Available online at www.sciencedirect.com
ScienceDirect
Current Opinion in Pharmacology

Dr R Shiffmann's Asthmador: relevant to our times, or a snake oil remedy?

Editorial overview

Jeffrey S Fedan and Giovanni Piedimonte

Current Opinion in Pharmacology 2010, **10**:213–217

Available online 17th June 2010

1471-4892/$ – see front matter
Published by Elsevier Ltd.

DOI 10.1016/j.coph.2010.06.005

Jeffrey S Fedan

Pathology and Physiology Research Branch, Health Effects Laboratory Division, National Institute for Occupational Safety and Health, Morgantown, WV 26505, USA
e-mail: jsf2@cdc.gov

Jeffrey S Fedan, PhD is a pulmonary pharmacologist at the National Institute for Occupational Safety and Health in Morgantown, WV and adjunct professor in the Departments of Physiology and Pharmacology, and Basic Pharmaceutical Sciences at West Virginia University Schools of Medicine and Pharmacy. He attended Case Western Reserve University as an undergraduate and received his PhD in pharmacology at the University of Alabama at Birmingham. His primary research interest is epithelial regulation of airway reactivity.

Giovanni Piedimonte

Department of Pediatrics, West Virginia University School of Medicine, WVU Children's Hospital and Pediatric Research Institute, Morgantown, WV 26506, USA
e-mail: gpiedimonte@hsc.wvu.edu

Giovanni Piedimonte received his degree in Medicine from the University of Rome School of Medicine in Italy, completed his residency training in Pediatrics at the University of California San Francisco, and received fellowship training at the Cardiovascular Research Institute of the University of California San Francisco and at the University of North Carolina Chapel Hill. He holds certifications in General Pediatrics and in Pediatric Pulmonology from the American Board of Pediatrics. He is the first Wyeth Research Scholar and the professor and chairman of the Department of Pediatrics at West Virginia University School of Medicine. He also serves as the Physician-in-Chief of the WVU Children's Hospital in Morgantown, WV and as founding director of the WVU Pediatric Research Institute.

Introduction

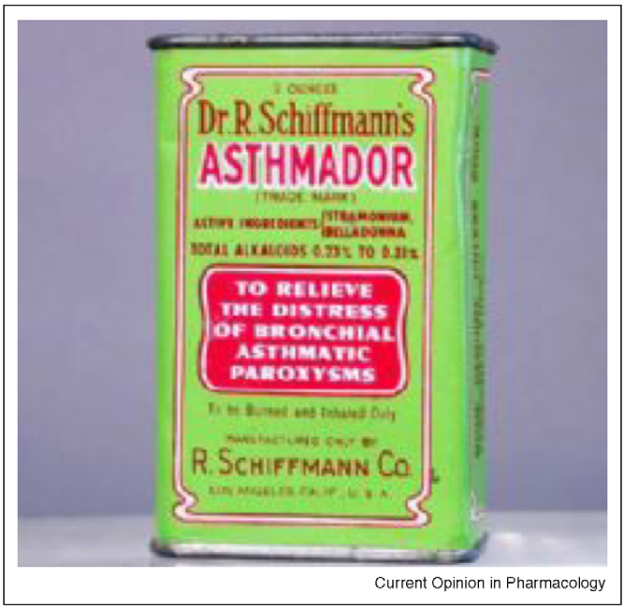
We really would have liked to have been able to title this issue: 'Cures for Respiratory Diseases Found!' But we and you reading this issue at the time of its publication realize that this claim cannot be made. Alas, lung researchers have amassed a gargantuan level of knowledge about the diseases that are discussed in this issue: how patients present; the several morphological and pathophysiological changes that occur as the disease begins and progresses; some genetic, possibly etiologic, predispositions; and the mechanisms of action of most of the drugs that are used to prevent and/or ameliorate patient symptoms. Not that the 'cure' for these diseases lies ultimately in pharmacotherapy. At the outset we decided to limit the areas covered by this issue to asthma and cystic fibrosis. This was not done to slight other diseases such as tuberculosis, pneumonia, sarcoidosis and the many others, but because of the limitations of space.

