A history of asthma
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Asthma is a common disease at the present time and there is evidence that its world incidence may be on the increase. In Great Britain, there are probably around two million cases of asthma and, among schoolchildren, one in 20 suffers from the condition.

Asthma is an ancient disease [1-6]. Part I of this study relates the history of concepts of the causes and nature of asthma, from earliest times until the end of the 19th century. The 20th century has witnessed dramatic developments in the management of asthma and the history of this is dealt with in Part II.

Part I
Development of concept of asthma

Egyptian, Chinese and Indian medicine

In ancient Egypt, respiratory problems were common and the Ebers Papyrus (1550 BC) refers to a condition, probably asthma, which was treated by oysters (enemas) and the administration of animal excreta, including that of camels and crocodiles, together with herbs such as squill (Scilla) and henbane (Hyoscyamus), an extract of the latter being placed on a heated brick and the emanation inhaled [7, 8].

The Chinese were familiar with asthma in the third millennium BC, and their earliest writings, such as Nei Ching (c. 1000 BC), possibly the oldest medical work in the world, mentioned the plant Ma Huang from which, in modern times, ephedrine was extracted for use in asthma. The disease was considered to be due to a disequilibrium of yin and yang principles and the traditional techniques of acupuncture and moxibustion were employed. This medical lore was later adopted by the Japanese who have perpetuated it in their kampo system of medicine.

In India, the teachings of Ayurvedic medicine were preserved in writings such as the Susruta Samhita (450 AD) in which the herbs Nardostachys jatamansi (datura or thorn-apple), from which stramonium was later extracted, and Saussurea lapta (kuth root) were recommended for their relaxant properties. Yoga and meditation were introduced later.

Graeco-Roman medicine

In ancient Greece, varying degrees of laboured breathing were differentiated: moderate distress was called dyspnoea; if this was more marked, asthma; and, if severe, orthopnoea. Homer used the term asthma in the Iliad, but in a non-medical sense, merely indicating panting or distressed breathing. To Hippocrates and his disciples, asthma was considered a symptom [9]. Based on the concept of the elements, qualities, humours and temperaments, asthma was thought to be the result of a cacochymia (disequilibrium of the humours) resulting in a defluxion (flow) of the evil humour (phlegm or pityuita) which was thought to arise in the brain and pass from the pituitary, via the cribiform plate at the base of the skull, into the nasal cavities whence it descended into the lungs. For Hippocrates, the remedy was to encourage the flow of phlegm by means of emesis, purging and bleeding. The regimen in the Asclepian temples also included special diet, hydrotherapy and massage, relaxation being encouraged by means of sedative herbs and suggestion [10].

Aretaeus (81-131 AD) of Cappadocia classified asthma as a disease and not merely a symptom. His description of asthma [11] was probably the best in ancient times:

The symptoms of its approach are a heaviness of the chest, sluggishness to one’s accustomed work and to every other exertion, difficulty in breathing on a steep road. . . But if the evil gradually get worse, a wheeze during the waking state, but the evil much worse in sleep, a desire of much and of cold air . . . they breathe standing as if desiring to draw all the air which they can possibly inhale and they also open the mouth . . . During the remissions, though they may walk erect, they bear the traces of the affection.

Claudius Galen (129-201 AD) of Pergamum systematised the ancient Greek ideas and his writings formed the basis of medical practice for the next millennium.

Medicine in ancient Rome was largely based on the Greek model. The first materia medica of the western world was that of Dioscorides, a Greek surgeon serving in the Emperor Nero’s army. Celsus in his De Medicina (30 AD) provided the following prescription for lung complaints [12], an example of the doctrine of similitude (like treating like):

It is not a foolish idea that the lung of a fox should be dried and powdered . . . or that the lung of that animal, as fresh as possible, roasted without touching iron in cooking, should be eaten.
Mediaeval and Arabic medicine

The decline and fall of the Roman empire (5th century AD) heralded the commencement of the so-called Dark Ages, when progress in medical ideas remained at a standstill until the Renaissance.

