5

Mayrhofer's Discovery

About one hundred miles west of Vienna, a short distance south of Austria's main east-west Autobahn, is an ancient Benedictine monastery named Kremsmünster, founded in the eighth century. Its present buildings date from the seventeenth and eighteenth centuries, and, like most Austrian architectural monuments, they are predominantly baroque. The abbey is located in the hilly transition zone between the Danube basin to the northeast and the Austrian Alps to the southwest and is beautifully situated on the shoulder of a steep hill overlooking the Krems river. The hills surrounding the abbey are mostly covered with farms and pastures, but also with vineyards and isolated patches of pine forest.

In 1839 Karl Wilhelm Mayrhofer was appointed physician to the Kremsmünster abbey. Mayrhofer and his wife, Josepha Wildschgo Mayrhofer, moved into a large gray building located just outside the northern walls of the monastery. At the time, the couple had a son named Carl, who had been born two years earlier on 2 June 1837. As he grew older, Carl attended school in the abbey, where his teachers recognized that he was unusually bright. Following his father's example, Carl Mayrhofer went on to study medicine at the University of Vienna.

In 1860, the same year in which Semmelweis's book appeared, Mayrhofer was awarded an M.D. degree. After studying surgery for two additional years, he decided to specialize in obstetrics. In 1862 he was appointed second assistant to Carl Braun, who had replaced Johannes Klein as professor of obstetrics at the university. Thus, Mayrhofer began working in the first section of the Viennese maternity clinic—in the same facility where, fifteen years earlier, Semmelweis had instituted chlorine washings.

During the 1850s, in various books and articles, Carl Braun had identified thirty possible causes of childbed fever. Among these, he had given particular attention to the possibility of infection by airborne germs. In the 1850s, tissue decomposition, as is regularly observed in childbed fever, was believed to resemble organic fermentation; and the young French chemist Louis Pasteur had argued that fermentation occurred when a fermentable substance, such as grape juice, was invaded by airborne germs. This made it seem likely that childbed fever could also be caused by the invasion of germs. Semmelweis ridiculed Braun for trying to explain the disease in this way;[1] he insisted that airborne germs were irrelevant and that the disease always arose from the resorption of decaying animal-organic matter. At the time that Mayrhofer became Braun's assistant, Braun was intensely interested in this dispute. Mayrhofer later wrote: "[Professor Braun] encouraged me to the highest degree. He said he had such an interest in resolving the affair he would gladly cover the research costs from his own resources and make available to me, for this purpose, all the clinical materials [i.e., maternity patients and corpses]."[2] Braun probably expected that Mayrhofer would confirm his own views about the etiology of childbed fever.

Mayrhofer immediately began studying the possible role of microorganisms in the disease. Because childbed fever often seemed to originate in the uterus, Mayrhofer began looking for living organisms in the uterine discharges of puerperal fever

victims. At first he found nothing, because the only microscope available in the Viennese obstetrical clinic was not powerful enough to make such organisms clearly visible. However, through Braun's efforts, a new instrument was procured, and Mayrhofer's search began to yield results. One year later, in 1863, he published his first paper.[3] Later in the same year, Mayrhofer delivered a lecture on childbed fever before the most prestigious medical association in Vienna. This lecture was also published.[4] Both of Mayrhofer's papers were abstracted and reviewed in Viennese medical periodicals.

In these two publications, Mayrhofer referred to earlier research on the role of microorganisms in certain animal diseases and to earlier conjectures that some infectious human diseases could be caused by microorganisms. He also cited Pasteur's research on fermentation. Mayrhofer reported having studied the uterine discharges of more than one hundred living and dead victims of childbed fever, and he characterized and classified the various organisms he found. He noted that they differed in size and shape, in their motility, in their reactions to acidic media, and in their capacities to ferment various liquids. Following common usage, Mayrhofer referred to all of these organisms as "vibrions."

Mayrhofer became particularly interested in a certain class of motile vibrions that were consistent in size, that were incapable of living in acids, and that fermented various sugar solutions. Mayrhofer reported that these vibrions were especially abundant in the uterine discharges of diseased patients. Sometimes he found the same organisms in healthy patients, but never until five days or more after delivery. He hypothesized that the normally acidic vaginal secretions of healthy patients protected them from invasion by these parasites.

Mayrhofer tried to decide whether vibrions actually caused childbed fever or whether the diseased patient simply provided a suitable medium in which they could flourish. To accumulate evidence of causation, Mayrhofer sprayed fluids containing organisms

into the genitals of newly delivered rabbits. Most of the rabbits became diseased and died, and postmortem examinations revealed large numbers of the same vibrions as well as morbid changes similar to those in puerperal fever victims.

For more conclusive evidence of causality, Mayrhofer cultivated vibrions in a sugar and ammonia solution. After filtering the solution to isolate the vibrions from other decomposition products, he sprayed the vibrions into the rabbits' genitals. Again the rabbits died, and again Mayrhofer found the familiar morbid remains in their carcasses.

Mayrhofer's early work was based directly on Braun's concept of childbed fever, and his initial results were entirely compatible with Braun's views. Perhaps this contributed to the favorable reception that Mayrhofer's first publications received in Vienna.

By 1864 Braun had good reason to feel vindicated. His views seemed to be supported by Mayrhofer's discoveries. Another of Braun's students, August Theodor Stamm, presented papers in which he argued that improved ventilation, rather than the use of chlorine washings, was responsible for the favorable mortality rates in the first section of the clinic.[5] Braun himself published papers maintaining that proper ventilation was the most important prophylaxis against childbed fever.[6] On the strength of the accumulating evidence, Braun persuaded the Viennese authorities to install an expensive new ventilation system in the maternity clinic.

However, just as Braun seemed to be winning the dispute about the nature of childbed fever, further research led Mayrhofer to conclude Braun's concept of the disease was fundamentally wrong.

Toward the end of 1864 Mayrhofer delivered a second lecture on childbed fever. This lecture was published in 1865—the same year in which Semmelweis died in the Viennese insane asylum. It was to be Mayrhofer's last work on childbed fever.[7] After this lecture, Mayrhofer completely abandoned his innovative research on vibrions. Over the next several years, he published a few articles on various topics in obstetrics, but in only one passage did he ever again discuss childbed fever, and in that passage he merely reaffirmed his earlier claims about the disease.[8]

Mayrhofer's second lecture marked a turning point in his relations with Braun, and the reason is obvious. In this lecture, Mayrhofer rejected Braun's concept of childbed fever and adopted a position that was much closer to Semmelweis's view. Mayrhofer revealed his change of allegiance in two ways. First, although he had originally agreed with Braun that vibrion germs were usually conveyed through the air, in his second lecture, he gave up trying to explain how this could happen. While Mayrhofer left open the possibility of airborne germs, he concluded, exactly as Semmelweis had before him, that infection was usually due to the contaminated hands of examining physicians. This meant that chlorine washings were indispensable—a conclusion that was in direct opposition to Braun, who continued to insist that inadequate ventilation was a far more common cause of the disease.

