinebulizer in the Journal of the American Medical Association (JAMA) 1899.
From *www.inhalatorium.com* .

By 1884 G. Evans, having also recognized the problem of large droplets produced with the Bergson tube design, set about inventing a device to overcome this. His work, published in 1891, showed a more sophisticated arrangement that prevented larger droplets being emitted [7].

An important landmark in the 1860's was the inclusion of inhalants. This was described for the first time in 1864 in the American "Medical Formulary" and in 1867 in the British Pharmacopoeia. Five inhalants were listed; vapor acidi hydrocyanici (vapor of hydrocyanic acid), vapor chlori (vapor of chlorine), vapor coniae (vapor of hemlock), vapor creasoti (vapor of creosote), and vapor iodi (vapor of iodine). This reflected the rising importance and popularity of inhaled drugs and stimulated a vast number of inventive ideas by both physicians and medical device manufacturers, which thrived in an unregulated market (Figure 6).

The late 19th century was a period when the availability of new raw materials such as hard rubber created many possibilities for the development of new nebulizers. Advertising became a means of marketing the new nebulizers, and numerous unrestricted claims were made as

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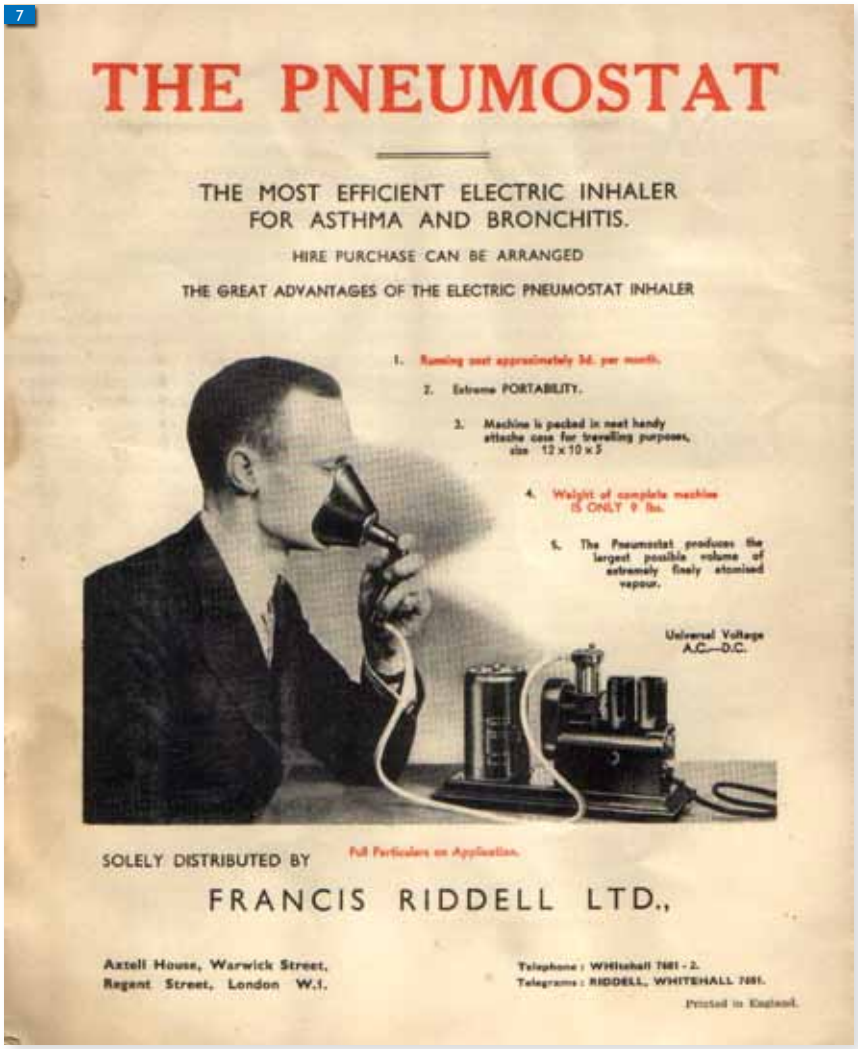

