HISTORICAL ARTICLE

Evarts Ambrose Graham, Empyema, and the Dawn of Clinical Understanding of Negative Intrapleural Pressure

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The concept of negative intrapleural pressure is fairly new. Although the phenomenon had already been described, Wirz provided the first definitive analysis of its significance to the mechanics of breathing in 1923. By contrast, empyema has been known since antiquity; from the time of Hippocrates, treatment has consisted of open drainage. Open drainage was often successful and did not result in pneumothorax, because most cases of empyema were associated with adhesions and thickened visceral pleura that prevented the lung from collapsing. The epidemic of group A streptococcal pneumonia in military camps in 1917–1918 was associated with the rapid and early accumulation of empyema fluid and was the catalyst for renewed study of empyema. Use of open drainage to manage this illness resulted in a high immediate mortality rate, probably because patients developed pneumothorax. The work of Evarts Graham and the Empyema Commission married physiological understanding of pleural mechanics with rational clinical treatment and paved the way for further advances in thoracic surgery.

The influenza pandemics of 1917 and 1918 caused 21 million deaths worldwide; in the United States alone, there were more than half a million deaths. The United States had just entered World War I, and in the crowded barracks of US military camps, influenza took a heavy toll. Soldiers with influenza frequently developed bacterial pneumonia caused by what was then termed "hemolytic streptococci"—what we now know as group A streptococci. One striking feature of hemolytic streptococcal pneumonia was the rapid, almost concurrent development of a hemorrhagic pleural effusion progressing to empyema; when this complication occurred, the mortality rate was very high [1–8]. According to Edward Churchill [9], "The streptococcal pneumonia and empyema which accompanied the influenza epidemic was a new disease….Early evacuation was a dogma of surgery of the period….The operation was rib resection with open tube drainage. Death occurred quite frequently about half an hour after the operation" (p. 288).

In early 1918, the Surgeon General established an Empyema Commission to address this new and unique problem. The high mortality rate associated with empyema in American soldiers made it urgent for there to be a clear consensus on treatment of this disease.

Few modern-day students who encounter a patient with a chest tube connected to underwater seal drainage realize how recent is our understanding of the dynamics of the pleural space and how much we owe to the work of the Empyema Commission. The Commission's findings are most closely associated with the name of Evarts Ambrose Graham (figure 1), a captain in the Army Medical Corps who was appointed to the Empyema Commission and assigned to Camp Lee near Petersburg, Virginia. Here, we describe the evolution of clinical and physiological concepts concerning the pleural space and empyema. Graham's former student, Lord Russell Brock, commented that "[Graham's] first major contribution to surgery resulted from his appointment

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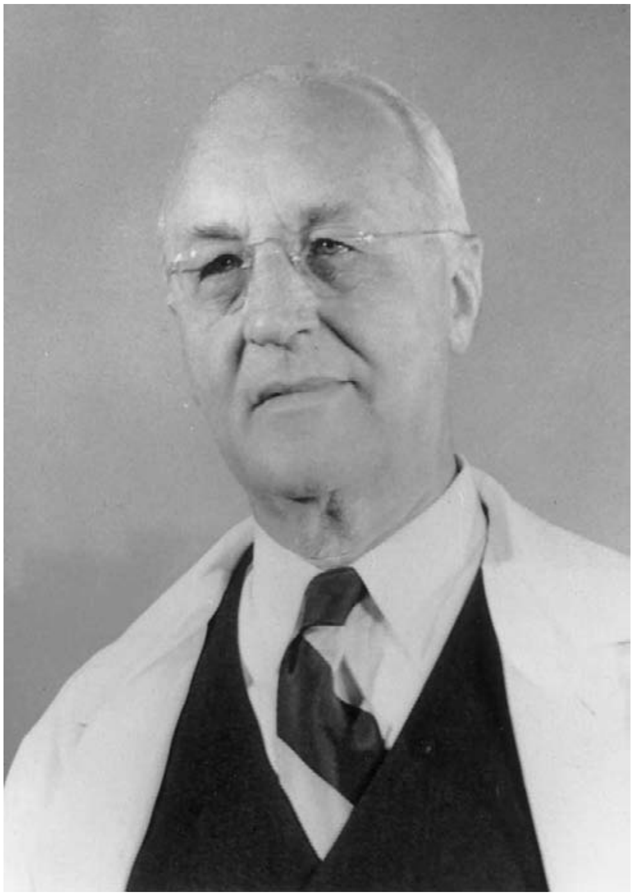