Second, in his final lecture, Mayrhofer, like Semmelweis, identified a universal necessary cause for all cases of childbed fever. As in Semmelweis's account, the existence of such a cause followed from a new characterization of the disease. Mayrhofer defined "childbed fever" as a fermentation disease in which tissues decompose under the influence of living vibrions.[9] This meant that childbed fever could never occur without vibrions. By contrast, in the same year Mayrhofer delivered his final lecture, Gustav Braun—Carl Braun's brother and former student—published a book identifying the same range of causes Carl had listed in the 1850s.[10] By insisting on one necessary cause—a cause present in every case of childbed fever—Mayrhofer adopted the one central claim that distinguished Semmelweis's account from Braun's and from those of all of Semmelweis's other critics. Because Mayrhofer's concept of the disease focused on vibrions, his definition differed in content from the definition that Semmelweis had adopted, but his strategy of characterizing the disease in terms of a single universal cause was exactly the same.

It was immediately apparent that Mayrhofer's concept of the disease was closer to Semmelweis's than to Braun's. While Mayrhofer worked in the first section of the obstetrical clinic, Joseph Späth supervised the second section—the section in which midwives were trained. In 1863 and 1864 Späth published several statistical and historical studies of the incidence of childbed fever. In one such study, Späth wrote that Mayrhofer's discoveries confirmed Semmelweis's view because, according to Mayrhofer, the infective agents in the disease were vibrions that flourished in decomposed animal matter.[11] Späth also noted that, in spite of what may be said in public, every obstetrician now believed that Semmelweis had been correct.[12] Another Viennese obstetrician went even further: A. C. G. Veit wrote that, in addition to *confirming* Semmelweis's view, Mayrhofer and Späth had actually *refuted* Braun's opinion that ventilation significantly influenced the incidence of childbed fever.[13]

Contemporary physicians at the Viennese General Hospital were dismayed by the unusual bitterness manifested by advocates of the opposing theories of childbed fever.[14] By openly disagreeing with his chief, Mayrhofer sealed his own fate: his second lecture was poorly received, and, in spite of his initial success, Mayrhofer's work was rejected. Looking back a few years later, one contemporary physician observed, "If one says that Mayrhofer's work attracted universal attention, this should not be understood in one sense only. Such an energetic talent that transcends the mass of mediocrity often finds itself all too vulnerable."[15]

Soon after giving his second lecture, Mayrhofer left the first clinic and entered private practice. In 1870 he was appointed private docent of obstetrics and women's diseases, and a few years later he was appointed adjunct professor of the same specialty. At first, Mayrhofer met success in his private practice. However, through the 1870s, he experienced a series of misfortunes. While still working in the Viennese first clinic, Mayrhofer had suffered from lymphangitis and had begun to spit up blood. These

symptoms indicated the onset of phthisis or tuberculosis, and in the nineteenth century, the disease was almost always fatal. As he entered private practice, his health continued to deteriorate. Then two of his children died. Mayrhofer also encountered frustrations in his medical practice. "The undeserved disappointments that Mayrhofer continued to experience soon drove him to morphine and lamed the vitality of this otherwise energetic individual."[16]

In 1878 Mayrhofer left Vienna. One contemporary ascribed the move to "a loss of interest in the affairs of practical life."[17] After a successful beginning in Tiflis (now Tbilisi in the Republic of Georgia), he moved to St. Petersburg, Russia, where he experienced further disappointments and frustrations. In 1881 he moved again, this time to the spa town of Franzensbad (now Franziskovy in the western end of the Czech Republic). During the following winter he became seriously ill. He died on 3 June 1882, one day after his forty-fifth birthday. A contemporary observed that "everyone who was close to Mayrhofer recognized that for him, death was a salvation."[18]

The striking parallels between Mayrhofer and Semmelweis have long been apparent. In a necrology, one nineteenth-century writer observed that Mayrhofer's "professional life was reminiscent of the tragic experiences of another gynecologist from the Vienna school, the genial Semmelweis."[19] In a book on the history of obstetrics in Vienna, I. Fischer notes that Mayrhofer's study of the role of germs in puerperal fever, which followed Pasteur's work and preceded Joseph Lister's, together with the circumstance that he was never properly appreciated in Vienna, earned him the title of a second Semmelweis.[20] Erna Lesky also refers to Mayrhofer as the second Semmelweis; in her book *The Vienna Medical School of the Nineteenth Century* she observes that Mayrhofer took up the problem of puerperal disease at the point at which Semmelweis had abandoned it.[21]

There has been a long-standing tradition that Semmelweis and Mayrhofer were generally ignored through the middle decades of the nineteenth century. While this was true in Austria and in Hungary, in Germany the situation was quite different.

Semmelweis's book was published in the fall of 1860. In 1861, at a meeting of German physicians and scientists, Wilhelm Lange, professor of obstetrics in Heidelberg, declared himself to be an adherent of Semmelweis's theory. Lange claimed that his own experiences and the mathematical basis of Semmelweis's work had persuaded him that Semmelweis was correct.[22] Between 1860 and 1865, the year in which Semmelweis died, Semmelweis's work was discussed in more than forty major medical publications and in more than a dozen reviews.[23] Most of these accounts appeared in German periodicals. Semmelweis, who had become preoccupied with past events, seems never to have realized that his ideas were being discussed and accepted in Germany.

In 1868, just three years after Semmelweis died, a German professor named Max Boehr noted that Semmelweis's theory of the infectious origin of childbed fever

> has the characteristic of every good pathological and physiological theory: it provides a unified, clear, and entirely intelligible meaning for a whole series of anatomical and clinical facts, and for the relevant experiences and discoveries of reliable observers of epidemics among maternity patients. None of the earlier or alternative theories or hypotheses regarding the occurrence of childbed fever has this characteristic to the same degree.[24]

Boehr believed Semmelweis's theory could account for every case of the disease. He observed that Semmelweis's work dealt a severe blow to "the superstitions of our predecessors, who believed in unknown cosmic-telluric-atmospheric influences and . . . in miasms."[25] Boehr mentioned that Veit, Späth, and Mayrhofer had supported Semmelweis's theory.