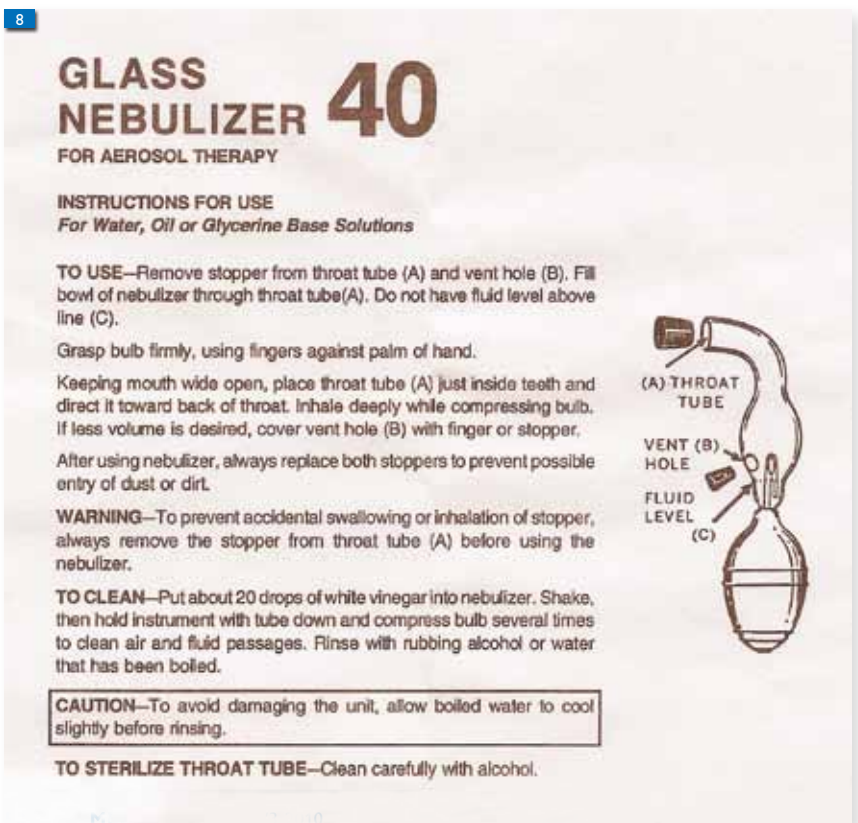

Figure 7. An advertisement for the Pneumostat electrical compressor-nebulizer-facemask combination from 1935. From *www.inhalatorium.com*.

to the curative properties of various inhaled drugs. The world was also changing for the physician, as scientists and engineers were moving towards the forefront of the development of inhaled drug delivery and pharmaceutical companies were beginning to emerge.

Jet nebulizer with handbulb, compressor or oxygen

In the early 20th century the clinical effects of adrenalin (epinephrine) in asthma were identified and documented. D.M. Kaplan and J.J.M. Bullowa, working in New York, identified the value of hypodermic administration of adrenalin in asthma in 1903-04, and this became the foundation of what we can consider modern drug inhalation therapy [12].

In 1910 A. Ephraim published a paper in the Berliner Klinische Wochenschrift on the treatment of asthma attacks with adrenalin, either instilled or sprayed through a bronchoscope [13]. L Pick, in 1911, reported successful nebulization of adrenalin in two patients and it rapidly became standard therapy, administered by a hand-held nebulizer [14]. The same year G. Zuelzer published a paper in the Berliner Klinische Wochenschrift on the delivery of adrenalin by the Spiess's drug nebulizer, made by Dräger in Lübeck, Germany, with either compressed air or oxygen [15]. The availability of domestic electrical supplies permitted machines to be developed utilizing this form of power, and the Pneumostat is an example of an early compressor (Figure 7). In the early days of compressors it was not unusual for the pharmacist to own the device and patients would come to pharmacy to inhale the contents of their ampoule in the shop. In 1926 C. Sachse described the Spiess-Dräger nebulizer in more detail, claiming that both drug output and droplet size could be regulated [16].

The administration of adrenalin by nebulization apparently spread over Europe fairly rapidly. In 1929 P.W.L. Camps wrote in the Guy's Hospital Reports that "About three years ago I had three obstinate cases of asthma, who, tired of my

Figure 8. The DeVilbiss No. 40 jet nebulizer. Note the design of the body of the nebulizer which acts as a baffle forcing larger droplets to deposit on the glass wall opposite the mouthpiece.

efforts, sought relief by a treatment at that time advertised in the lay press, and having obtained it reported the good news to me in the right spirit" [17]. The solution of adrenalin was named "apneugene" and marketed together with the "apparatus", Spiess-Dräger or Hirth's jet nebulizers, which were supplied with facemasks and run with oxygen at a flow of 7 L min^{-1}. Camps also credited the Germans on the work done "on the physical aspect of the atomization".