The past

One of us has a tin of Dr R Shiffmann's Asthmador (Figure 1) in his office that was acquired at a flea market about 20 years ago. It contains between 0.23 and 0.31% alkaloids, which are listed as stramonium and belladonna. You will recall that these alkaloids arise from *Datura stramonium* and *Atropa belladonna*, which are both members of the 'nightshade' plant family and, as such, contain the muscarinic receptor antagonists atropine, hyoscyamine and scopolamine. Notice that the directions on the front of the tin state: 'To be burned and inhaled only.' The arithmetic would indicate that between 99.69 and 99.77% of the contents of the tin are inert ingredients, none of which are specified but some of which are flammable. The directions on the back of the tin direct: 'USE BY INHALATION ONLY. DO NOT TAKE INTERNALLY. [Does this remind you of any contemporary respiratory medications?] Put one-half to one teaspoon of the powder on a plate or saucer. Ignite powder (allow sulfur to burn off match before lighting) and inhale the smoke into the lungs.' The label states further that: 'ASTHMADOR CIGARETTES AND ASTHMADOR PIPE MIXTURE are also available. They contain the same active ingredients [but different inactive ingredients?] as the Powder.' Elsewhere, 'If Dr. R. Schiffmann's preparations do not afford the relief claimed for them, when used as directed, the purchaser's money will be refunded upon return of the unused portion to the manufacturer.' No need for that, however, because some claimed Dr Schiffmann's Asthmador as an asthma cure, at least in Australia (Figure 2).

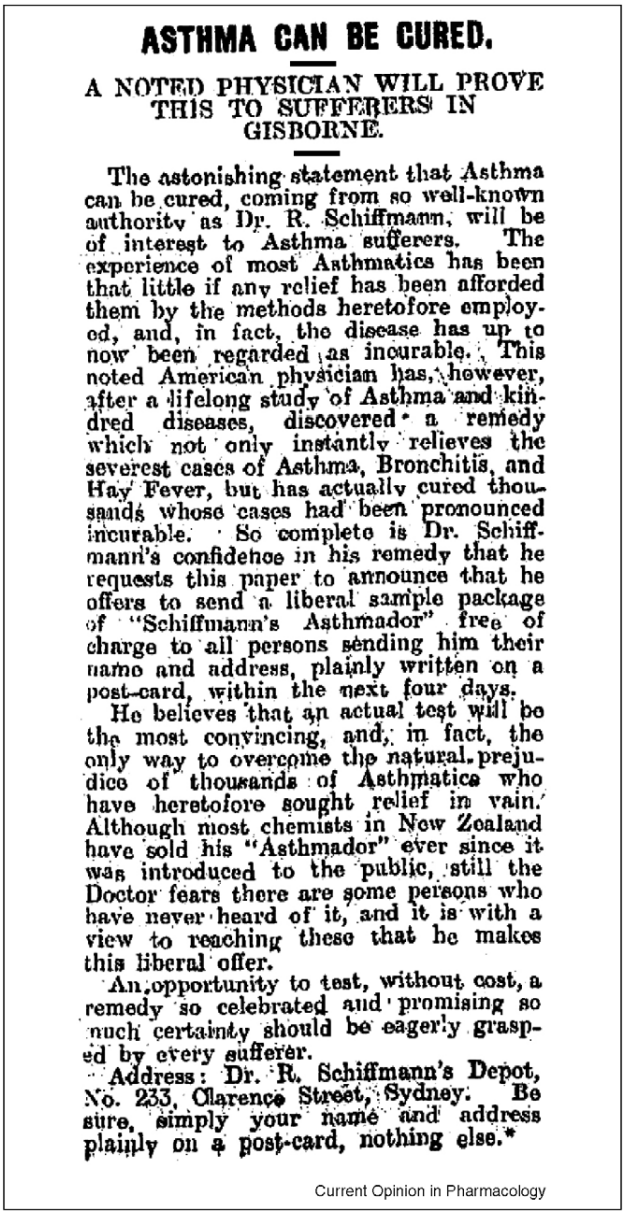
Was Dr Schiffmann selling a snake oil type of remedy that, hopefully, did not kill any patients, or was there clinical insight behind the use of Asthmador? There may have been recognition at the time that some asthma

Figure 1



Old advances in inhalation delivery of probably useful drugs. Ipratropium, beware.

Figure 2



ASTHMA CAN BE CURED.

A NOTED PHYSICIAN WILL PROVE THIS TO SUFFERERS IN GISBORNE.

