

THE HISTORY OF ASTHMA FROM HIPPOCRATES TO MELTZER

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THE Greek word *ασθμα*, used by Hippocrates and Aretaeus, meant "panting,"¹ but the term also implied an attending noise or sound and the condition was considered more severe than dyspnea and less severe than orthopnea.² Furthermore, the ancients, like those of us today, spoke of asthma as being spasmodic or paroxysmal in nature, and, unlike some of the dogmatic moderns, held that between paroxysms breathing was still difficult and distressing.²

Hippocrates (460 to 370 B.C.) (Fig. 1), who freed internal medicine from the bonds of superstition and saw in disease a natural process that developed in logical steps like a Greek play, mentioned asthma only infrequently but did inculpate cold and moisture as its principal causes.²

While the Greeks were discarding magic and superstition and incorporating scientific spirit and ethical ideals into medicine, Roman medicine was overrun with magicians, nostrum venders, and charlatans. With the destruction of the ancient Greek city of Corinth (146 B.C.), celebrated for its artistic elegance, luxury, and licentiousness, Greek medicine migrated west and into Rome. Although hindered by the aphorisms of the elder Pliny, who claimed that Rome had gotten on successfully for 600 years without doctors, Aesclepiades finally established Greek medicine on a respectable footing there, and Galen (A.D. 131 to 201), although a Greek, became her most illustrious physician.³

Galen (Fig. 2), who wrote in Greek, did not use the word *ασθμα* as had Hippocrates before and Aretaeus a little later. To him, the terms *asthma* and *dyspnea* were the same, and the words described any kind of difficult breathing.² The concept of spasmodic nature was lost. Galen, a theorist, may still be considered the founder of experimental physiology, and he is said to have produced asthma by severing the spinal cord²—which only means that he produced some type of a difficulty in breathing by the procedure.

Aretaeus (second to third century A.D.), who came nearer to the spirit and methods of Hippocrates than Galen, was to live in oblivion until his Greek manuscript was discovered and published at Paris in 1554. In this work, asthma was vividly described in two forms: (1) as a difficulty in breathing produced

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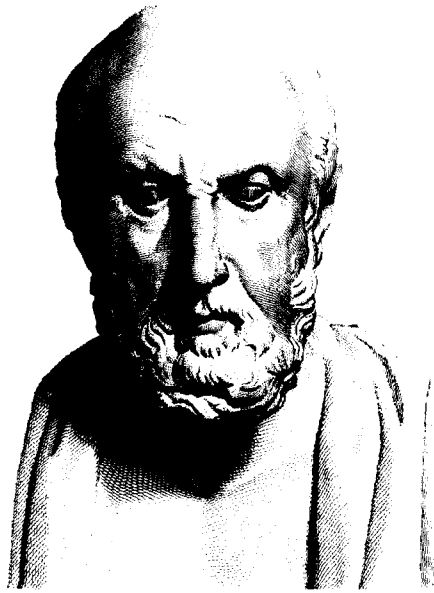


Fig. 1.—Hippocrates (460 to 370 B.C.) incriminated cold and moisture as principal causes of asthma.

by running, and (2) as a spasmodic difficulty in breathing caused by cold and humid air.²

Galen and Aretaeus gave ancient medicine a spectacular finale just before Western civilization faded into the darkness of the Middle Ages.

After centuries came a light, generated from a wave of terror out of the East. In the one hundred years after Mohammed's death (A.D. 632), his turbaned horsemen fanned out across three continents, and in the end the great Arabian empire was split into Caliphates, with Bagdad and Cordova as the eastern and western capitals. During the years of plundering, purloined Greek manuscripts bearing the medical wisdom of Hippocrates and Galen reached Bagdad and Cordova by camel and ship, and the Moslems became the purveyors of classic medicine.

In Cordova, the Jewish scholar and physician Moses Maimonides was born and lived until he fled to escape religious persecution. His life was devoted to instilling a sense of science and philosophy into Jewish culture, which had been wholly dependent on the teachings of the Talmud. He became physician to the great Saladin and later treated Saladin's successor for asthma. As a result of his experiences with the disease of this patient, he wrote in Arabic his treatise on asthma.³

For the most part the Jews lived peaceful and productive lives in Arabian society, and the caliphs soon recognized and encouraged the linguistic aptitudes of Jewish scholars. Consequently, the classics of medicine which had been translated from Greek into Arabic were rendered finally into Hebrew and Latin. Jewish physicians brought these translations to Central Europe and thereby exercised a growing influence on medicine.