In the USA, at least two papers appeared in 1935 describing the use of glass nebulizers with a more concentrated solution of adrenalin. E. Matzger stated that the idea of inhaling adrenalin developed shortly after the drug was available for injection [18]. He referenced a paper from 1921 by A. Ephraim on the subject. Matzger developed his own nebulizer, which was commercialized by The Vaporizer Products Company in San Francisco.

J.B. Graeser and A.H. Rowe published their first paper on the use of nebulized adrenalin in The Journal of Allergy and started by claiming that "Although epinephrine given hypodermically is the drug par excellence for relief of asthmatic symptoms, scant attention has been paid to the possibility of its administration by inhalation" [19]. The early German papers on the subject are not mentioned. Their paper ends with a discussion in which a colleague comments that "In New York and the Metropolitan area for the past eight years, we have been plagued with the commercial apparatus referred to by Dr. Rowe". The same colleague ends his comments by "I, for one, am extremely grateful to Dr. Rowe for making it possible to prescribe ethically this apparatus at a reasonable cost to the patient who needs it".

The new glass nebulizer was supplied with a rubber bulb and the patient was instructed to place the nozzle just within the open mouth and to inhale deeply while pressing the bulb. In 1936 the same authors reported on the successful use of nebulized adrenalin in asthmatic children [20]. A combined facemask and nebulizer was used with either a rubber bulb or a compressor. There was, however, no information on the flow or pressure of the compressor. D.W. Richards Jr. et al. "reinvented the wheel" in their 1940 paper on a "continuous inhalation method" with the nebulizer powered either by oxygen from a pressure tank or a compressor with a flow of 4 to 7 L min^{-1} [21]. A 1 mL nebulizer charge was nebulized in 3 to 10 minutes.

In 1945, A.L. Barach et al. published their paper on treatment with nebulized penicillin [22].

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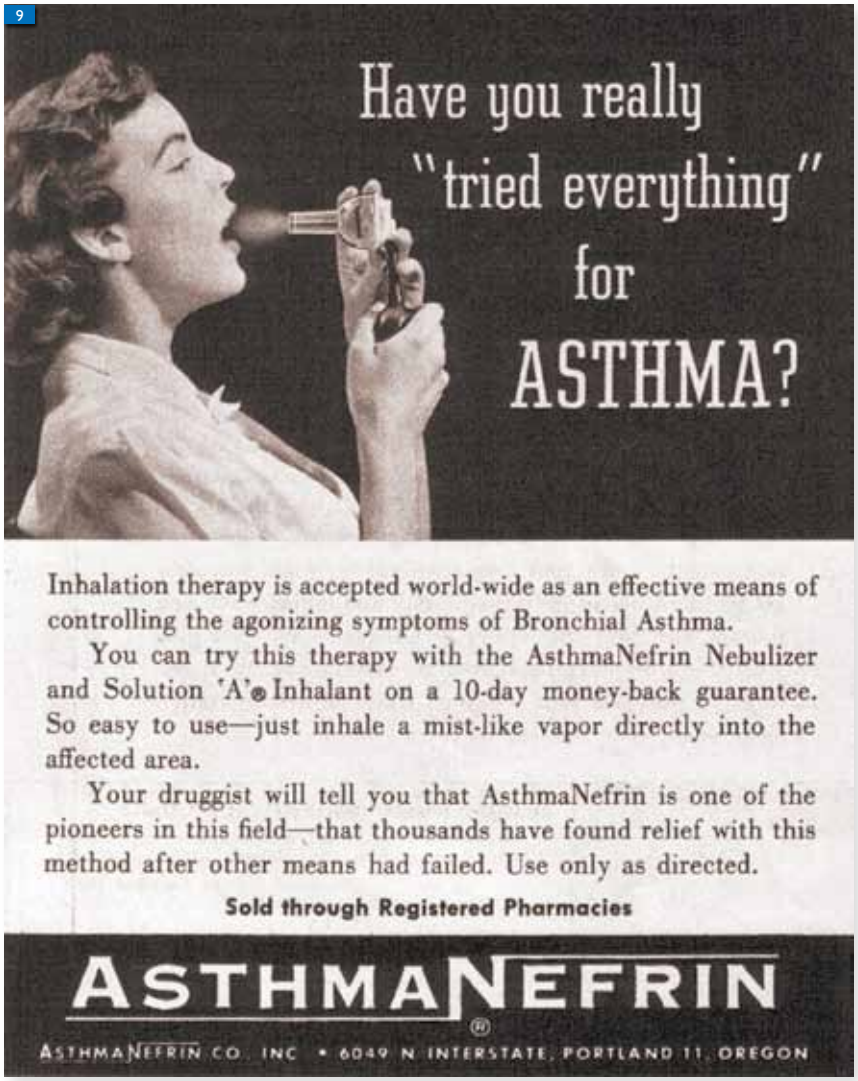

