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# THE MICROBIOLOGICAL HISTORY AND EVOLUTION OF TYPE II NECROTIZING FASCIITIS FROM INFECTION EXCLUSIVELY BY STREPTOCOCCUS PYOGENES TO INCLUDE MONOMICROBIAL METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS

MEGHAN GARNETT

**SUMMARY:** Type II Necrotizing Fasciitis is a deep-seated infection of the subcutaneous tissue which has historically been seen as being caused by *Streptococcus pyogenes*, and more recently has been attributed to types of *methicillin-resistant Staphylococcus aureus* (MRSA).

MRSA is hypothesized to have evolved shortly after the introduction of the antibiotic methicillin in 1959. MRSA was first reported in Canada in 1981 and nation-wide monitoring began in 1995. Community-acquired MRSA has emerged as a significant, independent cause of type II necrotizing fasciitis and empiric antibiotic therapy is increasingly included in treatment plans as the bacteria becomes endemic in more communities. The rapid addition of a second pathogen to the aetiology of a disease that already does not discriminate based on the status of the immune system, age, or intensive medical problems deserves close examination by clinicians and researchers. Heightened awareness, increased education and further comparison of *S. pyogenes* and MRSA are necessary for improved identification and treatment of this aggressive disease. The right combination of persistent scientific curiosity and avoidance of unnecessary panic will yield the most efficient route to understanding the virulence factors that make *S. pyogenes* and MRSA the sole two causes of type II necrotizing fasciitis, to date.

**KEYWORDS:** Necrotizing fasciitis, *Streptococcus pyogenes*, Methicillin-Resistant *Staphylococcus aureus*, Gangrene.

**PRECEPTOR:** Dr. Geoffrey Hudson ■ **INSTITUTION:** Northern Ontario School of Medicine

## Introduction

Necrotizing fasciitis (NF) is a deep-seated infection of the subcutaneous tissue at the level of fat, fascia, nerves, and blood vessels that may spare the overlying dermis and epidermis. Currently two types are identified: Type I NF is polymicrobial in origin and usually occurs in patients with diabetes, peripheral vascular disease, and post-surgery; Type II traditionally refers to a monomicrobial infection by *Streptococcus Pyogenes*, and more recently, includes monomicrobial infection by methicillin-resistant *Staphylococcus aureus* (MRSA).<sup>1</sup> In this paper, I will examine the discovery and development of this fascinating disease, as well as Canadian research and health care responses to it, with some closing comments about potential areas for future research based on an historical awareness of the concept.

The entity known today as type II necrotizing fasciitis was first reported as hospital gangrene in 1871 by Confederate Army surgeon Joseph Jones. However, various flesh-eating diseases have been reported for centuries. In 1924, Dr. Frank Lamont Meloney (1889-1963) published a case analysis that pointed to haemolytic streptococcus as the etiological agent of hospital gangrene, and the term necrotizing fasciitis was coined by Wilson in 1952. Province-wide monitoring of *S. pyogenes* began in Ontario in 1992 and reporting invasive Group A *Streptococcus* became mandatory in 1995.

## Bacteriological Developments in the 19<sup>th</sup> Century

A proper historical account of necrotizing fasciitis needs to include a brief review of some major bacteriological developments that make up the foundation for isolating and identifying microbiological entities in the 19<sup>th</sup> century. Small microscopic living beings, called “animalcules” were first observed in 1676 by Antonie van Leeuwenhoek (1632-1723) in Leyden, North Holland and later termed bacteria (“small rods”) by Christian Gottfried Ehrenberg (1795-1876) in 1838. While these observations were of a rather empirical and descriptive nature, pathogenic features only became later attributed to bacteria, when Louis Pasteur (1822-1895) identified them as major causes of disease while working in Paris. Robert Koch (1843-1910), in the latter part of the 19<sup>th</sup> century, even formulated a complete germ theory of disease which was based on his six famous

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<sup>1</sup> Denis L. Stevens, *Necrotizing Infections of the Skin and Fascia. Up To Date for Patients 2008*; retrieved 1 June 2009 (<http://www.uptodate.com>).