Arab physicians, exemplified by Avicenna (980–1037), incorporated alchemy and astrology into their medical practice. There were, however, some physicians of the period who adhered to Hippocratic concepts. The great Jewish physician Moses Maimonides (1130–1204) (Fig. 1) renowned also as theologian and philosopher, was born in Cordova, but persecution of the Jews in Spain led him to seek refuge in Egypt. He became physician to the court of the Sultan Saladin, whose son Almalik Alafdal was asthmatic. To advise the latter, Maimonides wrote his Treatise on asthma, (1190), the first work composed specifically on the subject. This book was written in Arabic (al-rabu is Arabic for asthma) and later translated into Hebrew and Latin. Maimonides’ concept of asthma was as confused as that of the Greeks before him but his advice to the prince was sound. Thus, he considered dry air advisable and therefore the prince should reside in Cairo in preference to Alexandria where the air was more humid; an even temper should be maintained and emotional turmoil (and sexual activity) avoided; hot chicken soup was a favoured remedy and he emphasised: ‘Sleep during an attack is harmful’ [13, 14].

15th and 16th centuries

The Renaissance provided a fresh impetus to medical thought in Europe. That extraordinary personality, Paracelsus (1493–1541) burned the works of Galen and Avicenna as a symbolic gesture of his break with the past. The discovery of America by Christopher Columbus in 1492 was followed by the introduction of new herbal remedies, described by Nicolas Monardes in his Joyfull Newes out of the new found world (1567) [15]. Thus, the dried root of the Brazilian shrub ipecacuanha (Cephaelis) came into use for its expectorant properties. Tobacco, originally introduced by Sir Walter Raleigh in 1559 for its medicinal properties, was recommended in respiratory ailments. Balsam of Peru and of Tolu are used to this day as constituents of cough medicines.

An historic case of asthma in the 16th century was that of John Hamilton, Archbishop of St Andrews, Scotland, a severe asthmatic, who was visited in 1547 by Geromo Cardano of Pavia, famous as a physician but also an astrologer, mathematician and philosopher. One of the features of the treatment which he recommended was the avoidance of feathers [16].

17th century

Many of the physicians who have contributed to our knowledge of asthma suffered from the disease themselves. Jean B. van Helmont, born in Brussels, became a disciple of Paracelsus and invented the term ‘gas’. He suffered from asthma, which he described as due to ‘a drawing together of the bronchi.’ He recognised the asthmatic diathesis and the individual sensitivities capable of provoking an asthmatic attack. In 1662 he wrote [17]:

A certain Monk . . . is busied in pulling down Houses or Temples. And forthwith, as oft as any Place is swept or the Wind doth otherwise stir up the Dust, he presently falls down almost choked . . . And while he eateth Fishes fried in Oyl he presently falls down, being deprived of Breathing, so that he is scarce distinguished from a Strangled Man.

Van Helmont compared the asthmatic attack to an epileptic fit (‘the Falling Sickness’) and continued: ‘We may therefore, by a Philosophical Liberty, name an Asthma “The Falling Sickness of the Lung”.’

Thomas Sydenham, the ‘English Hippocrates’, was called upon to advise on the asthma suffered by John Locke, famous as physician and philosopher. Sydenham’s prescription consisted of the traditional galenical remedies as well as bleeding and purging [18, 19].

The treatment offered by other practitioners of the period was often quite bizarre. ‘Drek-therapie’ (animal excrement), especially the dung of stallions, was popular for the treatment of asthma. The London Pharmacopeia, published by the College of Physicians in 1618, included prescriptions such as Lohoch e Pulmone Vulpis (linctus of
fox’s lung) similar to that recommended by Celsus fifteen hundred years earlier [20]. Some practitioners still employed astrology and that anti-establishment figure, Nicolas Culpepper, the bane of the College of Physicians, maintained that: ‘A physician without astrology is like a lamp without oil.’

