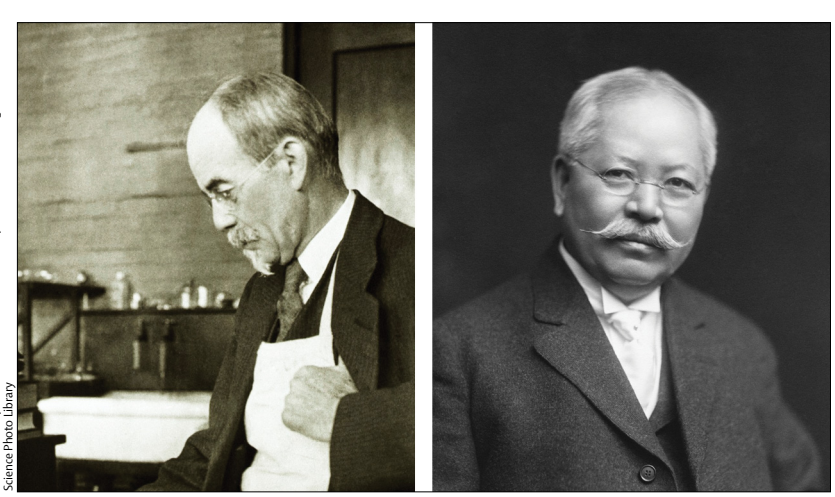
Features

Epinephrine: a short history

For **references** see appendix

In 1859, English physician Henry Salter reported that "asthma is immediately cured in situations of either sudden alarm or violent fleeting excitements". Examining that statement might lead you to believe that this could be the first description of the therapeutic effects of circulating endogenous epinephrine and its ability to activate adrenergic receptors. More than 150 years later, adrenergic receptor agonists are the oldest and most common emergency treatment for asthma exacerbations and anaphylactic reactions. Guidelines from the Global Initiative for Asthma, and the British Thoracic Society and the Scottish Intercollegiate Guidelines Network, recommend administration of β2-agonists for rapid bronchodilation, thanks to their ability to mimic the action of epinephrine. Deservedly, the discovery of epinephrine as a non-specific agonist of α and β adrenoceptor subtypes has been hailed for spearheading the development of asthma relief and emergency treatment.

Despite asthma being recognised as a respiratory problem in ancient Egypt, and by Hippocrates around 450 BCE (the Greek verb for "panting", aazein, forms the basis of asthma's name), advances towards effective asthma relief instead of palliative treatment did not begin until the late 19th century. In 1894, at the University College of London, George Oliver, an English physician, and Edward Schafer, an English physiologist, visualised the potent effect of adrenal medulla extract on the heart rate and blood pressure of animals using handmade laboratory apparatus constructed from steel hooks, fine cotton threads, pulleys, and a few writing pens. Their conclusion captured the attention of the scientific community: the extract of adrenal glands (also known as suprarenal glands), which sit just above the kidneys, increases heart rate and blood pressure by stimulating arteriole contraction.



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John Jacob Abel and Jokichi Takamine

Oliver and Schafer's next move was to challenge the adrenal extract with whatever they could find—including heat, acid, and peptic digestion—to determine the physical and biochemical properties of this substance. Their work provided the perfect base for John Jacob Abel, an American biochemist and pharmacologist at Johns Hopkins University in Baltimore. Abel's research culminated in the purification of the extract's active ingredient, epinephrine, in 1899. Somewhat frustratingly for Abel, the purity of his isolated epinephrine was challenged by Otto von Furth, an Austrian physician, physiologist and biochemist, and by Jokichi Takamine, a Japanese biochemist. Takamine, driven by the widely recognised "marvellous therapeutic value of the suprarenal extract", successfully isolated the "pure, stable, crystalline form" of epinephrine, which he named adrenalin. The final empirical formula of $C_9H_{13}NO_3$ was soon determined by Aldrich in 1901, and the purified product was quickly patented by Parke-Davis & Company.

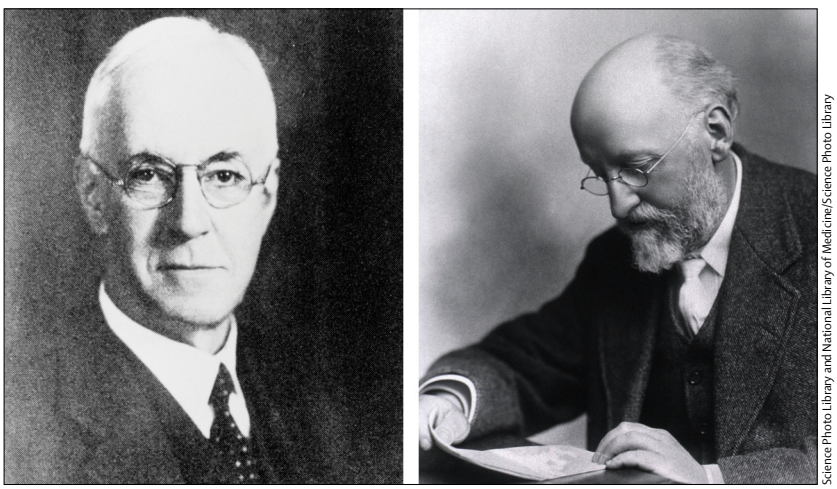
With purification established, and with the role of the adrenal extract in arteriole contraction well documented, scientific and medical researchers naturally turned their attention towards identifying a therapeutic use for adrenalin, which was henceforth also called epinephrine. Crude epinephrine extract was initially tested on patients with asthma and hayfever in around 1900 by Solomon Solis-Cohen, a professor of clinical medicine in Philadelphia. Solis-Cohen reported that oral doses of desiccated adrenal glands relieved symptoms, and described the mechanism as "vasomotor ataxia of the relaxing variety". This finding accorded with one of the favourite premises of asthma pathophysiology, the vasodilator hypothesis; at the time, asthmatic airway obstruction was attributed to vasodilation and subsequent swelling of the bronchial mucosa. Jesse Bullowa and David Kaplan (Montefiore Home for Chronic Individuals in New York), who successfully treated patients with asthma by hypodermic injection of pure epinephrine, also supported this idea. Bullowa and Kaplan's triumph led to epinephrine becoming a recommended relief treatment for severe asthma attacks. However, findings of airway smooth muscle relaxation in response to epinephrine treatment in 1907 also led to increased support of the bronchial muscle spasm hypothesis. Thus, two hypotheses were considered for asthma pathophysiology. Study of these hypotheses