principles; from isolation to cultivation of a pathogenic bacterium. German bacteriologist Anton Julius Friedrich Rosenbach (1842-1923) was credited with designating the first species of the genera *Streptococcus* and *Staphylococcus* in 1884. These species were, ironically, *Streptococcus pyogenes*, *Staphylococcus aureus*, and *Staphylococcus albus* which were specifically seen at many surgical wards at the time.<sup>2</sup>

Although necrotizing fasciitis has existed for many centuries, the modern history of necrotizing fasciitis began in 1871 with Joseph Jones (1833-1896) in the United States.<sup>3</sup> Jones was a respected medical professor and a surgeon who served in the Confederate Army during the American Civil War between 1862 and 1866. As a military surgeon he saw many cases of the dreaded hospital gangrene (as it was known at the time) in the many wounded soldiers he treated after they returned from the battlefields. After his active army service, Jones worked as the Secretary of the Southern Historical Society in the United States of America and published several reports at the request of the US Sanitary Commission about the quality of medical care that soldiers received during the American Civil War.<sup>4</sup> Multiple descriptions of hospital gangrene represented an important part of these publications, as the disease infected an astounding 2,642 estimated soldiers during the war, while killing nearly half of its victims.<sup>5</sup>

## Hospital Gangrene and the Military

Hospital Gangrene remained predominantly a military disease during the 19<sup>th</sup> century; it was only seen sporadically in civilian hospitals. There are several possible explanations for this phenomenon. One theory suggests that because soldiers sustained more deep-tissue injuries from ammunition and lived in very close quarters, they were more likely than civilians to

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<sup>2</sup> Raymond W. Beck, *A Chronology of Microbiology in Historical Context* (Washington DC: ASM Press, 2000), p. 105; Kenrad E. Nelson and Carolyn F. Williams, eds., *Infectious Disease Epidemiology: Theory and Practice* (Boston MA: Jones and Bartlett Publishers, 2005), p. 9.

<sup>3</sup> William F. Quirk and George Sternbach. "Joseph Jones: Infection with Flesh Eating Bacteria," *Journal of Emergency Medicine* 14 (1996), pp. 747-753; esp. pp. 747.

<sup>4</sup> Mike Miller, *Biography of Jones, Joseph, M.D. 1998*, retrieved 18 December 1998 (<http://files.usgarchives.org/la/orleans/bios/j-000011.txt>).

<sup>5</sup> Quirk and Sternbach, *Joseph Jones*, p. 747; William A. Altmeier III, "A Pediatrician's View: A Brief History of Group A Beta Hemolytic Strep," *Pediatric Annals* 27 (1998), pp. 264-267; esp. p. 266.

catch this disease. Furthermore, military hospital records might have been more accurately maintained due to the number of staff available and the general emphasis on discipline in the army. The largest civilian outbreak, with a reported ninety two cases, occurred in 1863 in London, England. The majority of these cases were community-acquired rather than infections that were first observed in hospital patients. The spike in disease outbreak that year however corresponded to a significant increase in incidents of scarlet fever in many other London hospitals. This demonstrated the difficulties of the time to pathologically differentiate between different types of feverish diseases.<sup>6</sup>

Unlike many other diseases, the descriptions of hospital gangrene throughout the centuries have remained strikingly similar and characteristic of a streptococcal infection. Historic records are often very consistent with contemporary accounts given of the disease:

Within twenty-four hours after the appearance of the original lesion, the affected member becomes greatly swollen, hot, red, and tender [...]. The early swelling makes the skin tense, smooth and shiny [...]. In a day or two, certain areas gradually turn darker, changing from red to purple and then to blue. About this time, blisters and bullae begin to form, in which clear yellow fluid collects [... and] fluid becomes dark [...]. Usually on the fourth or fifth day, the purple areas of skin become frankly gangrenous [...]. From the seventh to the tenth day [...] the dead skin begins to separate at the margins or break in the center, discharging pus and revealing an extensive necrosis of the subcutaneous tissue.<sup>7</sup>