▲ Figure 9. An advertisement for the AsthmaNefrin Nebulizer. Note how the patient positions the nebulizer mouthpiece several centimeters from her mouth.
From *www.inhalatorium.com*.

They designed a glass nebulizer that created droplets smaller than 1 micrometer (µm) and used oxygen at a flow of 8 L min^{-1}. An extra orifice was designed in the nebulizer to facilitate air entrainment. They mention that even small nebulizers like the Vaponephrin or the DeVilbiss No. 40 (Figure 8) could be used as the droplet size was less than 1 µm.

H.A. Abramson published a paper in Annals of Allergy in 1946 on "Principles and Practice of Aerosol Therapy of the Lungs and Bronchi" [23]. He defines the terms "aerosol", "atomization" and "nebulization" and argues that "The word 'nebulization' should be restricted to the special type of atomization in which the large particles are removed by the introduction of a suitable baffle into the construction of the atomizer". He points out the design of the DeVilbiss No. 40 nebulizer as a nebulizer that baffles out the large particles, and reports that the particle size (the "radii") extended from 0.3 to 2 µm.

G.F. Harsh published his paper on "A comparative study of commercial nebulizers" in

Figure 10. The Philips Respironics I-neb Adaptive Aerosol Delivery (AAD) System.

The "intelligent" mesh based nebulizer represents the latest patient-focused nebulizer technology.

Annals of Allergy in 1948 [24]. Fifteen different jet nebulizers were compared regarding output per squeeze with the rubber bulb, the capacity of the bulb, droplet size and nebulization time. The amount of solution delivered by one compression was highly variable, ranging from 0.4 mg to 13.0 mg. For the DeVilbiss No. 40 nebulizer the figure was 1.6 mg. The nebulization time for the delivery of 1 mL ranged from 31 s to 450 s with compressed air. The droplet size was determined using an ocular micrometer in a microscope. The "median" droplet size ranged from 8 to 29 µm whereas the "largest" droplets ranged from 40 to 308 µm. The AsthmaNefrin nebulizer had the smallest droplet size at 8 µm (Figure 9). It is interesting that the early testing of droplet or particle size could range from 0.3 to 308 µm in two different papers published in the same journal two years apart. Abramson does not give any additional information on the technique used for the particle size measurements reported in his paper, so the reason for the difference remains unknown.

The modern nebulizers

The development of new nebulizers and other inhalers after the 1950's is relatively well covered in most textbooks in the field. The characterization of inhalers including nebulizers have become a science with relatively clear demands for respirable aerosols, and in some cases defined delivered doses of aerosol to the patient. The jet nebulizer has been developed from the compressor-driven constant output jet nebulizer into breath-enhanced jet nebulizers and further into small portable jet nebulizers. The early ultrasonic nebulizer has been developed into small portable ultrasonic nebulizers, and further into portable mesh-based ultrasonic nebulizers.

The recent introduction of an "intelligent" mesh based nebulizer - the I-neb Adaptive Aerosol Delivery (AAD) System (Philips Respironics) - represents the latest patient-focused nebulizer technology (Figure 10). It has been designed to adapt to the patient's breathing pattern in order to minimize the potential for errors and waste of drug during the inhalation of drugs [25]. The I-neb AAD System is described in another article in this issue of Medicamundi [26] ■

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