An important milestone in the history of asthma was the demonstration by both Conrad V. Schneider in Germany in 1660 and Richard Lower in England in 1672 that the ancient Greek concept of catarrh having its origin in the brain was an anatomical impossibility [21, 22].

**Willis and Floyer**

Fresh light was thrown on the essential nature of asthma by the renowned Oxford physician Thomas Willis who wrote:

> Among the diseases whereby the Region of the breast is wont to be infested, if you regard their tyranny and cruelty, an Asthma doth not deserve the last place; for there is scarce anything more sharp and terrible than the fits hereof, the organs of breathing, and the Precordia themselves, which are the foundation and Pillars of Life, are shaken by this disease, as by an Earthquake . . . for breathing, whereby we chiefly live, is very much hindered by the assault of this disease, and is in danger, or runs the risk of being quite taken away.

Willis defined asthma as

> ... a difficult, frequent and pursie breathing, with a great shaking of the breast and for the most part without any fever.

He differentiated two varieties—the ‘pneumonick’ and the ‘convulsive’, the latter being of nervous origin due to

> ... cramps of the moving fibres of the bronchia and of the vessels of the lung, the diaphragm and muscles of the breast.

He ascribed nocturnal asthma to ‘the heat of the bed’ and advised sleeping on a chair. For convulsive asthma, he recommended antispasmodics (‘remedies against convulsions’) such as spirit of hartshorn, as well as sedatives (‘medicines which are used to be administered in hysterial passions do conduce in a convulsive asthma’). He nevertheless had little hesitation in also prescribing such archaic remedies as: ‘Powder of shells, millipedes prepared, spirit and volatile salts . . .’ [23].

A major step forward was taken by Sir John Floyer (Fig. 2), the Lichfield physician, author of A treatise of the asthma (1698), the first monograph on the subject in the English language. Floyer, himself an asthmatic, was the first to differentiate the condition clearly from other varieties of dyspnoea. He described two types of asthma: ‘continued’ and ‘periodic’ and of the latter he wrote:

> When the Muscles labour much for Inspiration and Expiration thro’ some Obstruction, or Compression of the Bronchia, etc. we properly call this a Difficulty of Breath, but if this Difficulty be by the Constriction of the Bronchia, ’tis properly the Periodic Asthma. And if the Constriction be great, it is with Wheezing; but if less, the Wheeziness is not so evident.

Floyer was the first to appreciate the importance of the expiratory component of bronchial constriction:

> The Muscles which serve for Expiration cannot easily perform the Contraction of the Thorax, being hindered in that by the Stiffness or Inflation of the Membranes in the Thorax: for though the Asthmatic expire more easily than they can draw in their Breath, yet the Expiration is very slow and leisurely and wheezing, and the Asthmatic can neither Cough, Sneeze, Spit or Speak freely; and in the Asthmatic Fit, the muscular fibres of the Bronchia and Vessels of the Lungs are contracted and that produces the Wheezing Noise, which is most observable in Expiration.

Floyer also recognised the several factors underlying the asthmatic state—heredity, weather and seasons, atmospheric pollution (including smoking of tobacco), occupational influences, infection, personal idiosyncracies, exercise and the emotions (‘the passions’). He tried all the galenical medicines then in vogue and found he derived most benefit from squill (Scillae) [24, 25].

**18th century**

The 18th century witnessed further significant develop-
ments. The importance of occupation was emphasised by the great Italian physician, Bernardino Ramazzini. He described [26, 27] asthma occurring in the handlers of old mattresses and dusty old clothes—with hindsight, these were probably infested with the house dust mite.