While descriptions of the disease have remained consistent for centuries, its name has not. Before the American Civil War, for example, it was vividly referred to as the “*Malignant Ulcer*”, “*Gangrenous Ulcer*”, “*Putrid Ulcer*”, “*Phagedenic Ulcer*”, “*Phagedena Gangraenosa*”, “*Phagedena*”, or “*Hospital Gangrene*”, etc. Between the time of the American Civil War and the Second World War, however, only the latter two terms were commonly used.<sup>8</sup> In 1952, Dr Robert Wilson (1899-1969) coined the term “Necrotizing Fasciitis”, which he deemed to be the most accurate

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<sup>6</sup> Irvine Loudon, “Necrotizing fasciitis, hospital gangrene, and phagedena,” *Lancet* 344 (1994), pp. 1416-1419; esp. pp. 1417-1418.

<sup>7</sup> Frank L. Meleney, “Hemolytic streptococcus gangrene,” *Archives of Surgery* 9 (1924), pp. 317-364; esp. 318-319.

<sup>8</sup> Loudon, *Necrotizing Fasciitis*, p. 1416.

description of the disease which many modern biomedical scientists have evidently agreed to.<sup>9</sup>

## Streptococci and Staphylococci as Causes

In 1909, the British surgeon, W. Fedde Fedden (1879-1952), a consulting surgeon to St. George's Hospital in London, described six cases of Acute Infective Gangrene caused by *Streptococcus pyogenes*, *Staphylococcus aureus*, and *Bacillus* species, including *B. aerogenes capsulatus*, *B. coli*, and *B. pyocyaneus*. Pure *Streptococcus*, Pure *Staphylococcus*, and combinations of the aforementioned organisms were obtained from the lesions of these patients. *Streptococci* were noted to be the most virulent bacteria.<sup>10</sup>

In his 1924 article on Haemolytic *Streptococcus* Gangrene, the American surgeon Frank Meleney (1889-1963) focuses on *Streptococcus* as an etiological agent of gangrene. A series of twenty cases were analyzed and blood cultures were collected in seventeen of the cases, with seven positive for haemolytic *Streptococcus*. Pus analysis occurred in eight of the cases, with seven showing pure haemolytic *Streptococcus*, and the eighth sample containing *Staphylococcus* and a gram-positive bacillus. In the twelve other samples, haemolytic *Streptococcus* was mostly present in isolation or in combination with *Staphylococcus aureus*, *Bacillus pyocyaneus*, *Staphylococcus albus*, and other gram-positive and gram-negative bacilli. Only one wound contained an anaerobic organism, which could not be confirmed as present at the onset of infection. With the help of Dr. Carl Ten Broeck (b. 1885), a Commissioner of the Armed Forces Epidemiological Board, Meleney found strong evidence to suggest that haemolytic *Streptococcus* was the cause, rather than secondary manifestation of hospital gangrene. He also showed that the rapidly progressive gangrene in his cases had a clear and distinct etiological origin from anaerobic gangrenes, such as the gas gangrene caused by *Clostridium perfringens*.<sup>11</sup>

The outbreaks of Group A *Streptococcus* gangrenes waned throughout the twentieth century, with the wide acceptance of the germ theory of disease, improvements in personal hygiene and public health measures,

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<sup>9</sup> Robert Wilson, "Necrotizing fasciitis," *American Surgeon* 18 (1952), pp. 416-431; Quirk and Sternbach, *Joseph Jones*, p. 748.

<sup>10</sup> W. Fedde Fedden, "Six Cases of Acute Infective Gangrene of the Extremities," *Proceedings of the Royal Society of Medicine* 2 (1909), pp. 213-218; esp. p. 217.

<sup>11</sup> Meleney, *Haemolytic Streptococcus Gangrene*, pp. 317-319.

and medical advances. The discovery of penicillin by Scottish scientist Alexander Fleming (1881-1955) in 1928 revolutionized the treatment of bacterial infections. In 1942, the first clinical trials with penicillin took place at Yale University in New Haven and at the Mayo Clinic in Rochester, Minnesota, with great success. Further trials in an American military hospital confirmed its effectiveness and the widespread manufacturing of penicillin came into effect by the end of World War Two.<sup>12</sup>