In the same year, Rudolf H. Ferber wrote that Semmelweis had initiated a revolution in the understanding of childbed fever. Ferber pointed out that "with only a few exceptions, the Semmelweis theory is now universally recognized in Germany."[26]

In 1876, Joseph Amann, professor of obstetrics in Munich, observed that Semmelweis's theory had become the shared property of the entire German medical profession.[27] Two years later, in 1878, another German physician observed that thirty-one years had passed "since Semmelweis first spoke the truth that every case of childbed fever comes about through the resorption of decaying animal-organic matter."[28] In the same year, Otto Spiegelberg, professor of medicine in Breslau, Germany, wrote that "Semmelweis deserves credit for placing the understanding of puerperal disease on the new and proper path." According to Spiegelberg, Semmelweis "explained that every case of puerperal fever is resorption fever, arising from the reception of decaying animal matter. . . . These claims hold today. In general, they contain everything there is to be said about puerperal fever."[29] Spiegelberg also credited Mayrhofer with having been the first to prove that puerperal fever was a parasitic process. Spiegelberg observed that once it had been clearly shown that puerperal fever was only a wound disease resting on a septic infection, this view "was rapidly accepted as common property, at least among the physicians in Germany."[30]

Until the 1870s, no important human disease had been conclusively traced to microorganisms, but there was a growing interest in establishing such a connection. In that decade, most physicians who studied the role of germs in disease etiology focused on infected wounds. This was true, in part, because every hospital contained patients suffering from wound infections, and such infections were easier to study than were internal disease processes. Moreover, the organic decomposition of infected wounds resembled fermentation, and Pasteur had shown that fermentation was always the result of living organisms that he called "ferments." This

made it seem plausible that wound infections were due to living parasitic organisms. In the 1870s more than half of all publications associating bacteria with diseases concerned wound infections.[31] In the 1880s, both French and German physicians observed that the germ theory of disease had originated from studies of wound infections and especially from the investigation of childbed fever. Thus, while the Austrians and the Hungarians ignored Mayrhofer and seemed ashamed of Semmelweis's memory, elsewhere, their work was recognized and became part of the foundation for the modern germ theory of disease.

Through the nineteenth century, obstetricians gradually came to accept the views of Semmelweis and Mayrhofer, but, for tens of thousands of women, this acceptance came too late.

Sophia Jex-Blake, one of the first women to be awarded an M.D. degree in modern times, gave the following account of the origin of a childbed fever epidemic that occurred in Boston during the winter of 1866 and 1867:

> On *Friday, Nov 2nd*, A. S. was admitted to the Hospital and delivered of a female infant, which had apparently died two or three weeks previously. . . . A. S. was a married woman, but exhibited evident signs of syphilis, and to this infection the death *in utero* was probably due. On the following day, Saturday, one of the assistant doctors in the Hospital made a postmortem examination of the fetus, removing the uterus and other organs, and being thus occupied probably for some hours.
>
> On *Sunday, Nov 4th* K. M. entered the Hospital in the second stage of labor. Age 22; unmarried; primipara [first delivery]. . . . She had had labor pains to a greater or lesser extent, since the preceding Thursday, and, being homeless and friendless, she had been exposed to great hardships, and had, on the morning of her admission, walked into Boston from a distance, and then wandered about the streets for hours before she was brought to the Hospital. It so happened that on her admission she was received and first examined by the assistant just mentioned, though subsequently delivered by another person. The baby . . . was born about 4 p.m., and a severe laceration of the perineum took place.[32]

Five days later, after great suffering, the woman died of childbed fever, and over the next few weeks several other maternity patients died.

During the second half of the nineteenth century—in spite of the evidence generated by Semmelweis, Mayrhofer, and others—many doctors continued dissecting cadavers, examining patients, and arguing about etiology. Each year, oblivious to the suffering and tragedy by which they were engulfed, they consigned thousands of young women to early deaths.

Notes

1. Ignaz Semmelweis, *The Etiology, Concept, and Prophylaxis of Childbed Fever*, ed. and trans. K. Codell Carter (Madison: University of Wisconsin, 1983), pp. 246 f.
2. Carl Mayrhofer, "Vorläufige Mittheilung über das Vorkommen von Vibrionen bei Wöchnerinnen und deren allfällige Bedeutung für Puerperaler krankungen," *Wochenblatt der Zeitschrift der k. k. Gesellschaft der Ärzte zu Wien* 19 (1863): 17–20, at p. 17
3. Mayerhofer, "Vorläufige Mittheilung," p. 17.
4. Carl Mayrhofer, "Untersuchungen über Aetiolgie der Puerperal-processe," *Zeitschrift der k. k. Gesellschaft der Ärzte zu Wien* 19 (1863): 28–42.
5. August Theodor Stamm, "Ueber die Vernichtungsmöglichkeit des epidemischen Puerperalfiebers," *Wiener medizinische-Halle* 5 (1864). The essay appears in short segments between pages 157 and 477.
6. Carl Braun, "Über Luftwechsel und Puerperalkrankheiten," *Wiener medizinische Wochenschrift* 14 (1864): cols. 257–259, and Carl Braum, "Über Luftwechsel, den neuen Ventilations-Bau mit Benützung der natürlichen Temperaturdifferenzen und Luftströmung," *Medizinische Jahrbücher* 20 (1864): 165–208.
7. Carl Mayrhofer, "Zur Frage nach der Ätiologie der Puerperalprocesse," *Monatschrift für Geburtskunde und Frauenkrankenheiten* 25 (1865): 112–134.
8. Carl Mayrhofer, *Sterilität des Weibes, Entwicklungsfehler und Entzündungen der Gebärmutter* (Stuttgart: Ferdinand Enke, 1882), p. 143.
9. Mayrhofer, "Ätiologie der Puerperalprocesse," pp. 128, 134.
10. Gustav August Braun, *Compendium der Geburtshilfe* (Vienna: Braumüller, 1864), p. 305.
11. Josef Späth "Statistische und historische Rückblicke auf die Vorkommnisse des Wiener Gebärhauses während der letzten dreissig Jahre mit besonderer Berücksichtigung der Puerperal-Erkrankungen," *Medizinische Jahrbücher* 20 (1864): 145–164, at p. 162.
12. Späth, "Rückblicke," pp. 161 f.
13. A. C. G. Veit, "Über die in der geburtshilflichen Klinik in Bonn im Sommer 1864 und Winter 1864–65 aufgetretenen puerperalen Erkrankungen," *Monatsschrift für Geburtskunde und Frauenkrankheiten* 26 (1865): 127–155, 161–208, at pp. 195 f.
14. Josef Späth, "Über die Sanitäts-Verhältnisse der Wöchnerinnen an der Gebärklinik für Hebammen in Wien vom October 1861 bis Jänner 1863," *Medizinische Jahrbücher* 19 (1863): 10–27, at pp. 10–13.