That colourful character Thomas Dover was not averse to prescribing dried toad in cases of asthma. Known as the ‘quicksilver doctor’ because of his advocacy of the use of mercury [28], he also favoured ipecacuanha (a constituent of Dover’s Powder) which had the unfortunate property of occasionally provoking asthma—the first example of an iatrogenic cause of the condition [28].

William Cullen, the great Edinburgh clinical teacher and founder of the Glasgow medical school, largely accepted the views of Willis and Floyer with regard to asthma [29] and defined asthma thus:

A difficulty of breathing, returning at intervals, with a sense of straitness in the breast, respiration performed with a wheezing noise at the beginning of a paroxysm, a distressing cough, sometimes more, but towards the end easy and free, often with a copious discharge of phlegm.

A further work on asthma appeared in 1769 by yet another asthmatic physician, John Millar, who had the distinction of being the first President of the Medical Society of London. His Observations on asthma and hooping cough (1769) unfortunately confused asthma in children with croup [30]. Robert Bree however produced a much more authoritative work on asthma [31]. A noted Birmingham physician, he too ‘suffered from the tyranny of asthma’, and gave a classic description of the asthmatic attack, although his definition was less precise than that of Floyer:

... an excessive contraction of the muscles of respiration, in breathing, without acute fever, excited by in some one of the viscera which these muscles serve.

Bree considered that ‘The asthmatic is ill calculated for Venereal Pleasures, however he may be permitted by sensation or taste to pursue this indulgence, Gratification not uncommonly excites the paroxysm.’ He used the remedies of his time but was also prepared to give a trial to the inhalation of ‘factitious gases’ (oxygen and carbon dioxide) then being advocated by Thomas Beddoes at his Pneumatick Institute in Bristol.

After William Withering published his masterpiece An account of the foxglove (1785) he was approached by the scientist Jean H. de Magellan for advice as to whether digitalis might help the latter’s asthma. In an unpublished, handwritten essay The spasmodic asthma (1786), Withering made no claim for digitalis in asthma but favoured exercise, long sea-voyages and strong coffee [32].

19th century

In 1808, Franz D. Reisseisen of Strasbourg demonstrated that the bronchial wall contained a distinct layer of muscle, which when it contracted, constricted the bronchial airways [33]. The brilliant French physician, Rene T. H. Laennec (Fig. 3), himself a sufferer from attacks of asthma which complicated his phthisis, clarified the nature and diagnosis of asthma by physical examination of the thorax, using the stethoscope which he invented in 1816. In his classic work, De l’Auscultation Mediate (1819), his definition of asthma was not too precise: ‘Le mot asthme signifie proprement difficulté de respirer.’ In the second edition (1826) however, by which time he had studied the French translation (1822) of Reisseisen’s work on the bronchial muscles, he was convinced that bronchial spasm was an essential feature of asthma [34, 35]:

On conçoit très bien que la contraction spasmodique de ces fibres puisse être portée assez loin pour étrangler les conduits aériens et empêcher la pénétration de l’air dans une grande partie des poumons.

Laennec’s clinical concept of bronchospasm was later confirmed experimentally by François Longet in 1842 and by Alfred Volkmann in 1844, who both demonstrated that stimulation of the vagus nerve produced bronchoconstriction [36, 37].

Another notable work on asthma was that by Francis Ramadge, physician to the Infirmary for Asthma, Consumption and other Diseases of the Chest, London (founded 1814). His Asthma, its species and complications (1835) demonstrated improved understanding of the nature of the condition, although his treatment still

Fig. 3. R. T. H. Laennec. From coloured engraving. (By courtesy of Wellcome Institute Library, London.)
included such remedies as spa therapy, galvanism and the inhalation of ‘factitious airs’ [38].

