



History Repeating? Avoiding a Return to the Pre-Antibiotic Age

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History Repeating?
Avoiding a Return to the Pre-Antibiotic Age

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Abstract

Antibiotics are among the most important discoveries of medical science. Analysis of infectious disease mortality data from the U.S. government reveals that antibacterial agents may save over 200,000 American lives annually, and add 5-10 years to U.S. life expectancy at birth. The spread of antibiotic immunity among bacteria – an evolutionary phenomenon mediated by plasmids, transposons, and integrons (carrying DNA encoding attack enzymes, efflux pumps, and other protective devices) – threatens these public health achievements. The examples of increasingly resistant strains of *Staphylococcus aureus*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* demonstrate the importance of continued development of new antimicrobials, especially ones to treat nosocomial, gram-negative infections. Unfortunately, studies indicate that antibiotics comprise less than 1.5% of compounds under investigation at the largest pharmaceutical and biotechnology

companies. Data from papers on drug costs and revenues show that antibacterial agents are simply not as profitable as other types of pharmaceuticals. “Wild-card patent extension” – in conjunction with restrictions on the use of new antibiotics (to prevent the emergence of resistance) – provides one possible solution to the twin problems of “bad bugs, no drugs.”

I. Introduction: The Golden Age of Antibiotic Discovery

In September 1928, Alexander Fleming – a Scottish physician working as a bacteriologist at St. Mary’s Hospital in London – noticed an interesting phenomenon.¹ A Petri dish on which he had grown colonies of the bacterium *Staphylococcus aureus* had become contaminated with a fungus. In the vicinity of the mold, the staphylococci had lysed, or dissolved. Instead of forming a yellow, opaque mass, the colonies appeared translucent: “ghostly,” in Fleming’s words.² The Scotsman, who had spent years investigating lysozyme – an enzyme that dissolves cells in the human body – was intrigued to discover an example of lysis involving a medically important pathogen.³ The fungus contaminating the Petri dish was eventually identified as *Penicillium notatum*, and Fleming termed the lytic compound produced by this mold, “penicillin.”⁴

Fleming, in collaboration with other physicians and scientists, struggled in vain for many years to purify penicillin.⁵ In the meantime, he conducted studies demonstrating the substance’s safety in animals (even in its impure form, and in large doses).⁶ In May 1929, Fleming published a paper in which he suggested that

¹See PETER BALDRY, THE BATTLE AGAINST BACTERIA 89-125 (1976). See also MILTON WAINWRIGHT, MIRACLE CURE: THE STORY OF ANTIBIOTICS, 14-31 (1990); SEBASTIAN AMYES, MAGIC BULLETS, LOST HORIZONS, 23-31 (2001).

²WAINWRIGHT, *supra* note 1, at 17.

³See *id.* at 17-18. See also AMYES, *supra* note 1, at 27-29 (detailing Fleming’s pioneering work with lysozyme).

⁴See AMYES, *supra* note 1, at 30.

⁵See WAINWRIGHT, *supra* note 1, at 27-29; BALDRY, *supra* note 1, at 99-101.

⁶See AMYES, *supra* note 1, at 31.

penicillin might be beneficial in the treatment of infections due to “sensitive microbes” like staphylococci.⁷ Both he and Cecil Paine – a physician in Sheffield who had studied under Fleming at St. Mary’s Hospital – used filtrates of *Pencillium notatum* between 1930 and 1932 to treat bacterial eye infections. The two men irrigated the infected orbits of babies and adults with solutions of crude penicillin, achieving the first clinical cures attributable to the compound.⁸

Further studies of penicillin awaited purification of the compound. Howard Florey and Ernst Chain (who shared the Nobel Prize for Medicine with Fleming in 1945) accomplished this feat at Oxford University between 1938 and 1940.⁹ In February 1941, an Oxford policeman dying of staphylococcal septicemia became the first person in the world to receive intravenous penicillin.¹⁰ Within twenty-four hours of treatment, the man’s fever had broken and the patient was able to sit up and eat. Unfortunately, the small amount of purified product prepared by Florey and Chain ran out, and the policeman died of recurrent septicemia.¹¹ Subsequent treatment of three other seriously ill patients with penicillin confirmed the compound’s miraculous healing properties.

The shortage of purified product did not last long. Unable to secure commitments from British chemical companies to produce the substance, Florey traveled to America in 1941, armed with strains of *Penicillium notatum*.¹² His fungus captured the interest of both the United States Department of Agriculture and

⁷See WAINWRIGHT, *supra* note 1, at 100; BALDRY, *supra* note 1, at 26-27.

⁸See WAINWRIGHT, *supra* note 1, at 27, 42-43.

⁹See BALDRY, *supra* note 1, at 105-112; WAINWRIGHT, *supra* note 1, at 50-59.

¹⁰See BALDRY, *supra* note 1, at 110; AMYES, *supra* note 1, at 34.

¹¹See AMYES, *supra* note 1, at 34.