15. An obituary notice of the death of Carl Mayrhofer, signed "r," *Wiener medizinische Blätter* 5 (1882): col. 725.
16. An obituary notice of the death of Carl Mayrhofer, signed "Ch.," *Wiener medizinische Presse* 23 (1882): cols. 778–779, at col. 779.
17. An obituary notice, *Wiener medizinische Presse*, col. 779.
18. An obituary notice, *Wiener medizinische Presse*, col. 779.
19. An obituary notice, *Wiener medizinische Presse*, col. 778.
20. I. Fischer, *Geschichte der Geburtshilfe in Wien* (Vienna: Vogel, 1909), p. 353.
21. Erna Lesky, *The Vienna Medical School of the Nineteenth Century* (Baltimore: Johns Hopkins, 1976), pp. 189 f.
22. Wilhelm Lange, "Semmelweiss'schen Theorie über die Entstehung des Puerperalfiebers," *Monatsschrift für Geburtskunde und Frauenkrankheiten* 18 (1861): 375 f.
23. K. Codell Carter, "Ignaz Semmelweis, Carl Mayrhofer, and the Rise of Germ Theory," *Medical History* 29 (1985): 33–53.
24. Max Boehr, "Über die Infectionstheorie des Puerperalfiebers und ihre Consequenzen für die Sanitäts-Polizei," *Monatsschrift für Geburtskunde und Frauenkrankheiten* 32 (1868): 401–433, at p. 403.
25. Boehr, p. 404.
26. Rudolf H. Ferber, "Die Ätiologie, Prophylaxis und Therapie des Puerperalfiebers," *Schmidt's Jahrbücher der Medizin* 139 (1868): 318–346, at p. 318.
27. Joseph Amann, *Klinik der Wochenbettkrankheiten* (Stuttgart: Ferdinand Enke, 1876), p. 67.
28. Brennecke, "Der puerperalfieber Frage," *Berliner klinische Wochenschrift* 16 (1878): 744–747, 758–761, at p. 744.
29. Otto Spiegelberg, *Lehrbuch der Geburtshülfe* (Lahr, Germany: Moritz Schauenburg, 1878), p. 714.
30. Otto Spiegelberg, "Die Entwicklung der puerperalen Infection," *Berliner klinische Wochenschrift* 17 (1880): 309–312, at p. 309.
31. Carter, p. 46.
32. Sophia Jex-Blake, "Puerperal Fever: An Inquiry into Its Nature and Treatment," M.D. diss., University of Bern, 1877, p. 23.

6

Puerperal Infection

What is the current medical concept of puerperal fever, and how common is the disease today? The U.S. Joint Committee on Maternal Welfare has defined "standard puerperal morbidity," as a "temperature of 100.4 [or higher], the temperature to occur in any two of the first ten days postpartum, exclusive of the first twenty-four hours, and to be taken by mouth by a standard technique at least four times daily."[1] A similar definition has been adopted in England: "a fever of 100.4 over a period of twenty-four or more hours during the three weeks after childbirth."[2] However, it is almost impossible to determine how frequently these standards are met. Women are usually discharged from maternity facilities within one to four days of delivery; and once they are discharged, no one regularly records their temperatures.

Moreover, even if one had such records, it is not clear exactly what they would reveal. An elevated temperature is not always a sign of morbidity. Fever is a common postpartum phenomenon, and it can have various causes, such as hormonal changes, reaction to drugs, or various medical conditions unrelated to delivery. Most postpartum fevers subside spontaneously within a few days and have no adverse consequences, so they may not really indicate

puerperal morbidity. As nineteenth-century physicians often observed, not all fever in puerperae is puerperal fever.

At present, medicine favors concepts of diseases that describe either an observable change in body tissues or the cause of symptoms. These preferences reflect the influence of pathological anatomy and of the quest for causal definitions. Thus, the concept of "puerperal fever" is no longer favored as a diagnostic category. In its place, modern medical texts employ two kinds of terms. First, as was the case in the nineteenth century, it is common to identify the specific organs or tissues that are changed in puerperal disease. For this purpose, physicians use such terms as "endometritis" (inflammation of the mucous membrane of the uterus), "metrophlebitis" (inflammation of the veins of the uterus), and "peritonitis" (inflammation of the serous membrane that lines the walls of the abdomen)—terms invented by eighteenth- and nineteenth-century pathologists. However, there is this difference: in the nineteenth century, these terms simply identified inflammations in particular tissues and were strictly neutral with respect to causation; today, the use of a term like "endometritis" often presupposes that the inflammation in the specified tissue is due to an infection by parasitic microorganisms.

Second, in place of the term "puerperal fever," physicians also speak of infection, sepsis, shock, or toxicity. These terms differ from terms like "metrophlebitis" or "peritonitis" in that they give no indication where the disease process is focused. They also differ from terms like "fever" or "inflammation" in that they name different ways in which fever and other observable signs and symptoms originate. In this latter sense, each of these concepts is at least partially causal. "Infection" is any abnormal multiplication of parasitic organisms in a living host, and "sepsis" is the destruction of living tissues by parasitic organisms. Thus, these terms are closely related. "Shock" refers to a sudden reduction in the volume of blood returning to the heart from the peripheral circulatory system. Shock can be caused by different

conditions, such as hemorrhage or allergy, but it can also be caused by infection. "Toxicity" refers to the accumulation of toxins or poisons within the body; this also can have various causes, one of which is infection. Thus, in the context of puerperal morbidity, while infection, sepsis, shock, and toxicity are distinguishable conditions, they occur regularly in combination. The earlier concept of puerperal fever included many, but not all, of the cases that would now fall into each of these categories. The modern terms used most commonly in reference to what earlier physicians would have called "childbed fever" are "puerperal infection" and "puerperal sepsis."