The astonishing statement that Asthma can be cured, coming from so well-known authority as Dr. R. Schiffmann, will be of interest to Asthma sufferers. The experience of most Asthmatics has been that little if any relief has been afforded them by the methods heretofore employed, and, in fact, the disease has up to now been regarded as incurable. This noted American physician has, however, after a lifelong study of Asthma and kindred diseases, discovered a remedy which not only instantly relieves the severest cases of Asthma, Bronchitis, and Hay Fever, but has actually cured thousands whose cases had been pronounced incurable. So complete is Dr. Schiffmann's confidence in his remedy that he requests this paper to announce that he offers to send a liberal sample package of "Schiffmann's Asthmador" free of charge to all persons sending him their name and address, plainly written on a post-card, within the next four days.

He believes that an actual test will be the most convincing, and, in fact, the only way to overcome the natural prejudice of thousands of Asthmatics who have heretofore sought relief in vain. Although most chemists in New Zealand have sold his "Asthmador" ever since it was introduced to the public, still the Doctor fears there are some persons who have never heard of it, and it is with a view to reaching these that he makes this liberal offer.

An opportunity to test, without cost, a remedy so celebrated and promising so much certainty should be eagerly grasped by every sufferer.

Address: Dr. R. Schiffmann's Depot, No. 233, Clarence Street, Sydney. Be sure, simply your name and address plainly on a post-card, nothing else.*

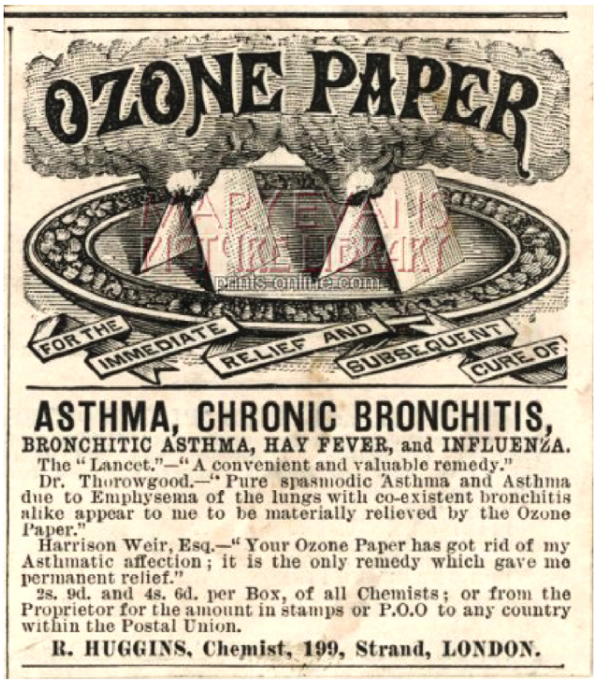
Current Opinion in Pharmacology

Results of early clinical trials demonstrating an asthma cure with Dr R Schiffmann's Asthmador.

patients respond to muscarinic blockers, as they do today. The idea of delivering a drug by inhalation in an attempt to restrict its effects to the lungs is good pharmacological practice which is still in the mainstream. In a day when inhaler technology was not even fantasized, how best to generate and deliver aerosols of drugs into the lungs? As for the other ingredients in the powder, who can imagine what their effects and the effects of other combustion products were on the lungs? Fortunately, no contemporary pharmaceutical company relies upon fire to deliver aerosols into the lungs.

Whereas Dr Schiffmann may have had it partly right, others advocating the use of combustion for asthma therapy may have been well meaning but were certainly misguided. In Wendy's restaurants many years ago the tables were covered with a formica surface that featured what looked like replicas of advertisements from days of yore. One described the use of 'ozone paper' for treating asthma (Figure 3). One of us saw this over a period of years and wondered whether this was a legitimate advertisement or a graphic made up for Wendy's restaurants tables. There were testimonials in the ad from *Lancet*, Dr. Thorowgood and a certain Harrison Weir. A postdoc in J.S.F.'s lab, David Raeburn, being a pharmacist and on a whim thinking that nothing would come of it, wrote an open letter to a pharmacist professional trade journal in the U.K. asking whether anyone knew anything about ozone paper; was this ad real or conjured? We were astonished when he received a reply from a gentleman who had worked for R Huggin, Chemist on The Strand in London. The ad was legitimate. He described going down to the basement of the pharmacy to make the ozone paper according to a recipe he followed. He said that he always doubted whether any ozone was released by the burning of this paper but would not himself breathe the smoke. We now know that, had ozone been released, it would have been harmful to asthmatics rather than helpful. This is snake oil pharmacology and there is little room for further

Figure 3



The marketing of the cure for all respiratory ailments at Wendy's restaurants. Clinical trial results are indicated.

development of the concept. Apparently the building housing the Chemist no longer exists, as it was in was bombed during World War II.