The greatest authority on asthma in Victorian England was Henry Salter (Fig. 4), physician to Charing Cross Hospital. He suffered from asthma and, based on his study of several hundreds of patients, he published in 1860 his magnum opus On asthma: its pathology and treatment. He defined asthma as ‘Paroxysmal dyspnoea of a peculiar character, generally periodic, with intervals of healthy respiration between the attacks.’ He recognised the idiosyncracy which some of his patients showed to emanations of hay and animals. He wrote: ‘One lady hardly dares to pass a poultry shop’. He reported the provocation of asthma by ipecacuanha and took full account of the influence of the emotions on the condition. He opposed the use of opiates since he believed that ‘sleep favours asthma’. It was for this reason that he employed hot strong black coffee to relieve an attack. He also recommended the use of belladonna as well as other medicaments then in vogue, such as stramonium, nitre, potassium iodide and lobelia [39, 40].

Another doctor-sufferer was the great French clinician, Armand Trouseau, who regarded asthma as a nervous disorder, which was not serious to life (‘Le brevet de longue vie’). He described the typical attack at 3.0 am and, although aware of his own sensitivity to the dust of oats, he noted that he suffered an especially severe attack in the barn when he witnessed his dishonest coachman stealing. A few puffs of tobacco usually served to relieve Trouseau’s asthma [41].

Charcot-Leyden crystals and Curschmann spirals

In 1853, Jean Charcot, the great neurologist at the Salpêtrière Hospital, Paris, together with his colleague, Charles-Philippe Robin, described the finding of characteristic crystals in the blood of a case of leukaemia as well as in the sputum of a bronchitic, but Charcot did not associate these crystals with asthma [42]. In 1871, Ernst von Leyden of Königsberg, together with Max Jaffe, noted similar crystals in the sputum of asthmatics [43]. These crystals came to be named Charcot-Leyden crystals and were thought by some to be the cause of the asthmatic attack. In 1882, Heinrich Gurschmann, then at Hamburg, described spiral mucoid casts in asthmatic sputum which he claimed were the cause of asthma [44]. Paul Ehrlich demonstrated the eosinophil in 1879 and this white blood cell was soon found to be a feature of the clinical pathology of asthmatics. In recent years, the close connection of the so-called ‘asthma crystals’ and eosinophils has been established but the presence of these crystals and spirals is no longer considered to be of great diagnostic or aetiological importance [45].

Allergy in asthma

The idiosyncracies of some asthmatics to various foreign substances had been observed for centuries. In 1547, Geromo Cardano advised the avoidance of feathers and in 1565 Leonardo Botalio described how the smelling of a rose could provoke respiratory catarrh (‘rose catarrh’) [46]. A similar condition was described in 1673 by Johann Binninger [47]. In 1662, van Helmont recorded the case of a monk whose asthmatic attacks occurred on eating fish and in 1700 Ramazzini related how workers handling old mattresses were similarly affected. Thomas Wither, in 1786, again drew attention to feather beds being a cause of asthma [48].

The first clear description of seasonal hayfever and asthma was by John Bostock, physician to Guy’s Hospital, who wrote two papers on the subject of ‘a periodic affection of the eyes and chest’ which he later designated ‘Catarrhus Aestivus’ or summer catarrh. Bostock suffered from the condition himself but also described 28 other cases [49, 50].

In 1831, John Elliotson, Professor of Medicine at University College, London, gave a classic description of seasonal hayfever and asthma and suggested that exposure to pollen might be the cause in one case and contact with a rabbit in another [51]. In 1873, Charles Blackley, a Manchester physician, found that the application of grass pollen to the conjunctiva or a skin scratch in hayfever patients produced a local reaction [52]. That this was not merely a mechanical effect was proved in 1903 by William Dunbar of Hamburg, who produced the same phenomenon, using a soluble extract of pollen (pollatin) [53]. In the USA ‘autumn catarrh’ was de-
scribed in 1872 by Morill Wyman of Harvard and shown to be related to the pollen of ragweed [54]. The term ‘allergy’ was coined in 1906 by Clement von Pirquet of Berlin, based on his research (together with Bela Schick) on serum sickness [55]. The derivation from the Greek ‘alloς’ (meaning ‘other’) indicated the altered reaction to a foreign substance after previous sensitisation. In 1907, von Pirquet introduced the tuberculin test, which he considered to be based on this concept.