Figure 1. Evarts Graham. From the collection of the Becker Medical Library, Washington University School of Medicine.

to the United States Army Empyema Commission….No thoracic surgeon's training should be considered complete if he is not familiar with the Commission's observations and conclusions" (p. 273) [10]. A fortunate twist of fate brought Graham, a man who was uniquely prepared to undertake rigorous scientific inquiry, to the study of empyema, a disease that was complex and politically touchy. One wonders how both the man and the disease would have fared had their paths not crossed.

BACKGROUND

The fact that air moves in through the nose and mouth in response to muscular effort must have been a fairly early physiological observation. But the task of establishing the precise historical evolution of concepts of respiratory mechanics is difficult; the topic has been reviewed excellently by Otis [11] and Perkins [12]. Erasistrasus (born circa 304 B.C.) is generally given credit for recognizing the diaphragm as the muscle of breathing. Galen observed that the intercostal muscles were also important and worked with the diaphragm. Around 1640, Giovanni Borelli discovered that atmospheric pressure carried air into the lung as the chest expanded. In 1674, John Mayow, an Englishman, first produced an elegant model of breathing by enclosing a balloon within a bellows, with the mouth of the balloon being open to the outside. The bellows had a window through which the balloon could be seen. On expansion of the bellows, the passive expansion of the balloon by air rushing in through its mouth could be observed.

Ludwig first made graphic recordings of intrapleural pressure in 1847 by use of a water-filled balloon placed in the pleural space and connected to a mercury manometer. Aron reported the first measurement of intrapleural pressure in a healthy human in 1900. Meanwhile, in the clinical arena, surgeons continued to be limited in their ability to operate on intrathoracic structures because of the immediate development of pneumothorax. As Ferdinand Sauerbruch wrote in his autobiography [13], "The decreased air pressure in the chest was a vital necessity to life. Lung and thoracic wall had to remain in intimate adhesive contact, like two superimposed panes of polished glass, if respiration were to be maintained. The movements of the thoracic cage demanded an elastic lung, and by adhesive force the lung followed the movement of the ribs. And with that realization, all became suddenly clear: surely, the technical potentialities of our time made it possible to create conditions in which the thoracic wall could be opened in an atmospheric pressure that approached the reduced pressure within the thoracic cavity" (p. 40). In 1904, Sauerbruch, working with von Mikulicz, built a low-pressure chamber within which the chest might be safely opened [14]. The anesthetist and the patient's head were outside the chamber, whereas the surgeon and the patient's trunk were in the chamber, which was then made subatmospheric by use of a pump. By use of this cumbersome contraption (which would eventually be replaced by endotracheal intubation and positive-pressure ventilation), surgeons were able to operate on the esophagus, the lungs, and even the heart. Still, it was only in 1923 that the physiologist Wirz provided a thorough analysis of negative pleural pressure and its significance to the mechanics of breathing [11]. When Graham embarked on his work with the Empyema Commission in 1918, the concept of negative intrapleural pressure was known, but the nuances were not widely understood by clinicians.

The clinical condition of empyema, by contrast, has been recognized since antiquity. Hippocrates first described the drainage of patients with empyema more than 2000 years ago. He taught that adequate drainage, done by either an intercostal incision or rib resection, was necessary. The magnitude of Hippocrates's contribution to the understanding of empyema is underscored by the fact that few true advances were made in either the diagnosis or treatment of this entity for the next 2 millennia [15, 16]. Roe, in Britain, and Stokes, an Irish physician, first advocated repeated aspirations of empyema collections in 1844. In the late 1800s, Hewitt and von Bulau independently described closed-drainage by underwater seal, with irrigation and sterilization of the pleural space. Although insightful, the methods were nevertheless variations on the principles laid out by Hippocrates [15]. The problem of pneumothorax that complicated surgery on the thorax was not usually a problem with empyema, because the thickened visceral pleura and the loculation of the pus prevented collapse of the lung. Against this backdrop of physiological and clinical knowledge, Evarts Graham began his work with the Empyema Commission.