### **Group A Streptococci Gain Special Medical Notice**

Group A Streptococcus causing necrotizing fasciitis came to the forefront of medical attention again in the late 1980s with the emergence of more virulent strains.<sup>13</sup> A series of headlines in the 1990s about the deadly flesh-eating disease and loss of limbs by the former Premier of Québec Lucien Bouchard (b. 1938) in 1994 fostered considerable public concern in the media. The Ontario Group A Streptococcal (GAS) Surveillance System became established in 1990 after an outbreak in Toronto. This resulted in the invasive GAS becoming a reportable disease in Ontario in 1995.<sup>14</sup> The data showed that the incidence of Group A Streptococcus necrotizing fasciitis rose four-fold from 0.085 per 100,000 in 1991 to 0.40 per 100,000 in 1995. Of the seventy-seven cases that were included in the study, seventy-five patients had GAS-pure cultures; and the other two patients were infected with GAS and *S. aureus*.<sup>15</sup> According to the Ontario Group A Streptococcal Study, 2,351 cases of invasive GAS were recorded from 1992 to 2000. Out of the 2,351 reported cases, 253

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<sup>12</sup> Laurence L. Brunton, ed., *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th ed. 2006; retrieved 18 December 2008 (<<http://www.accessmedicine.com/content.aspx?aID=948655>>).

<sup>13</sup> Dennis L. Stevens, "The Flesh-Eating Bacterium: What's Next?" *Journal of Infectious Diseases* 179 (1999): pp. 366-374; esp. p. 368.

<sup>14</sup> Ontario Ministry of Health, *Guidelines for Management of Contacts of Cases of Invasive Group A Streptococcal Disease (GAS) including Streptococcal Toxic Shock Syndrome (STSS) and Necrotizing Fasciitis*. 1995; retrieved on 18 December 2008 (<http://microbiology.mtsinai.on.ca/protocols/pdf/k5c.pdf>).

<sup>15</sup> Robert Kaul, Allison McGeer, Donald E. Low, Karen Green, et al., "Population-based surveillance for group A streptococcal necrotizing fasciitis: Clinical features, prognostic indicators, and microbiologic analysis of seventy-seven cases. Ontario Group A Streptococcal Study," *American Journal of Medicine* 103 (1997), pp. 18-24; esp. p. 19.

(11 percent) of these cases involved necrotizing fasciitis.<sup>16</sup> In 2006, Health Canada reported that there has been between ninety to two-hundred cases of necrotizing fasciitis per year in Canada, with a 20-30 percent mortality rate.<sup>17</sup>

No stranger to increased virulence, the history of methicillin resistant *S. aurea* (MRSA) begins some fifty years ago with the yet-to-be entirely elucidated acquisition of methicillin resistance by *S. aureus*. The antibiotic Methicillin was introduced in the year 1959 as a semi-synthetic beta-lactam antibiotic used to treat bacterial infections. Shortly thereafter, reports of MRSA began to emerge in England<sup>18</sup> and in Denmark.<sup>19</sup> By definition, MRSA must have an oxacillin minimum inhibitory concentration of  $\geq 4$  mcg/mL. It is also seen to express the *mec* gene, and its structural component, *mecA*, which encodes the penicillin binding protein 2a that renders the streptococci resistant to methicillin.<sup>20</sup> It is has further become theorized that *S. aureus* acquired the *mecA* gene from an indeterminate source, most likely coagulase-negative staphylococci, in the late 1950s or early 1960s, after penicillinase-resistant oxazolidinones were clinically introduced.<sup>21</sup>

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<sup>16</sup> Nick Daneman, Karen A. Green, Donald E. Low, Andrew E. Simor, et al., "Surveillance for Hospital Outbreaks of Invasive Group A Streptococcal Infections in Ontario, Canada, 1992 to 2000," *Annals of Internal Medicine* 147 (2007), pp. 234-241; esp. p. 235.

<sup>17</sup> Health Canada, *Flesh-eating Disease*. 2006; retrieved on 18 December 2008 (<<http://www.hc-sc.gc.ca/hl-vs/iyh-vsv/diseases-maladies/flesh-chair-eng.php>>).

<sup>18</sup> M. Patricia Jevons, "Celbenin"-resistant Staphylococci," *British Medical Journal* 1 (1961), pp. 124-125.