In 1902, the phenomenon of anaphylaxis was described by Charles Richet, Professor of Physiology in Paris, working together with Paul Portier and based on their canine experiments using injections of extracts of Portuguese Man of War and sea anemones [56]. This was followed in 1906 by Alfred Wolff-Eisner’s suggestion that hayfever was an anaphylactic phenomenon [57] and in 1910 by Samuel Meltzer of New York, who showed that asthma had a similar pathogenesis [58]. Asthma now came to be classified among the allergic diseases.

In 1911, Leonard Noon of St Mary’s Hospital, London, introduced specific allergy skin testing, using an extract of grass pollen. The amount of pollen ‘toxin’ extracted from one millionth gram of Timothy Grass pollen was designated the Noon unit [59]. Skin allergy testing and attempts at hyposensitisation by means of a specific vaccine were now pursued, notably by John Freeman [60], also at St Mary’s Hospital, London, and, in the USA, by Robert Anderson Cooke [61]. During the past half century, skin allergy testing and specific vaccine therapy have become more sophisticated, using purer extracts of allergens of every variety.

In 1967, Reindert Voorhorst and his colleagues in Leiden, drew attention to the importance of allergy to the house dust mite (Dermatophagoides pteronyssinus) in asthma [62]. Also in 1967, Kimshige and Teruko Ishizaka identified immunoglobulin gamma E (IgE) as the carrier of reagin, in the serum of asthmatics [63].

Although the importance of allergy in asthma cannot be denied, it must be conceded that attempts at hyposensitisation have been successful in a relatively small proportion of cases.

In 1910, Sir Henry Dale and Sir Patrick Laidlaw, in the course of their research on ergot poisoning, discovered histamine [64]. The theory that histamine was involved in the anaphylactic phenomenon raised hopes that an antagonist to its action might be therapeutic in allergic states. An antihistamine was first synthesised in 1933/37 by Daniel Bovet and his colleagues in Switzerland [65] and was first tried clinically in asthma in 1942 by Bernard Halpern in Paris [66]. Although antihistamines have proved useful in the treatment of hayfever, they are less effective in asthma.

**Respiratory function tests in asthma**

The invention of the spirometer in 1846 by John Hutchinson was an important development in the investigation and management of respiratory disorders [67]. In the 1950s, the vitalograph came into general clinical use and provided a useful means of monitoring expiratory airways obstruction.

In 1959, Martin Wright of the National Institute for Medical Research, England, together with C.B. McKerrow, introduced the peak expiratory airflow meter, which had the advantage of being small and easily portable, enabling a simple measurement to be made by which the asthmatic state could be assessed objectively [68]. A later development was the ‘mini’ peak flow meter which has provided the patient with a simple means of self-monitoring his or her asthmatic condition.

The fresh light shed by these new tools of respiratory measurement has led to attempts, in recent times, to redefine asthma. In 1971, a Ciba Foundation Study Group considered asthma to be essentially a disease characterised by variability in air flow resistance, a definition which did not satisfy the purists. The situation may be summed up by the title of a recent American article [69]:

*What is this thing called love?—or asthma defined.*

We all know what love is, even though we may not be able to provide a scientific definition of the phenomenon. So it is with asthma.

**Part II**

**Development of modern drug therapy of asthma**

**Anticholinergics**

Ayurvedic medicine included in its materia medica the solanaceous plant *Nardostachys jatamansi* (datura) which was prescribed as a relaxant in conditions such as epilepsy or mania. The root of *Datura ferox* was smoked in a pipe for the relief of asthma. In 1802, Dr Anderson, Physician-General of Madras, confirmed the beneficial effect on himself and then presented a specimen to General Gent. He offered it for trial to Dr Sims of Edinburgh, who found it a useful remedy in asthma but substituted the British variety of the plant *Datura stramonii* (thorn apple). Following the publication of his experiences in 1812 [70] stramonium was soon on sale in the London apothecaries shops and was widely adopted as an anti-asthma remedy, being smoked like tobacco or taken internally. The popular ‘Potter’s Asthma Cure’ contained stramonium. Subsequent experiments showed that datura acted by abolishing the effect of the vagal influence on the bronchi.