GRAHAM'S BACKGROUND

Evarts Ambrose Graham was born in Chicago in 1883. From an early age, he pursued an academic program that emphasized critical thinking and broad, interdisciplinary learning [4, 5, 8, 17–19]. While he was an undergraduate at Princeton, Graham requested that a special course in scientific German be taught to himself and a few classmates. As a sophomore, he had already decided that his 3 objectives after he completed his training would be "to do major surgery, to engage in research…and to have a clinic of younger men…interested in…developing ideas" (p. 5) [8].

Graham returned to Chicago in 1904 to attend Rush Medical College. While interning at Presbyterian Hospital, Graham met Rollin Woodyatt, who was to have a major impact on his career. Woodyatt had recently worked with Friedrich Mueller in Munich and was an admirer of the German approach to medical education [8] and a fan of Mueller, who he said represented "a type superior to any we had in the United States" (p. 8) [8]. Mueller was a first-rate clinician who worked in his own chemical laboratory and, at the same time, trained young men to follow in his footsteps [20]. Despite much disapproval, Graham followed Woodyatt's and Mueller's example and withdrew from surgery to conduct research and study basic science. According to Alfred Blalock [21], "[This] decision was probably the most important one in his professional life" (p. 13).

During his hiatus from surgical training, Graham completed a fellowship in pathology at Rush. He also studied chemistry at the University of Chicago and worked at Woodyatt's research institute [8]. Churchill [8] commented that Graham gained confidence that his vision of the work of a surgeon "formed a pattern that could be realized and that [this pattern was] spearheading a trend in medicine that was rapidly gaining momentum" (p. 8). Graham's sabbatical from surgery lasted 12 years [8]. He returned with "a prepared mind, not merely with hands trained in technical skills" (p. 11) [8].

FINDINGS OF THE EMPYEMA COMMISSION

The Commission had 15 members and was chaired by Edward K. Dunham, a well-known microbiologist; its location was at the base hospital at Camp Lee, Virginia. A previous "Pneumonia Commission" had already established that the hemolytic *Streptococcus* was the cause of most of the cases of empyema seen in military camps. The Empyema Commission sent out questionnaires to 32 US Army camps to establish the incidence and course of empyema, and it assigned teams consisting of a surgeon, an internist, and a bacteriologist to camps with significant numbers of cases. It also performed experimental studies of empyema.

Graham and his associates compiled the results of the questionnaires and found that the average empyema-associated mortality rate was 30%, although, in some camps, the rate was as high as 90%. Graham thought that the high mortality rate was due to the common practice of open surgical drainage of patients with empyema with resultant pneumothorax and death caused by asphyxia [1–7]. It was evident to Graham that most physicians treating patients with empyema had a poor understanding of respiratory physiology. He wrote, "Tragedy and catastrophe lie in waiting for any surgeon who ventures inside the chest wall unfamiliar with the harmonious laws of Nature [governing] the functions of the important organs in this region" (p. 17) [3].

Elegant pathological studies of the 1917–1918 pneumonia epidemic in the military camps by MacCallum [22] showed an important difference in the pathology of streptococcal and pneumococcal pneumonia. Empyema encountered in civilian settings was usually secondary to pneumococcal pneumonia, and the empyema presented after the resolution of acute pneumonia. Fibrinous adhesions formed early, which restricted pus to the region immediately adjacent to the involved lobe, and, therefore, open drainage did not result in pneumothorax. Streptococcal empyema, however, was different both clinically and pathologically. The pneumonia prominently involved the bronchioles and the air space, and to quote MacCallum, "Dyspnea of the most extreme type especially during inspiration is characteristic and results in a livid cyanosis" (p. 90) [22]. The massive pleural serofibrinous exudates arose concomitantly with the pneumonia; they were synpneumonic, unlike the postpneumonic effusions of pneumococcal disease. The streptococcal pleural fluid was, according to MacCallum, "like thin pea soup, like turbid urine, like unstrained bouillon, like muddy water, but generally like thin pea soup" (p. 98) [22]. This massive exudate eventually became purulent, but it took approximately 2 weeks for it to be compartmentalized by adhesions. If an incision was made into the pleural space prematurely, it created an open pneumothorax, which, in many cases, resulted in death [1–4, 7, 18, 23–27]. (Of note, the clinical picture of group A streptococcal pneumonia in the penicillin era has changed little since the time of MacCallum's original description. In 1968, Basiliere et al. [28] reported an epidemic in San Diego that involved 95 military recruits; empyema occurred in 54 of them.)