Fig. 2.—Galen (A.D. 131 to 201) is said to have produced asthma by severing the spinal cord. The words *asthma* and *dyspnea* did not differ in meaning to him.

In this manner, medicine moved west, and the new school at Salerno wrested leadership from the Arabs so that once again the spirit of Hippocrates inspired physicians to concentrate upon patients and bedside observation. But the spirit soon departed and darkness descended again.

For four-hundred years the study of asthma, with the science of medicine, was stifled by feudalism and ecclesiasticism. Bigotry, pedantry, and cruelty were rampant, and truth was suppressed by overbearing and underhanded methods. Yet, the governed consented; and so man was shackled until he once more began to contemplate himself and the universe. This was the beginning of the Renaissance.

Closely associated with and just preceding the Renaissance, the English adopted from the Greek word for asthma two words of their own, *asma* and *asmy* (A.D. 1400). As far as one can ascertain, these English words retained the meaning of the Greek word as it was used by Hippocrates. But in A.D. 1600,



Fig. 3. Gerolamo Cardano (1501 to 1576) treated asthma successfully by substituting a bed of unspun silk for one of feathers.

the English word began to appear as *asthma* and in A.D. 1700 as *astma*.¹ There have been no further alterations, and during the present and last centuries we have settled upon *asthma*, although I must admit that *asmy* has a certain native and homey charm.

In 1443, fourteen centuries after Aurelius Cornelius Celsus had compiled his encyclopedia of medicine, Pope Nicholas V found his heretofore misplaced manuscript and had it printed at Florence in 1478.² *De re Medicina* was one of the first medical books printed, and its date of publishing is a good choice to mark the beginning of the medical Renaissance.

For us, the first Renaissance physician of significance was Gerolamo Cardano (A.D. 1501 to 1576) (Fig. 3). A mathematician as well as physician, he was called from Italy to Edinburgh to treat John Hamilton, Archbishop of St. Andrews. For six weeks Cardano studied the Archbishop before diagnosing the ailment as asthma. His therapeutic regimen included diet, exercise, purging to decrease the cough-producing secretion of mucus (then called pituita) in the throat, and the substitution of a bed of unspun silk for one of feathers. Happily for Cardano, John Hamilton recovered, but only to live long enough to be hanged by the Scotch Reformers.³

While all of this was taking place, William Harvey was studying the circulation of the blood, and across the channel in Belgium another and different sort of student was trying to explain complex problems of the body's activity through the study of chemistry. This man was Jean Baptiste van Helmont (1577 to 1644) (Fig. 4), founder of the iatrochemical school and a sufferer from asthma. He indicted the bronchi as the seat of asthma, and, according to Osler, also had some notion of immunity.⁴ Equally astonishing for a seventeenth century scientist, he described attacks of asthma produced by inhaling house dust and eating fish.⁵



Fig. 4.—Jean Baptisti van Helmont (1577 to 1644) indicted the bronchi as the seat of asthma; he may have had some notion of the mechanism of immunity.



Fig. 5.—Thomas Willis (1621 to 1675) considered that certain persons were predisposed to asthma.



Fig. 6.—Giovanni Battista Morgagni (1682 to 1771) pointed out that anatomical obstructions in the bronchi could cause asthma.

Van Helmont gave physiologic chemistry many fanciful trappings, and Thomas Willis (1621 to 1675) (Fig. 5), along with his teacher Franciscus Sylvius, did much to divest it of them. Willis, who is credited with the discovery of diabetes mellitus, considered that persons were predisposed to asthma, and from this we might assume that he intimated a hereditary tendency.²

With the entrance of Sir John Floyer (1649 to 1754) into the world of science, we approach the age of investigation. From Hippocrates to John Hunter (1750) there had been a long traffic in hypotheses (Osler).³ Floyer, himself an asthma sufferer, recorded the first anatomical account of emphysema in a mare with the heaves.² He distinguished asthma from emphysema and theorized that asthma was caused by a contraction of the bronchial muscle fibers.