The present

This issue updates respiratory pharmacology well beyond its combustion phase in a number of areas where significant advances have been made over the past few years or where debate still exists about the mechanisms, effectiveness or toxicity of drugs.

If the 'cure' for asthma is not known, neither is 'the' cause. However, the stage is set by Karim Shalaby and James Martin, who remind us of the central role of T cells in the initiation, progression and resolution of asthma in the landscape of airway inflammation.

We are, each of us, a phenotype and those phenotypes are derived from our DNA. Our genetics, therefore, contribute to the diseases that inflict us and our abilities to respond predictably to drugs designed to mitigate asthma. The role that pharmacogenetics plays in asthmatic patient response is of great interest, as it is in the case of several other diseases. A description of these general principles is provided in this issue by Rodolfo M Pascual and Eugene R Bleecker.

The use of β-adrenoceptor agonists for the treatment of asthma is a mainstay for eliciting bronchodilation in patients. Over the years the desirability of β_2-adrenoceptor agonists with longer durations of action became apparent, but recent studies have suggested that risk to patients is increased if maintenance involves the use of long-acting β_2-adrenoceptor agonists. But is it? Victor E Ortega and Stephen P Peters consider various aspects that have to be considered before the final verdict is in.

A greater understanding of the concepts and mechanisms of inverse β-adrenoceptor agonists has had large impact on the treatment of cardiovascular disease with β-adrenoceptor antagonists. Once contraindicated in congestive heart failure, β_1-adrenoceptor antagonists which have the property of being inverse agonists are now indicated and increase long-term survival. Now there is possible spillover of these ideas into asthma treatment modalities using β_2-adrenoceptor antagonists that are inverse agonists to control airway inflammation that may actually be promoted, at least in part, by β_2-adrenoceptors. We turn to Burton F Dickey, Julia KL Walker, Nicola A Hanania and Richard A Bond to clarify these interesting paradoxes and paradigms.

There is no doubt in the effectiveness of inhaled glucocorticoids in asthma management in appropriate patients. Here particle size, bioavailability and the possible growth-stunting effects in children are important considerations. Is it possible to improve efficacy and reduce side effects using smaller aerosol particles? This question is well-addressed by Deborah A Gentile and David P Skoner. Bottom line. . .there may be room for improvements in currently used drugs.

The complications of treating severe asthma stem from the diversity of phenotypes. Where is the perfect drug? The complexity of asthma demands fresh thinking about pharmacotherapy and procedures that can be used to treat difficult patients. In their paper Rafael Firszt and Monica Kraft ably evaluate some newer treatment options that, hopefully, will prove efficacious and become available routinely.

Arguably, one of the most controversial aspects of asthma physiopathology in the last decade has been the concept of airway remodeling and the possibility that chronic inflammation may lead to fixed airway obstruction. Despite intense research efforts worldwide, the relationship between inflammation and remodeling is still highly debatable and incompletely understood. What seems acknowledged by most experts is that the presence of airway inflammation in patients with asthma does not always translate to airway remodeling and that the correlation between the degree of inflammation and the degree of remodeling is variable. Rabih Halwan, Saleh

Al-Muhsen, and Qutayba Hamid did a great job in distilling the current knowledge in this critical area.

Asthma is frequently developing as part of an atopic diathesis and is associated to allergic co-morbidities; hence the need to modulate aberrant immune reactivity, either pharmacologically or by immunotherapy (IT). Recently, sublingual IT (SLIT) has become popular in Europe for its potential to minimize the discomfort and risks associated with the conventional subcutaneous administration (SCIT). Unfortunately, several studies have shown that SLIT is less effective than SCIT, which is likely to limit its use. It is also likely that future IT strategies will utilize recombinant allergens, as discussed by Shyam S Mohapatra, Momina Qazi, and Gary Hellermann in their article.