However, in using these two modern terms, one must be careful not to introduce an ambiguity. Both terms could be taken to refer to some condition in puerperae that is either unrelated or only indirectly related to delivery. For example, urinary tract infections are fifteen times more common in women than in men, and the incidence of such infections increases during pregnancy. One could refer to a urinary tract infection in puerperae as a puerperal infection. However, using the term so broadly would reduce its usefulness and would also be inconsistent with the historical context from which the term has emerged. Insofar as they were able, nineteenth-century physicians would have excluded these cases from their category of "childbed fever," and this is also done today. Thus, "puerperal infection" and "puerperal sepsis" are usually limited to genital tract infections that follow and result from labor, delivery, or abortion; this is the sense in which we will use these terms.

How common is puerperal infection? A study conducted in 1951 at Queen Charlotte's Hospital in London found that of 2,701 deliveries there were 1,423 cases of fever but only 141 cases—just over 0.5 percent of the total births—of "true genital tract infections."[3] However, many physicians routinely prescribe prophylactic antibiotics to all puerperae, and antibiotics are always administered promptly to any patient who seems especially at risk.

Thus, many incipient puerperal infections are controlled before they become clinically apparent, and the 1951 study is not a reliable indication of the true incidence of such infections. Obviously it would be unconscionable to withhold treatment for the sole purpose of determining the ordinary frequency of infection; therefore, one must be content with estimates. In the United States at the present time, puerperal infection is believed to occur in between 1 and 8 percent of all deliveries,[4] a rate close to the incidence of puerperal fever reported in successful nineteenth-century maternity facilities. On the other hand, in the United States at the present time, only about one hundred women die each year from puerperal sepsis—about three for every one hundred thousand deliveries. This rate of mortality—although a substantial part of the overall rate of maternal mortality and a terrible burden—would be regarded by nineteenth-century obstetricians as incredibly favorable.

Today, the single most important risk factor for puerperal infection is cesarean section.

> Both for frequency and severity of pelvic infection, cesarean section has emerged in the last few decades as the major predisposing clinical factor. . . . [Cesarean section involves] a five to thirty fold increase in risk of puerperal infection. Published accounts of post cesarean section infection reveal that endometritis occurs in twelve to fifty-one percent. . . . Bacteremia develops in eight to twenty percent, and other serious complications . . . occur in two to four percent of indigent patients with endometritis after cesarean section. . . . Reasons for higher infection after cesarean section include increased intrauterine manipulation, foreign body (suture material), tissue necrosis at the suture line, hematomaseroma formation, and wound infection.[5]

Another important risk factor for puerperal sepsis is socioeconomic status: indigent women have higher than normal rates of infection.

The rates may be higher because these women are more likely to deliver in teaching hospitals, where they are examined more frequently during labor. In other words, as in Semmelweis's day, their increased risk stems not from a lack of medical attention, but from too much of it.

Other risk factors include the frequency of vaginal examinations, the level of fetal monitoring, and the length of stay in hospitals. As in the past, most of today's risk factors for puerperal infection involve forms of medical intervention. Other things being equal, the less the medical involvement in the birth process and the shorter the patient's stay in the hospital, the healthier she is likely to be.

Within thirty years of the publication of Semmelweis's *Etiology of Childbed Fever*, physicians had concluded that microorganisms—rather than decaying organic matter—caused what was then called "childbed fever." By the late 1880s, physicians had concluded that a particular kind of microorganism—streptococci—were most frequently involved in the disease. Which microorganisms are now regarded as the causes of puerperal sepsis?

Postpartum genital tract infections ordinarily involve a variety of organisms; in most cases, there is no one causal agent. In a recent study, more than 80 percent of cases of puerperal endometritis were found to involve more than one species of organism. On average, about three different organisms would be identified in each case of the disease.[6]

At any given moment, the human body is inhabited by billions of microorganisms. Those that regularly inhabit the body are called "endogenous"; those that invade opportunistically are called "exogenous." Usually, both kinds of organisms are relatively harmless, and many endogenous organisms actually contribute to good health in various ways. The body's defenses repel most invasions of potentially pathogenic organisms before they cause observable disease symptoms. Even many infections of streptococcal

bacilli have no harmful consequences. On average, people experience symptomatic disease episodes caused by streptococci about every three to four years, and asymptomatic infections are even more common.

As a part of their ordinary metabolic processes, microorganisms create various chemical byproducts that are either given off as waste or become incorporated into the structure of the parasite. Metabolic wastes diffuse more or less randomly through the tissues surrounding the parasite; and while some of these byproducts are harmless, metabolic wastes and even parts of the microorganism itself can be poisonous to the host. Some metabolic wastes from microorganisms are exceptionally virulent. Indeed, they include the most deadly of any known poisons: for instance, "it has been calculated that as little as seven ounces of crystalline botulinum type A toxin would suffice to kill the entire human population of the world."[7] When pathogenic parasites multiply within the body, the toxins they generate may become so abundant in the living tissues that they gradually poison the host. The result is what we call "disease." At present, it is not possible to trace each specific disease symptom to the production of a specific toxin. However, most of the symptoms associated with ordinary infectious diseases are assumed to result from this process of intoxication.

Streptococci are unable to produce for themselves all the vitamins and amino acids that they require, and these nutrients must ordinarily be derived by breaking down the host's tissues. For this reason, streptococci cannot easily be grown outside living animals. However, in the late nineteenth century, researchers found that streptococci could flourish on a combination of sheep blood and agar; this red opaque gelatin came into common use as a culture medium. When streptococci grow on blood agar, some colonies become surrounded by a greenish margin while others form a margin that is transparent. When examined under a microscope, agar from the greenish margins can be seen to contain many discolored blood corpuscles, whereas agar from transparent

margins contains no blood corpuscles at all. This is interpreted to mean that the streptococci that form greenish margins are unable to disintegrate completely the red blood cells embedded in the agar, while those that form transparent margins are able to do so. In 1903 Hugo Schottmuller proposed using this difference as a basis for classifying streptococci. Strains of organisms that form greenish margins on blood agar are called "alpha-hemolytic," and those that produce clear margins are called "beta-hemolytic" or, frequently, just "hemolytic." Still other strains produce no visible changes in blood agar, and these strains are called "gamma-hemolytic." All three varieties can cause human and animal diseases, but the overwhelming majority of all pathogenic streptococci are beta-hemolytic.