Another solanaceous plant, *Atropa belladonna* (deadly nightshade), a native of Central and South Europe, was used at the end of the 18th century as a treatment for whooping cough. In 1833, atropine was isolated by Philipp Lorenz Geiger and Hermann Hesse [71]. Henry Salter reported on the successful use of belladonna in asthma in 1869 [72]. Thereafter, belladonna or atropine, administered internally, by nasal spray or by smoking, became standard remedies for the relief of asthma. Their adverse effects led to their falling out of favour but in recent years there had been a renewal of interest and new derivatives such as ipratropium, delivered by metered aerosol, are now frequently prescribed.
Smoking and inhalers in asthma

From ancient times, the inhalation of medicated smoke or steam has been employed for the relief of asthma. In ancient Egypt, henbane (Hyoscyamus) was placed on heated bricks and the emanation inhaled.

When tobacco was first introduced into Europe in the 16th century it was smoked for medicinal purposes. Tobacco smoking then developed as a social habit but there were still those who were convinced that smoking tobacco relieved asthma.

Other medicaments were incorporated with the tobacco, in cigarettes, cigars and pipes. Thus, in the 19th century, stramonium cigarettes became popular. Brands included Grimaud’s (combined with cannabis), Cigarettes de Joly (with arsenic), Marshall’s (with culebs), Crevoisier’s (with foxglove) and Savory & Moore’s (with camphor). A popular pipe was ‘Maxim’s pipe of peace’ [73].

The other medicaments prepared as cigarettes included belladonna or atropine, hyoscyamus, aniseed, amber and nitre. In the latter, paper was previously impregnated with nitre (potassium nitrate) and on burning was converted to nitrite, which exercised an anti-spasmodic action on the bronchi.

Adrenergics (sympathomimetics)

The demonstration in 1895 by Sir Edward Sharpey-Schäfer and Sir George Oliver that a powerful blood-pressure elevating substance could be extracted from the adrenal gland [74] opened a new chapter in the pharmacological approach to the treatment of asthma. In 1900, Solomon Solis-Cohen, Professor of Medicine in Philadelphia, was the first to use this relatively crude ‘adrenal substance’ in hayfever and asthma [75]. The pure hormone adrenaline (epinephrine) was extracted from the adrenal gland by Jokichi Takamine [76] and, quite independently, by Thomas B. Aldrich [77], both in 1901. Adrenaline was synthesised by Friedrich Stolz in 1904 [78]. In 1903, Jesse Bullowa and David Kaplan reported the first successful use of adrenaline in asthma [79].

Adrenaline was soon in regular use in the treatment of asthma, given by injection, the intravenous route being reserved for emergencies. The first use of adrenaline for asthma by inhaler was reported in 1929 by Percy Camps at Guy’s Hospital [80]. Combinations of adrenaline, atropine and papaverine (Broyan) or of adrenaline and stramonium were in frequent use, but unfortunately adrenaline possessed cardiotoxic properties.

Ma huang (Ephedra sinica) had been known to the Chinese since ancient times. In 1887, Nagai Nagayasi extracted its active principle, which was named ephedrine [81]. Its pharmacology was worked out in Japan in 1917 by Imatsu and Kuboda who showed it to have an adrenaline-like action [82]. Ephedrine was introduced to the West following the report by Ka Kuei Chen and Carl F. Schmidt [83] and was universally adopted as a treatment for asthma, being administered by mouth or by inhalation.