Up to this time asthma was believed to originate in the bronchi and to result from their contracture. A word of warning was voiced by Giovanni Battista Morgagni (1682 to 1771) (Fig. 6), the pupil of Valsalva and the father of pathologic anatomy. He pointed out that anatomical obstructions in the bronchi could cause asthma, and he criticized the physicians for being deceived by the doctrines of Willis, who taught that all asthma was convulsive and of nervous origin.²

Like Willis, William Cullen (1710 to 1790) (Fig. 7), who was the first to lecture in the vernacular of England instead of in Latin, attached great importance to the influence of the nervous system in producing asthma. And like Floyer, he regarded spasmodic asthma as caused by bronchial constriction.²

Tools were needed to develop a system of diagnosis, and a French internist, seven years before his death from tuberculosis, was to become immortal. René-Theophile-Hyacinthe Laennec (1781 to 1826) made a paper cylinder. This paper cylinder, which he used to connect the ear of the examiner with the patient's



Fig. 7.—William Cullen (1719 to 1790) regarded asthma as the result of bronchial constriction.

chest, was described by him as an instrument for mediate auscultation. With this system, he gave to internists their hallmark—the stethoscope—and especially to those of us here, the names *sibilant* and *sonorous* for those beautiful piping and whistling rales that since have played a perennial and intimate role in our lives.^{3, 7}

Then the embryonic scientific world was taken by surprise. Francois Magendi (1783 to 1855), the scientific ragpicker, founder of experimental pharmacology and protagonist of experimentation on living animals, described in 1839 sudden death in dogs from repeated injections of egg albumin.⁶ This observation was to be disregarded for more than fifty years.

Observation and experimentation were coupled together firmly now and were making exciting discoveries. In 1840, an Englishman, C. J. B. Williams (1805 to 1889), placed a brass cannula in the trachea of dead animals and fitted a large sheet electrode around the lower margins of their lungs. As a current from a large battery coursed through the lungs, the bronchi constricted. This was the first investigation of the action of the vagus upon the musculature of the bronchial tree.⁸ Albert von Kölliker (1817 to 1905) (Fig. 8), the most distinguished histologist of the early modern period, demonstrated the presence of muscular fibers in both the large and small bronchi.² Henry Hyde Salter (1823 to 1871) emphasized the importance of a hereditary tendency in asthma and was the first to recognize the distinction between spasmodic and cardiac asthma.² Johann Heinrich Kopp (1777 to 1858) observed patients with sudden inspiratory spasm associated with cyanosis and a crowing sound, and unfortunately this syndrome of laryngeal spasm was earmarked as Kopp's asthma! The same Kopp used the term *thymic asthma* to describe the symptoms resulting from tracheal obstruction due to an enlarged thymus.² Ludwig Traube (1818



Fig. 8. Albert von Köhliker (1817 to 1905) demonstrated the presence of muscular fibers in both the large and small bronchi.²

to 1876), a pupil of Purkinje and an assistant of Schönlein, contended that edema of the bronchial mucous membranes was important as a cause of asthma.²

This was an era of earnestness and thoroughness. Nothing escaped examination, not even sputum, and one of Traube's pupils, Ernst von Leyden (1832 to 1910) (Fig. 9), found octahedral crystals in the sputa of asthma victims. But because Chareot had earlier described crystals in the spleen and blood of a leukemic patient, we have acknowledged his priority in observation by naming them Chareot-Leyden crystals.² Leyden theorized that the crystals provoked spasm of the bronchial musculature by mechanical and chemical irritation. In Leipzig, a physician named Heinrich Curschmann (1846 to 1910) observed that the sputa from patients with chronically recurring bronchiolitis complicated with asthma contained taut, rope-like strands of mucus; these we fondly speak of as spirals.³

Medicine, a vast structure, had much added to its foundations in the Eighteenth and Nineteenth Centuries. But a Gargantuan growth lay ahead in the Twentieth Century, and, although the story of asthma is a modicum of that of medicine, the profusion of names and the plethora of discoveries make of its telling an enormous task. It is therefore prudent to decide upon a terminus for this narrative, for which I have selected Samuel J. Meltzer's interpretation of the asthmatic paroxysm. The people and their discoveries that had bearing on this important concept must be mentioned.