Streptococci are also classified in terms of the immune reactions that they provoke when they invade a new host, and this classification cuts across the classification in terms of hemolytic reactions. When an alien substance is introduced into living tissues, the immune system may begin producing distinctive molecules that become attached to the alien ones just introduced. Alien substances that trigger this response in the immune system are called "antigens," and the molecules produced by the immune system are called "antibodies." By becoming attached to an antigen, the antibody helps reduce its harmful effect on the body. This can be accomplished in various ways. Some antibodies group antigens into clumps so that they cannot diffuse through the body; some mark antigens for subsequent destruction by other components of the immune system; and other antibodies merely coat antigens so that the host is shielded from their toxic effects. For the most part, each antibody is created specifically to attack one particular kind of antigen, so new antibodies must be created each time the body is invaded by antigens of a new kind.

In reality, streptococci and other bacteria are enormous in comparison to the size of individual antigenic molecules; and instead of treating an invading bacterium as a single antigen, the immune

system typically produces a variety of antibodies that attach themselves to various specific parts of the cell walls of the invaders. Thus, different segments of the cell walls of a given bacterium may function as different antigens and provoke the production of different antibodies. The cell walls of streptococcal bacilli contain particular carbohydrate molecules that function as antigens. In 1933 the American bacteriologist Rebecca C. Lancefield proposed classifying streptococci according to the antigenic properties of these carbohydrates. She originally distinguished five main groups of bacilli, which she labeled by the letters A through E.

Lancefield found that the streptococci recovered from most human infections were included in her group A. She originally isolated from cattle the bacilli that constituted group B. Group C strains came from various animals such as cattle, horses, rabbits, and guinea pigs. Group D organisms came from cheese, and group E streptococci were isolated from milk.[8] Two years later, Lancefield and Ronald Hare identified two new groups, F and G. They also reported research on the incidence of different groups of streptococci in infections of the birth canal of postpartum women. They noted that

> the vast majority of strains from definite infections of the uterus are members of group A. . . . The vast majority of hemolytic streptococci from the birth canal which do not bring about active infections are not members of this group. Most of them fall either into group B or D. . . . The human nasopharynx is the main reservoir of group A strains in nature. Because of this, and because of the great rarity of group A streptococci in the normal vagina, *ante partum*, there can be little doubt that the vast majority of puerperal hemolytic streptococci infections are due to inoculation from some other source than the patient's genital tract and probably arise from the above mentioned reservoir in the patient or attendants.[9]

This was an important discovery. In the 1930s, obstetricians believed that puerperal sepsis was ordinarily due to streptococci that were endogenous to the birth canal. This meant that the physicians themselves were not responsible for most cases of the disease and that they could do little or nothing to prevent it. Of course, this was a slightly more sophisticated version of the same general attitude that Semmelweis had opposed seventy years earlier. And as in Semmelweis's time, this belief fostered carelessness in the use of antiseptic measures. It was generally believed that obstetrical operations—such as delivery—required less stringent antiseptic measures than were required in surgery.[10] Lancefield's discovery that puerperal sepsis is usually caused by group A streptococci conclusively refuted this view and proved *once again* that most cases of puerperal infection were caused by the intervention of medical personnel.

Within Lancefield's classification scheme, which is still in use today, group A streptococci are recognized as the most important bacterial agents in human disease. Consequently, organisms of this group have been studied extensively. Group A bacilli seem to form two natural classes: strains from one class usually attack the skin, and strains from the other class attack the throat. Group A strains that cause skin infections are more common in warm climates, they seem not to occur epidemically, and they usually cause local rather than systemic disease symptoms. By contrast, group A strains that typically invade the throat are more common in cold climates and in the winter, they often occur in epidemics, and they frequently cause systemic symptoms such as fever. If allowed to invade the body under suitable conditions, group A strains of this second variety can also cause such diseases as erysipelas, pneumonia, rheumatic fever, scarlet fever, and puerperal fever.

Most of the horrible epidemics of childbed fever in the eighteenth and nineteenth centuries were probably caused by those strains of group A streptococcal bacilli that normally attack the throat. This conjecture is based on clinical, pathological, and

epidemiological similarities between what was reported in the great epidemics and modern observations of disease episodes known to be caused by these group A bacilli.

In contrast to group A organisms, group B streptococci are often endogenous to healthy humans; they are commonly found in the intestinal tract and in the female genitals. Between 5 and 30 percent of pregnant women have vaginal colonies of group B streptococci, and the rate seems to be highest for Caucasian women under twenty years of age. These bacilli can spread to the urinary tract, where they can cause infections.

In 1935, R. M. Fry reported finding group B bacilli in three cases of puerperal sepsis.[11] However, during the next three decades, group B streptococci received little medical attention. Reports of group B infections became more common in the medical literature during the 1960s; and in succeeding decades, such reports have become ever more prominent. Puerperal infections from endogenous group B strep usually occur when the genitals are damaged in delivery and the organisms invade the bloodstream or other tissues. Patients undergoing cesarean section are particularly at risk. Postpartum group B streptococcal infections typically involve the sudden onset of high fever, usually within twelve hours after delivery. However, the symptoms in group B infections are sometimes indistinguishable from those observed in group A infections, and conclusive identification of the causal agent requires bacteriological examination. Whether the increase in reported cases reflects a shift in the relative prevalence of the causal agents themselves or whether the change is to be explained in some other way remains to be seen.

In spite of the great notoriety of the puerperal fever epidemics in earlier centuries, sporadic cases of the disease have probably always accounted for at least as many total deaths as have the epidemics.[12] On the other hand, since the epidemics were mostly limited to the inhabitants of maternity clinics, sporadic cases are drawn from a larger population. Thus, while they may account for

more total deaths, they are proportionately less common. That many sporadic cases were caused by endogenous group B streptococci that exploited an opportunity to invade the damaged genital tissues of the puerperae now seems likely. These cases would explain many of the instances Semmelweis attributed to self-infection.

In the context of human birth, there is one striking difference between group A and group B infections. Group A streptococci generally attack the mother, usually when exogenous bacilli are introduced into the birth canal by medical attendants. By contrast, group B infections generally attack the fetus or the neonate when it is exposed to bacilli that are either endogenous to the birth canal or else carried by medical personnel. About 75 percent of babies delivered by women who harbor vaginal group B streptococci become contaminated in the course of delivery; however, only a small percentage of these babies become diseased. Moreover, between 16 and 45 percent of nursery personnel carry group B streptococci, and contamination of the newborn by medical attendants is also very common.