Slowly but surely, the concept that a child is not a 'small adult' is gaining ground among primary care physicians as well as specialists, and this has important implications for the management of childhood asthma. Children frequently wheeze for many reasons that have little to do with asthma (e.g. bronchiolitis, tracheomalacia, and gastroesophageal reflux), and even when the diagnosis is asthma many of them manifest non-atopic phenotypes that frequently fail to respond to standard anti-inflammatory therapies. Annabelle Quizon and Andrew A Colin address many of the unique aspects of asthma in childhood, whereas Robert Welliver gives us a comprehensive update on the pharmacotherapy of respiratory syncytial virus (RSV) infection, which is the most common cause of wheezing in infants and young children and has been implicated in the pathogenesis of non-atopic wheezing in the first decade of life.

Finally, Jennifer Goralski, Richard C Boucher, and Brian Button give us an update on the new strategies for airway surface rehydration, a novel attempt to address the basic pathophysiological abnormality of cystic fibrosis (CF) lung disease. Over the decades, CF research has not only helped the 70 000 children and adults affected by this terrible genetic disease, but also led the way to a better understanding of the respiratory system structure and function and to new therapeutic strategies (e.g. gene therapy) that may revolutionize the management of many other respiratory and non-respiratory diseases in a not too distant future.

The future

Coming to the completion of this challenging task to assemble the highlights of our current knowledge of respiratory pharmacology, we cannot help to have a bittersweet feeling about the collective achievements of pulmonary research and what the future will bring. On the one hand, our knowledge of respiratory structure and function in health and disease has expanded exponentially, evolving into new molecular dimensions, system analysis, and genomic/epigenomic decoding that was simply impossible to fathom just a few years ago even for a sci-fi book writer. On the other hand, when the authors of this editorial graduated from their respective professional schools (more than two decades ago, unfortunately) at least six or seven different drug classes were available for asthma therapy. Now that antihistaminics, cromons, and xanthins have virtually disappeared from the asthma armamentarium, we are left with chemically refined derivatives of adrenaline and cortisone for symptomatic management, certainly improved in terms of safety and therapeutic index, but still ridden with side effects and far from being the 'magic bullet' cure we have been waiting for. Surprisingly, something very similar to the Dr R Shiffmann's Asthmador is still a mainstay of therapy and one of the best selling drugs for both asthma and COPD in 2010.

The new 'concepts' that made it from bench to bedside pushed by trillions of dollars of R&D investments are limited to leukotriene modifiers and anti-IgE humanized antibodies, whose use is limited to second or third line therapy by all guidelines because they are clearly less effective than the good old medicines, and also their safety record has been questioned recently. Hardly a revolution, but at least those made it to the market, differently from many other shining stars that rapidly turned into meteors, like the anti-IL5 monoclonal and other biologicals.

The situation is not much better for CF pharmacotherapy. Antibiotics, mucolytics, and nutritional supplements have been for decades the mainstay of therapy in combination with chest physiotherapy. Anti-inflammatory medications (e.g. ibuprofen and steroids) have failed to gain popularity, in part because of safety issues, and bronchodilators are frequently ineffective. Plus, the benefit deriving from lung transplantation in advanced CF is increasingly controversial based on the most recent survival analyses. Undeniably each of the medicines and supplements we use today is more potent and safe, and they have contributed to a significant increase in life expectation. But it is also true that the gene therapy hailed as the definitive cure just around the block two decades ago never materialized. Now that the refinement of conventional therapies has approached its ceiling and survival curves are flattening, only radically new strategic weaponry can lead to the next level.

Perhaps the most humbling thought coming to our minds is that, even if suboptimal, the progress in the pharmacotherapy of asthma and CF is by far at the forefront of modern respiratory medicine, especially if compared to several other less common diseases like interstitial lung disease and pulmonary fibrosis where progress has been

minimal for decades. What to do? How to translate the quantum leaps of the basic sciences into rapid progress in clinical morbidity and mortality? How to maximize the benefits for public health deriving from the unprecedented investments both from federal and industry funding sources? The answers to these questions will define the future of pharmacotherapy, and consequently the future epidemiology of highly prevalent diseases like asthma. Our hope is that what is learned at the bedside can be integrated with results from the lab bench to speed up and streamline the development of new drugs and resolve the bottleneck that has emerged in the respiratory drug pipeline.

Acknowledgements

The authors declare that they have no conflicts of interest. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health. Mention of brand name does not constitute product endorsement. During the past 12 months, Dr. Giovanni Piedimonte's research has been supported in part by grants from the United States National Institutes of Health (NHLBI HL-61007 and NICHD NCS-07-11) and from the WVU Foundation, and he has also received honoraria and consultant fees from Merck.