The concepts of negative intrapleural pressure and vital capacity figured strongly into Graham's explanation of the high mortality rate associated with open drainage of patients with streptococcal empyema. Graham [3] argued that the intrathoracic organs functioned under a negative tension that resulted from the "counterplay of two forces: the tendency of the lungs to pull away from the chest wall and a strong adhesive force which holds the lungs against the chest wall" (p. 17). With inspiration, the intrapleural pressure fell (became more negative) and caused the lung to expand. An opening in the pleural cavity caused a sudden increase in the pleural pressure. According to Graham [25], "[the] ability…to withstand an open pneumothorax depends on one's ability to compensate by increasing the respiratory effort…for if the opening is so large that, despite…maximal respiratory efforts, [one] is unable to establish a negative pressure in the pleural cavity, [one] will be unable to get air into [the] lungs" (p. 993).

At Camp Lee, because the majority of the 140 patients with hemolytic streptococcal empyema had already undergone surgery, the clinical cohort left to study was limited to 23 patients. Armed with an understanding both of the pathologic characteristics of the *Streptococcus* species and of respiratory physiology, Graham and his associates set about to treat these patients. They opted for repeated aspirations of the pleural fluid with delayed open drainage, followed by sterilization of the empyema cavity. Of the 22 patients who survived this treatment, 13 healed completely and the remainder were at various stages of healing [1, 3–5, 7]. Graham published the commission's results in August 1918 and stated, "The chief factor in reducing the mortality has been the method of treatment" [7]. At Camp Lee, the mortality rate decreased to <5%, and other camps reported similar results when they abandoned early open drainage during the pneumonic stage [1, 3–5, 7].

These findings were published at a time when there was great controversy regarding the effects of an open pneumothorax on respiration [24]. In 1906, L. Mayer maintained that the mediastinum was fixed. He argued that opening the thoracic cavity caused a marked pressure inequality between the 2 pleural cavities: "On the healthy side negative pressure of 7 mm of mercury, on the other side atmospheric pressure" (p. 22) [1]. In 1911, Garre drew diagrams illustrating an open pneumothorax in which the mediastinum was depicted as a straight line, with one lung collapsed and the contralateral lung of normal size. Many of Graham's contemporaries maintained that "when an opening is made into one pleural cavity [that lung] becomes collapsed and respiration is maintained by the other lung" [1]. Throughout the literature, references were made to the "collapsed lung" on the one hand and the "sound" or "healthy" lung on the other [1]. Therefore, it comes as no surprise that many surgeons disagreed with the Empyema Commission's results and its indictment of their form of treatment. They attributed the better survival rates of Graham's patients to a change in the virulence of the organism. Two vocal opponents were Pierre Duval of France and Sir Berkeley Moynihan, a British surgeon. "[Surgeons, such as these, who successfully removed] shell fragments from the chest without any special equipment for combating the effects of pneumothorax…drew extravagant and unwarranted conclusions…that no special protection against the effects of pneumothorax are necessary," Graham wrote (p. 242) [27]. Duval and Moynihan publicly opposed Graham and "gave the dangerous impression that…operations in the chest could be performed with the same safety as those in the abdomen" (p. 436) [4].

Graham [3] acknowledged that the question seemed particularly complex because "sometimes a bold incision into the pleura was not followed by severe disturbance," whereas, on other occasions, death resulted (p. 28). Given that the tidal air requirements constitute approximately one-eighth of the vital capacity, he felt it was plausible that increasing respiratory depth could generate enough lung volume to maintain life. This explained why some patients could live despite having a relatively large unilateral opening, even if they had bilateral openings. The critical factor, Graham believed, was "the ability of the individual to compensate for the encroachment on his respiratory surface which is caused by the pneumothorax" (p. 29) [3]. Still, even as late as 1935, Graham's findings were not widely accepted. A surgeon of that period was quoted as saying, "[The] necessity of preventing collapse of the lung when but one pleural cavity is opened is largely theoretical and not real" (p. 29) [3].