At Leyden there was a young professor of physiology who was later to invent the string galvanometer. This man, Willem Einthoven (1860 to 1927), stimulated the peripheral end of the vagus nerves and caused a stenosis of the bronchi that was due exclusively to muscular contraction and not to mucosal edema.³ In the same year, Samuel Siegfried Karl von Basch (1837 to 1905),



Fig. 9.—Ernst von Leyden (1832 to 1910) found octahedral crystals in the sputa of asthma sufferers.

who had returned to Vienna after service in Mexico as personal physician to the unfortunate Maximilian,⁵ contended that bronchostenosis was caused by vascular changes in the bronchi.¹⁰ The year was 1892 and, across the Atlantic Ocean, America was beginning to feel the impact of European medicine.

Meanwhile, in 1890, Simon Flexner (1863 to 1946) (Fig. 10) arrived in Baltimore from his home in Louisville to work as a graduate student under William H. Welch in the new medical school that had been named after its benefactor, Johns Hopkins.¹¹ In 1894, Flexner injected rabbits with dog serum and described the symptoms of what would later be called anaphylaxis.¹²

Eight years thereafter, the French physiologist Charles Richet (1850 to 1935) (Fig. 11) injected the poison of the actinia into dogs and, after observing the reactions, reported that there were two different substances contained in this poison, one involved in establishing an immunity, the other eliciting hypersensitivity. The concept of anaphylaxis, which Richet sharply separated from that of immunity, has been maintained.¹³ It was to his publication that our English word *anaphylaxis* owes its origin.

At the instigation of Richet, Maurice Arthus (1867 to 1945) undertook similar experiments with horse serum in rabbits. It was found that a first injection of the apparently harmless substance so changed the organism that repeated injections of it caused severe tissue damage.¹⁴ Since 1903 we have called this kind of hypersensitivity the Arthus phenomenon.

As of then there were anaphylaxis and the Arthus phenomenon distinguished from immunity. Then, in 1906, an Austrian pediatrician, Clemens Freiherr von Pirquet (1874 to 1929), published a paper entitled "Allergie."¹⁵ The English word as we know it today was quickly adapted from the German, but it was not until 1913 that "allergy" was officially accepted in our lexicon.¹



Fig. 10. - Simon Flexner (1863 to 1929), who, along Jeremias, in rabbits and observed the signs and symptoms that were to be known later as anaphylaxis.

Now there were immunity, anaphylaxis, Arthus phenomenon, and allergy. And, of course, there were also two theories regarding the nature of the origin of bronchostenosis in asthma. One assumed that the stenosis was due to mucosal edema (von Basch) and the other, more popular, that stenosis was the result of contraction of bronchial musculature (Einthoven). Thus, the stage was set and onto it walked Samuel J. Meltzer (1851 to 1920) (Fig. 12).

This remarkable man, who was instrumental in the founding of the Harvey Society, the Society for Experimental Biology and Medicine, and the American Society for Clinical Investigation, emigrated to New York City in 1883.¹⁶ There he practiced medicine, worked with William H. Welch in the pathology laboratory of the Bellevue Hospital, and in 1904, at the request of Simon Flexner, became the head of the Division of Physiology at the Rockefeller Institute. He was then 53 years old.

In Meltzer's laboratory were two young men, John Auer and Paul A. Lewis, who were to play important roles in the development of Meltzer's concept. In 1910 the *Journal of Experimental Medicine*, whose guardianship Welch had transferred from Johns Hopkins to the Rockefeller Institute, published their studies that established bronchiolar stenosis as the principal manifestation of anaphylaxis in the guinea pig.¹⁷ That same year, Samuel J. Meltzer went to Washington, D. C., to speak before the twenty-fifth meeting of the Association of American Physicians, and it was there on May 4 that he interpreted the asthmatic paroxysm in the human as a phenomenon of anaphylaxis.¹⁸

A new gigantic and colossal era was in the making. Young men found themselves in possession of well-equipped laboratories and the challenge to put their increasing opportunities to good use. It was not enough to develop fundamental knowledge; the medical profession had to be convinced that facts

could only be established by use of scientific techniques. The profession needed a drastic upgrading of standards, and Samuel J. Meltzer, among others, dedicated himself to this task. In a way, all of us in this room are products of the effectiveness of that movement. Through the years our heritage has gained in stature and splendor, and we are obligated to maintain the momentum of scientific progress.



Fig. 11.—Charles Richet (1850 to 1935) sharply differentiated anaphylaxis, which he described, from immunity.



Fig. 12.—Samuel J. Meltzer (1851 to 1920) interpreted the asthmatic paroxysm in the human as a phenomenon of anaphylaxis.

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