<sup>19</sup> K[laus] R. Eriksen and J[ohn] Erichsen, "Inactivation of methicillin, oxacillin, cloxacillin, and cephalothin by staphylococcal penicillinase," *Acta Pathologica et Microbiologica Scandinavica Supplement* 52 (1964), pp. 255-275; Franklin D. Lowy, *Microbiology of methicillin-resistant Staphylococcus aureus*. 2008 UpToDate for Patients; retrieved 1 June 2009 (<http://www.uptodate.com>).

<sup>20</sup> Mark C. Enright, D. Ashley Robinson, Gaynor Randle, Edward J. Feil, et al., "The evolutionary history of methicillin-resistant *Staphylococcus aureus* (MRSA)," *Proceedings of the National Academy of Science USA* 99 (2002), pp. 7687-7692; esp. p. 7687.

<sup>21</sup> M. Inês Crisostomo, Henrik Westh, Alexander Tomasz, Marilyn Chung, et al., "The evolution of methicillin resistance in *Staphylococcus aureus*: Similarity of genetic backgrounds in historically early methicillin-susceptible and -resistant isolates and contemporary epidemic clones," *Proceedings of the National Academy of Science USA* 98 (2001), pp. 9865-9870; esp. 9865; D.E. Low, M. Garcia, S. Callery, et al., "Methicillin-resistant *Staphylococcus aureus* - Ontario," *Canadian Diseases Weekly Report* 7 (1981), pp. 249-250.



MRSA was first reported in Canada in 1981.<sup>22</sup> Nation-wide monitoring began in 1995, with 4,507 cases identified in the first five years. The mean incidence rate of MRSA increased nine-fold from 1995 to 1999.<sup>23</sup> By 2002, there were five major strains of MRSA worldwide.<sup>24</sup>

Methicillin-resistant *Staphylococcus aureus* can be classified as health care-associated MRSA (HA-MRSA) or community-associated MRSA (CA-MRSA), and they differ in several ways. HA-MRSA is a serious, invasive infection displaying wide antibiotic resistance that typically occurs in hospitalized and immunocompromised patients, whereas CA-MRSA causes skin and soft tissue infections in healthy people, but fortunately still responds to non-beta-lactam antibiotics.<sup>25</sup> CA-MRSA causes necrotizing fasciitis much more commonly than HA-MRSA due to its propensity to colonize in the skin and soft tissues.<sup>26</sup> Despite their distinct microbiological and clinical characteristics, it is becoming increasingly difficult to distinguish the exact origin of the MRSA in individuals who may contract the organism in one setting but develop symptoms in another.<sup>27</sup>

Given that there are thousands of microorganisms, and that *S. aureus* persisted in the environment long before the microscope, the emergence of a new pathogen causing necrotizing fasciitis merits explanation. Both staphylococci and streptococci release exotoxins, although the toxins emitted from staphylococci are more toxic to cells and consequently get walled off much quicker than streptococcal exotoxins.

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<sup>22</sup> *Ibid.*

<sup>23</sup> Andrew E. Simor, Marianna Ofner-Agostini, Elizabeth Bryce, Karen Green, et al., "The evolution of methicillin-resistant *Staphylococcus aureus* in Canadian hospitals: 5 years of national surveillance," *Canadian Medical Association Journal* 165 (2001), pp. 21-26.

<sup>24</sup> Lowy, *Microbiology of Methicillin-resistant Staphylococcus aureus*.

<sup>25</sup> Upton D. Allen, "Public health implications of MRSA in Canada," *Canadian Medical Association Journal* 175 (2006), p.161; John M. Boyce, *Epidemiology of methicillin-resistant Staphylococcus aureus infection in adults*. 2008 UpToDate for Patients; retrieved 1 June 2009 (<http://www.uptodate.com>).