Modification of these adrenergic drugs followed—iso-

propyl adrenaline (aleudrine) in 1903 and isoprenaline in 1948. The problem of how to administer a metered dose of a bronchodilator such as isoprenaline by inhalation was solved in 1956 by an American engineer, Philip Maschberg, who devised a special valve allowing a metered dose of aerosol to be self-administered by the patient. The device proved effective but unfortunately excessive use by patients led to cardiotoxic complications which were often fatal. During the 1960s, there was an alarming rise in deaths from asthma [84].

This problem was tackled by the development of a new generation of adrenergic bronchodilator drugs, which aimed to be broncho-selective and less dangerous to the heart. In 1948, R. P. Ahlquist had distinguished α and β receptors [85]. The β receptors were in 1967 sub-divided into β₁ and β₂ by A. M. Lands and his colleagues [86]. The new family of adrenergic bronchodilator drugs (e.g., salbutamol and terbutaline) are now in common use and are considered to be less cardiotoxic because of their selective β₂ effect.

Methyl xanithines

The drinking of coffee to relieve asthma had been recommended by Floyer, Withering, Bree, Laennec, Trouseau and Salter.

The active agent in coffee is caffeine (trimethyl xanthine) which was synthesised by Adolph von Streecker in 1861 [87]. Theophylline (dimethyl xanthine) was isolated from cocoa (Theobromine caaco) in 1888 by Albrecht Kossel and synthesised in 1895 [88]. A disadvantage of theophylline was its insolubility and tendency to be emetic. In 1908, P. Dessauer produced a derivative, aminophylline, which had the advantage of being soluble and therefore more suitable for administration by injection [89].

The bronchodilator effect of the methyl xanthines was demonstrated in 1921 by D. I. Macht and G. C. Ting [90]. Theophylline was first used in asthma in 1922 by S. Hirsch [91] and aminophylline in 1944. The methyl xanthines proved to be a useful addition to the medical armamentarium against asthma. Modern preparations and monitoring of blood levels have led to a revival of interest in their use [92].

Cromoglycates

It had been known for centuries that the seeds of the East Mediterranean plant, Ammi visnaga, possessed the property of relaxing spasm in cardiac, bronchial and intestinal conditions. Its active principle, khellin, was investigated as a treatment for angina in 1947 by G. V. Anrep and his colleagues [93], but was found to be an emetic when taken orally. In 1967 J. S. G. Cox studied the pharmacology of khellin, from which a cromone, disodium cromoglycate (FPL 670) was derived and synthesised [94]. This substance was insoluble and a special device (spin-haler) was devised to enable the inhalation of the powdered drug. Roger Altounyan, himself an asthmatic, carried out clinical trials and disodium cromoglycate was shown to be
non-toxic and effective as a prophylactic, especially of the allergic and exercise-induced varieties of asthma [95]. Later an oral preparation and an aerosol were introduced.

Corticosteroids

In 1936, Edward Kendall, working at the Mayo Clinic, extracted Compound E from the adrenal cortex [96]. It was renamed cortisone in 1939 and in 1948 Philip Hench carried out the first clinical trial of cortisone in rheumatoid arthritis [97]. Its dramatic effect in this disease was followed by its administration in asthma and by 1950 Haydon Carryer and others were able to report its successful use in that condition [98]. In 1951, M. L. Gelland described the use of cortisone administered as an aerosol [99] and in 1954 prednisone and hydrocortisone were introduced and corticosteroids now became a standard treatment of asthma. Beclohexasone, introduced in 1969, was originally intended for topical use in skin diseases but was adapted for administration as an aerosol and now plays an important part in the treatment of asthma.

The FitzPatrick Lecture concluded with a recording of Allemande l’Asthmatique (Pièces à une et à trois violons, 1717, Book IV, No. 70) composed by Marin Marais (1656-1728), bass viol player at the court of Louis XIV of France.

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