Altogether it has been estimated that twelve thousand to fifteen thousand newborns contract group B streptococcal infections each year and that within this group the mortality rate is about 50 percent.[13] A German study conducted between 1983 and 1988 examined 222 cases of neonatal septicemia and meningitis. The incidence of disease was just below 1 percent of all the babies delivered; and of those who became ill, the fatality rate was 45.9 percent. Group B streptococci were frequently isolated as one of the causal agents. Following criteria established by the U.S. Centers for Disease Control in Atlanta, these German researchers concluded that "152 (68.5%) of the 222 infections were nosocomial."[14] The term "nosocomial" refers to a condition contracted within the hospital environment. So the conclusion of this study is that well over half of all the neonates who became diseased had contracted their infections from their hospital surroundings.

There is also evidence that the rate of group B infection among neonates is increasing. A recent Swedish study found that the rate of neonatal group B infections increased consistently between 1973 and 1985. The authors concluded that the increase "probably reflects a true increment related to an increased rate of colonization of pregnant women with GBS [group B streptococci] during this period."[15] So group B streptococci present a real and growing threat to the health of mothers and especially of infants.

Streptococci from groups C and G are also found in the female genital tract, and both have been associated with epidemic and sporadic puerperal sepsis.[16] However, these are not common pathogens in puerperal disease.

In addition to streptococci, several other parasitic organisms can cause puerperal infections. From the middle of the nineteenth century, it has been recognized that many organisms—including streptococci—flourish in the presence of ordinary air while others can survive only in atmospheres that contain little free oxygen. The former are called "aerobic" and the latter "anaerobic." Various anaerobic microorganisms are normally endogenous to the female genitals. During the latter part of the nineteenth century, researchers established that various other anaerobic organisms could invade the human body opportunistically and cause different infections. Anaerobic organisms have probably accounted for a significant percentage of sporadic cases of puerperal infection.[17]

Escherichia coli, commonly known as *E. coli*, is an aerobic bacterium that normally flourishes harmlessly in the intestinal tract. However, when *E. coli* invades other tissues, it can cause several serious diseases, including gastric disorders among the newborn, urinary tract infections in adults, and puerperal sepsis. *E. coli* is readily spread by the bloodstream and can cause infections throughout the body. *E. coli* invasions of the vascular system are characterized by the sudden onset of alternating fever and chills, and, by a process not yet understood, such infections are usually accompanied by shock. Indeed, *E. coli* is the most common cause of puerperal septic shock.[18]

How effectively can puerperal sepsis be controlled by prophylactic cleanliness? Even in the last two decades of the nineteenth century there was good evidence that streptococci were the most common cause of childbed fever. One would expect this knowledge to have prompted the use of antiseptic measures that would have significantly reduced the incidence of infection. Yet, surprisingly, recognition of the causal agents seems to have had almost no impact on maternal mortality. In 1910, Arnold Lea of Manchester observed,

> In the five years 1851–5 the puerperal death rate from all causes [in England and Wales] was 4.9 per 1000 [births], and in the five years ending 1906 it still amounted to 4.2 per thousand. . . . [We] do no violence to the statistics if we put down the septic [puerperal fever] mortality in England and Wales at between 3000 and 5000 per annum.[19]

Maternal mortality remained essentially constant through the next twenty-five years. As Irvine Loudon has pointed out, any decline in morbidity probably resulted from a reduction in the virulence of the streptococci themselves or from a decrease in availability of the organisms in the population at large, rather than from improvements in medical practice.[20]

One reason for the persisting mortality rate was that until Lancefield proved puerperal sepsis was usually exogenous, obstetricians saw little reason to adhere to strict aseptic and antiseptic standards. So they continued to infect their patients. Another reason that mortality remained so high was the inherent difficulty of preventing infection by antiseptic measures alone. Once a person has been colonized by streptococci, he or she may continue to carry and to spread pathogenic organisms for weeks, months, or

even years—certainly long after all symptoms have disappeared. Moreover, many and possibly most cases of strep infection are asymptomatic. Thus, at any given time, a significant percentage of the population may be carrying and spreading group A streptococci without even knowing that they are infected.

> Following an epidemic that attacked twenty women in the Boston hospital in 1965, epidemiologists found that about five percent of the hospital staff and ten to fifteen percent of the neighboring community were asymptomatic carriers of hemolytic streptococci. Of the forty hospital carriers, four had positive throat cultures for group A and one had a positive skin lesion.[21]

Even if medical personnel were to wash conscientiously, many of them would be carrying group A streptococci in their noses and throats at any given time. From these sources they could constantly reinfect their hands. Moreover, the patients and visitors who enter delivery facilities may also carry streptococci. After delivery, patients can sometimes infect themselves or each other, or they can be infected by visitors.

Streptococci are usually spread by touching, but they can also be spread through the air by way of dust particles, called "fomites." It is not known how readily streptococci can be carried by fomites, and currently most hospitals give relatively little attention to this problem.

> Current infectious disease officers recommend a hospital practice that places less emphasis on the control of fomites and more emphasis on the isolation of carriers and the washing of hands between patients. This is designed to prevent the direct transmission of infection from patient to patient and from attendant to patient.[22]

But even if fomites are not the usual means by which infection is conveyed, such a conveyance can occur. Taking all of this into account, it is unlikely that even conscientious washing of the kind that Semmelweis recommended could, by itself, prevent dissemination of the causal organisms. At least given present opinion, the control of puerperal sepsis depends at least as much on therapy as on prophylactic cleanliness.

Irvine Loudon has shown that 1937 was the crucial year in which chemotherapy first significantly reduced maternal mortality. While it is possible that the decline in mortality was due, in part, to a spontaneous reduction in the virulence of streptococci, the decline seems to have been due primarily to the introduction of a class of drugs known as "sulfonamides."[23]

In 1932 a group of German chemists working at an industrial laboratory synthesized various chemical compounds in the quest for an antibacterial agent that could be taken internally. One of the chemicals they produced was called "prontosil." In 1935 a member of this group, Gerhard Domagk, announced that prontosil—although relatively ineffective against bacteria grown experimentally outside the body—protected living mice against virulent streptococci. Four years later in 1939, Domagk was awarded the Nobel prize for his work; but by that time the National Socialists (the Nazis) controlled Germany, and Domagk was obliged to refuse the award.

Shortly after the announcement of Domagk's discovery, French chemists showed that the specific part of the complex prontosil molecule that was effective against streptococci was an aminophenylsulfamide and that other related chemicals built from this same constituent could also be useful.