<sup>26</sup> Loren G. Miller, Françoise Perdreau-Remington, Gunter Rieg, Sheherbano Mehdi, et al., "Necrotizing Fasciitis Caused by Community-Associated Methicillin-Resistant *Staphylococcus aureus* in Los Angeles," *New England Journal of Medicine* 352 (2005), pp. 1445-1453; Todd J. Kowalski, Elie F. Barbari, and Douglas R. Osmon, "Epidemiology, Treatment, and Prevention of Community-Acquired Methicillin-Resistant *Staphylococcus aureus* Infections." *Mayo Clinic Proceedings* 80 (2005), pp. 1201-1208.

<sup>27</sup> Allen, *Public Health Implications of MRSA in Canada*; Boyce, *Epidemiology of methicillin-resistant Staphylococcus aureus infection in adults*, p. 161.

Conversely, streptococcus exotoxins, while less virulent, have a greater chance of invading tissues and causing diseases like necrotizing fasciitis. The evolution of methicillin-resistant *S. aureus* altered its toxin expression. For example, the USA300 strain releases Pantone-Valentine leukocidin cytotoxins and PSM-alpha, both of which are highly necrotic and unique to CA-MRSA. The *mecA* gene encodes penicillin binding protein (PBP) 2a, which aids the bacteria in establishing its resistance to certain cell wall inhibitors. By combining its lethal toxins and invasiveness, MRSA is able to cause type II necrotizing fasciitis just as GAS has traditionally done.

A 2005 Los Angeles study of 843 MRSA-positive patients indicated that 14 of them presented with necrotizing fasciitis, necrotizing myositis, or both. Twelve cases were monomicrobial for MRSA and the other two were polymicrobial with combination MRSA and *Klebsiella pneumoniae* or *Pseudomonas aeruginosa*.<sup>28</sup> The 2008 Denver study of thirty cases of community-acquired acute necrotizing fasciitis found that five (16.7 percent) patients presented with MRSA, of which two were polymicrobial and three were monomicrobial. The two polymicrobial cases were combination MRSA and predominantly *Acinetobacter* or GAS.<sup>29</sup> The microbiology of the other twenty-five cases was not described. The authors specify that patients should be treated with empiric MRSA antimicrobial therapy in regions vulnerable to CA-MRSA, given its pathogenicity.<sup>30</sup> In their analysis of the Denver study, the Infectious Diseases Society of America acknowledges that the disease formerly attributed to GAS is increasingly being caused by MRSA.<sup>31</sup>

## Conclusions

The examination of the microbiological history and evolution of type II necrotizing fasciitis points to the need for further comparison of *S. pyogenes* and MRSA for improved clinical understanding, epidemiological monitoring, and treatment of this aggressive disease. In his reflections on the past twenty-five years in emergency medicine, the

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<sup>28</sup> Miller et al., *Necrotizing Fasciitis*, pp. 1445-1450.

<sup>29</sup> Lisa M. Young and Connie S. Price, "Community-Acquired Methicillin-Resistant *Staphylococcus aureus* Emerging as an Important Cause of Necrotizing Fasciitis," *Surgical Infection* 9 (2008), pp. 469-474.

<sup>30</sup> *Ibid.*, p. 473; Miller et al., *Necrotizing Fasciitis*, p. 1450.

<sup>31</sup> *Infectious Diseases Society of America, MRSA Linked to Recent Antibiotic Use Increasing as Cause of Necrotizing Fasciitis*. 2006; retrieved on 18 December 2008 (<<http://www.idsociety.org/Content.aspx?id=3724>>).

American physician George Sternbach (b. 1943?) from the Stanford Medical Center in California comments that “although necrotizing fasciitis is still a dangerous entity, it has largely been replaced as a “rock star” bacterial menace by the methicillin-resistant *Staphylococcus aureus* ‘superbugs’”.<sup>32</sup> This certainly calls to question whether MRSA is the last addition to the aetiology of the disease, or if further pharmacological advances will create another favourable climate for the emergence of a newer, stronger flesh-eating bacterium. The right combination of persistent scientific curiosity and avoidance of unnecessary panic will yield the most efficient route to understanding the virulence factors that make *S. pyogenes* and MRSA the sole two causes of type II necrotizing fasciitis, as it is currently perceived in research literature.

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<sup>32</sup> George Sternbach, “Emergency medicine then and now,” *Journal of Emergency Medicine* 35 (2008), pp. 117-118.