eventually aided an understanding of the mechanism of action of epinephrine.

In 1905, the British physiologists William Bayliss and Ernest Starling introduced the idea of a hormone acting as an endogenous messenger, secreted by one organ to affect the functioning of another. When the effects of epinephrine were considered, the conclusion was soon drawn that it must be a hormone. John Langley, a British physiologist, and Thomas Elliott, a British physician and physiologist, set the foundations for the concept of drug receptors; Langley noted that the effects of adrenal extract were comparable to the electrical stimulation of sympathetic nerves, and Elliot suggested that epinephrine might be secreted from sympathetic nerve terminals. The work of George Barger, a British chemist, and Henry Dale, an English pharmacologist and physician, appeared to support this hypothesis; sympathetic nerve activity, assessed by the contractile response of cat uterus in vivo, could be triggered by epinephrine. Recognising the association of epinephrine with sympathetic nerve activity, Brian Melland, a London-based physician, suggested that epinephrine induces bronchial muscle relaxation by targeting the vagus nerve. The concept of epinephrine and other hormones participating in homoeostasis was initially developed by the American physiologist Walter Cannon. Eventually, this led to theories about internal and external signalling mechanisms and feedback responses.

The therapeutic potential of epinephrine was widely acknowledged and it was used before a precise understanding of the molecule's mechanism of action was fully developed. Manufacturers then began developing synthetic forms of epinephrine. In 1904, Friedrich Stolz, a German chemist, produced the first synthetic hormone by synthesising a ketone form of epinephrine (named adrenalone). Large-scale production of synthetic epinephrine became possible when Stolz converted adrenalone to adrenaline, or epinephrine, in 1906. The efficacy of synthetic epinephrine was declared favourable over crude adrenal extracts, which had little effect on disease. Carl Wiggers, an American physiologist, showed the vasoconstrictor effects of synthetic epinephrine on cerebral blood flow in 1905. Epinephrine, it seemed, was ready for use as a relief drug for asthma.

Deciding the optimum route of administration, however, was still debated by physicians. Parke-Davis & Company had manufactured different apparatus for the regulated administration of soluble medicines, such as glass ampules, marketed as Glaseptic Ampoules, in 1909. The ampules improved the accuracy and speed of soluble medicine preparation and administration by containing a fixed dose of drug, which could be administered hypodermically in an emergency. The method of hypodermic administration of epinephrine was endorsed by a report from Brian Melland, published in *The Lancet* in 1920. Melland claimed that the hypodermic route provided an effective treatment for asthma, and he supported this by publishing findings from his own cases. One such case was that of a 30-year-old woman, presenting with a 6-year history of asthma and "spasmodic attacks…present nightly". Epinephrine injection relieved her symptoms for 7 days, and repeating this treatment for 5 weeks reduced the frequency of her asthma exacerbations. Melland also noted that there was a lack of beneficial effects when epinephrine was given as an oral treatment.



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Sir Henry Dale and William Bayliss

However, enhanced symptomatic improvements were discovered in 1910 when Barger and Dale administered epinephrine as an aerosol. In 1913, James Adam, author of *Asthma and its Radical Treatment*, noted that the "absorption of the drugs from the nasal mucous membrane or larynx or trachea" should be seen an alternative route for epinephrine. By the 1930s, nebulisers such as the electric nebuliser Pneumovac were available. These products could be bought by physicians for use in their offices, but they were also suitable and safe enough for patients to treat themselves at home.

The discovery and purification of epinephrine provided not only long overdue relief from asthma exacerbations and anaphylactic reactions, but also the beginnings of our understanding of hormones, homoeostasis, and, perhaps most importantly, the later development of specific β adrenergic agonists, such as isoprenaline. Today, β adrenergic agonists are indispensable asthma rescue treatments. Recently, there has also been well-deserved recognition of Ulf von Euler's work on noradrenaline, and Earl Wilbur Sutherland Jr's valuable contributions to hormone signalling via cAMP pathways. Perhaps these early works on epinephrine merited a Nobel Prize, particularly since the combined diligence of previous researchers has enabled so many people to breathe a little easier.

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