Over the next few months, various physicians reported the use of prontosil on humans suffering from erysipelas and from puerperal fever. The reports were consistently favorable but were accompanied by too little clinical and bacteriological evidence to be really conclusive. In 1936 Leonard Colebrook and Meave Kenny published two reports of trials using prontosil on mice and on

a total of sixty-four victims of puerperal sepsis. Prontosil was found to be effective even in advanced cases in which streptococci could be readily isolated from the patient's blood—a condition that, in most instances, "made the prognosis extremely grave."[24] One very ill patient had a temperature of 105 degrees, and each cubic centimeter of her blood produced more than five thousand colonies of hemolytic streptococci. Colebrook noted that previously he had found bacilli concentrations of this magnitude only in terminal stages of fatal infections. Yet, incredibly, on the fourth day of treatment, the patient's blood was sterile and her temperature had fallen to the normal level. Although he tried to be appropriately cautious in reporting his work, Colebrook could only describe the effects of prontosil as spectacular. This was the first time any chemotherapy had been proven effective against streptococci. Within months, the sulfonamides were being so widely used that, even in the first year of their use, they significantly reduced maternal mortality in the British Isles.

However, the use of prontosil and of the other sulfonamides was subject to various problems. Strains of hemolytic streptococci soon emerged that were resistant to treatment by these drugs, and patients sometimes developed allergic reactions. There was clearly a need for other drugs that would be more effective and yet less toxic.

The discovery of penicillin by Alexander Fleming in 1928 (along with its subsequent development in the 1940s) was destined to have a greater impact on the treatment of streptococcal infections than any other single therapeutic measure before or since. Fleming made his initial discovery when airborne mold spores accidentally invaded a culture plate and began growing among colonies of the staphylococci that Fleming was cultivating. Fleming noticed that the bacilli colonies surrounding the mold disintegrated spontaneously. He removed the mold and cultivated it in a new medium. He then brushed streaks of different pathogens across the new mold cultures. As had happened with the colonies of staph,

many of the new pathogens were destroyed by the mold. Fleming identified the mold as a variety of *Penicillium*, and he demonstrated that the active substance, which he named "penicillin," was not toxic to humans. Fleming tried to concentrate and to purify penicillin but could produce only an unstable liquid unsuitable for medical purposes.

The development of the sulfonamides in the late 1930s stimulated interest in chemotherapy generally and provided the incentive to renew the investigation of penicillin. A group of Oxford chemists, especially Howard Walter Florey and Ernst Boris Chain, managed to concentrate penicillin and to produce from it a stable and solid substance that could be used medically. During the early 1940s, they also conducted animal trials showing that penicillin was not toxic to animals but was very effective against a wide range of pathogens. The results of the first human trials were published in 1941. Four years later in 1945, Fleming, Florey, and Chain were awarded a Nobel prize for their discoveries.

Penicillin and its numerous derivatives are generally effective against group A streptococci, and they remain the drugs of choice for dealing with most cases of puerperal sepsis. However, as we have seen, puerperal sepsis is usually a polymicrobial infection, and some of the possible causal agents—for example, group B streptococci—are not always fully responsive to penicillin therapy. For this reason, at present, puerperal sepsis is usually treated with a combination of different antibiotics.

Chemotherapy is successful in most cases, but serious problems remain: First, some patients continue to die or to suffer serious disabilities either in spite of the therapy or sometimes because of complications arising directly or indirectly from the therapy. Second, microorganisms change rapidly, and there is good evidence that their levels of virulence have fluctuated significantly during the past two or three centuries. There is also evidence that new and more virulent strains of group A streptococci may now be emerging.[25] But whether or not this proves to be true, the possibility

remains a constant threat. Third, in many cases the virulence of microorganisms is associated with ethnic and economic conditions; modern antibiotics have been less successful in controlling puerperal sepsis in non-Western cultures than in Europe and America. For these reasons, puerperal sepsis remains a formidable threat both to delivering women and to neonates throughout the world.

Notes

1. Ronald S. Gibbs and Richard L. Sweet, "Maternal and Fetal Infections," in Robert K. Creasy and Robert Resnik, *Maternal and Fetal Medicine Principles and Practice*, pp. 603–678 (Philadelphia: W. B. Saunders, 1984), at p. 622.
2. Margaret DeLacy, "Puerperal Fever in Eighteenth-Century Britain," *Bulletin of the History of Medicine* 63 (1989): 521–556, at p. 524.
3. DeLacy, p. 524.
4. Gibbs and Sweet, p. 623.
5. Gibbs and Sweet, p. 623.
6. D. Heather Watts et al., "Early Postpartum Endometritis: The Role of Bacteria, Genital Mycoplasmas, and *Chlamydia trachomatis*," *Obstetrics and Gynaecology* 73 (1989): 52–60, at p. 58.
7. Bob A. Freeman, *Burrows Textbook of Microbiology*, 21st ed. (Philadelphia: W. B. Saunders, 1979), p. 226.
8. Rebecca C. Lancefield, "A Serological Differentiation of Human and Other Groups of Hemolytic Streptococci," *Journal of Experimental Medicine* 57 (1933): 571–595.
9. Rebecca C. Lancefield and Ronald Hare, "The Serological Differentiation of Pathogenic and Non-pathogenic Strains of Hemolytic Streptococci from Parturient Women," *Journal of Experimental Medicine* 61 (1935): 347.
10. Irvine Loudon, "Puerperal Fever, the Streptococcus, and the Sulfonamides, 1911–1945," *British Medical Journal* 295 (1987): 485–490, at p. 487.
11. R. M. Fry, "Fatal Infection by Hemolytic Streptococci Group B," *Lancet* 1 (1938): 199.
12. Edward Shorter, *A History of Women's Bodies* (London: Allen Lane, 1983), chapter 6.
13. Gibbs and Sweet, p. 632.
14. E. L. Grauel et al., "Neonatal Septicaemia—Incidence, Etiology, and Outcome," *Acta Paediatrica Scandinavica* 360, Supplement (1989): 113–119, at pp. 117 f.
15. I. Sjöberg et al., "Incidence of Early Onset Group B Streptococcal Septicemia in Sweden 1973–1985," *European Journal of Clinical Microbiology and Infectious Diseases* 9 (1990): 276–278, at p. 277.
16. Isaac Ginsburg, "Streptococcus," in Abraham I. Braude, Charles E. Davis, and Joshua Fierer, *Infectious Diseases and Medical Microbiology*, 2nd ed., pp. 242–253 (Philadelphia: W. B. Saunders, 1986), at p. 250.
17. Stanley A. Seligman, "The Lesser Pestilence: Non-epidemic Puerperal Fever," *Medical History* 35 (1991): 89–102.