Always the clinical scientist, Graham was keen to confirm his studies in an experimental animal. Graham, along with Richard D. Bell, was assigned to the Hunterian Laboratory of pathologist William G. MacCallum at the Johns Hopkins School of Medicine (Baltimore). There they studied the effects of an open pneumothorax in healthy and diseased chests and the effects of early operation in a canine model of streptococcal empyema. Because of time constraints, and because their attempts to produce streptococcal empyema in canines turned out to be difficult, they focused mainly on the first part of the study. They inserted a cannula attached to a tambour into the pleural cavities of human cadavers and dogs killed with ether. A kymograph recorded pressure changes on smoked drums [1, 2, 4, 23–26]. When air was forced into one pleural cavity, "there was practically the same pressure in the opposite pleural cavity. [Furthermore], no difference was noted whether the right or left pleural cavity was inflated" (p. 25) [1]. Graham concluded correctly that the mediastinum offers negligible resistance to pressure changes. Experiments that used live dogs confirmed these findings.

Graham drew 2 critical conclusions that paved the way for more ambitious forms of thoracic surgery. The first was that the normal thorax could be considered 1 cavity, because the mediastinum offers negligible resistance to pressure changes; the second was that the size of the pleural opening compatible with life was directly proportional to one's vital capacity, unless the mediastinum is fixed in position. In patients with streptococcal pneumonia whose vital capacity was already low secondary to the active pneumonic process and who were further compromised by the presence of a large serofibrinous pleural exudate, "any opening, no matter how small, is likely to result in a fatal asphyxia" (p. 871) [23]. Open drainage was a reasonable procedure only after the pneumonia cleared, because, by that time, the vital capacity would have increased and the pus would be circumscribed by adhesions [1, 3, 4, 7, 21–24]. Patients did not die of empyema; they died of unwisely performed operations.

CONCLUSIONS

For his pioneering work, Graham was awarded the prestigious Samuel D. Gross Prize of the Philadelphia Academy of Surgery in 1920 [1, 3, 4]. Around the same time, he was offered the post of professor of surgery at Washington University School of Medicine in St. Louis [4]. In accepting this position, he became the second full-time professor of surgery in the United States, an honor befitting a man who was so profoundly influenced by Mueller and the German model of academic medicine. He took an active interest in the development of thoracic surgical training in America. In an address entitled "What Is Surgery?," Graham [29] complained that surgery was "empirical, based on precedent, rather than on reason," mainly because manual dexterity and rapidity of operation were overemphasized in surgical training (p. 864). He argued that students should be "encouraged to ramble" in the pure sciences and that they should be interested in "something more than cutting and sewing" (p. 866) [29]. Indeed, Graham did not impress his associates with his technical skills; by that measure, he was not an outstanding surgeon. Lord Russell Brock [10] remarked that Graham exemplified what really constituted greatness in a surgeon: "Is success based purely on technical ability, or does it lie in the scientific, detached, and original mind capable of introducing new thoughts and methods? … [This was] one of the great lessons of Graham's life and work" (p. 273).

Graham made important contributions in other areas of surgery, including gallbladder surgery. In 1933, he became the first person to perform a successful pneumonectomy for lung cancer on a 48-year-old gynecologist named Dr. Gilmore. (A simultaneous thoracoplasty was performed to avert the high risk of empyema; this occurred anyway, but there were no major catastrophes.) The patient resumed his gynecologic practice and died 30 years later at the age of 78. Graham was one of the first persons to suggest that there was an increased risk of lung cancer related to tobacco use. Graham himself was a smoker, and his own death was the result of lung cancer.

What Graham is best remembered for is his ability to translate physiological understanding of respiratory mechanics into rational treatment for empyema. When he spoke at Graham's memorial service, Joseph Hinsey [18] commented, "There have been three surgeons who have profoundly influenced the progress of surgery in our country in this century: Halstead, Cushing, and Graham" (p. 12).

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