¹²See BALDRY, *supra* note 1, at 111-16; WAINWRIGHT, *supra* note 1, at 60-63.

several U.S. chemical concerns (particularly Pfizer). The Americans made several major contributions to the development of penicillin, including discovery of a deep fermentation process that optimized output of the drug, and isolation of the active, benzyl form of the compound.¹³ The U.S. government, which early recognized the drug's value in treating wounded soldiers, prioritized production such that by 1943, there was sufficient penicillin to supply the Armed Forces.¹⁴ British firms also ramped up production. For example, Glaxo, which had manufactured about 1000 Units of penicillin in December 1942, was producing 40 billion Units by January 1945.¹⁵ By the end of World War II, the civilian populations of the United States and Great Britain had ready access to purified penicillin.¹⁶

In the twelve years that it took to purify penicillin after the drug's discovery, another chemical compound had emerged with the ability to treat bacterial infections. This was Protonsil, a substance developed by researchers at the German chemical company I.G. Farbenindustrie.¹⁷ Protonsil owed its discovery to the ideas of the great scientist Paul Ehrlich (known as the "father of antibacterial therapy"), whose work with chemical dyes – which bind differentially to different types of cells – convinced him of the existence of "magic bullets" that could bind and destroy bacteria while holding human cells harmless. In 1907, Ehrlich himself had produced Salvarsan, an arsenical compound active against the microorganism responsible for syphilis (*Treponema pallidum*), whose toxicity limited its widespread use.¹⁸ In 1932, the scientists at I.G. Farben attached a sulfonamide group – which was known to increase the activity of dyes – to a yellow dye called Chrysoidin to produce Protonsil. Tests on mice confirmed this compound's ability to cure infection without

¹³See WAINWRIGHT, *supra* note 1, at 63 (discussing deep fermentation); BALDRY, *supra* note 1, at 115 (relating the discovery of benzyl penicillin).

¹⁴See BALDRY, *supra* note 1, at 115.

¹⁵WAINWRIGHT, *supra* note 1, at 61.

¹⁶See BALDRY, *supra* note 1, at 115.

¹⁷See AMYES, *supra* note 1, at 8-12; BALDRY, *supra* note 1, at 82-86.

¹⁸See AMYES, *supra* note 1, at 6-8; BALDRY, *supra* note 1, at 74-82.

killing the bacterial host.¹⁹

After three years of clinical trials in Germany, Protonsil was reported to the world in 1935 as a potential treatment for infections due to gram-positive bacteria: in particular, the staphylococci and streptococci also susceptible to penicillin.²⁰ Though doctors initially viewed the drug with some distrust – perhaps due to the general (and justified) suspicion of “patent medicines” at the time – Protonsil soon gained wide acceptance in the medical community. It was used with great success in maternity hospitals to reduce the mortality rate from puerperal fever (often caused by streptococci), and its reputation in America was secured in 1936 when the drug saved the life of President Roosevelt’s son, who was dying of severe tonsillitis.²¹ Ironically, despite Protonsil’s conceptualization as a dye, its therapeutic effects were discovered to derive not from its properties as a dye, but from its conversion to sulfanilamide in the body.²² Thereafter, companies in America and Europe raced to develop new “sulfonamides” with improved antimicrobial activity and fewer dye-related side effects.²³ By the time that purified penicillin burst onto the scene in 1941-1943, the sulfonamides as a group were already fighting the good fight against gram-positive bacteria.

The third “miracle drug” to appear in the 1930s and 1940s was the first in a long series of antibacterial agents derived from the actinomycetes: a group of gram-positive bacteria that resemble fungi and reside in the soil.

The central figure in the drug’s discovery was Selman Waksman, a soil microbiologist at Rutgers University.²⁴

¹⁹See AMYES, *supra* note 1, at 10-11; BALDRY, *supra* note 1, at 83-84.

²⁰See AMYES, *supra* note 1, at 11-12; BALDRY, *supra* note 1, at 84-85.

²¹See AMYES, *supra* note 1, at 12.

²²BALDRY, *supra* note 1, at 85-86.

²³See AMYES, *supra* note 1, at 13.

²⁴See BALDRY, *supra* note 1, at 130-34; WAINWRIGHT, *supra* note 1, at 120-26; AMYES, *supra* note 1, at 42-48.

Waksman believed that the actinomycetes held particular promise as potential inhibitors of bacterial growth, given their co-existence in nature with numerous strains of pathogenic bacteria. He was determined to isolate species that could cure infections due to gram-negative organisms, against which penicillin and sulfonamides were largely powerless.²⁵ To that end, he instituted a systematic screening program (subsidized by Merck) in which numerous actinomycetes were tested for their ability to inhibit the growth of gram-negative bugs.²⁶

In 1943, Waksman and his colleagues extracted a substance from a species of actinomycetes – which they styled *Streptomyces griseus* – that had exhibited good gram-negative activity. They called this compound “Streptomycin.”²⁷ Of particular interest was the fact that Streptomycin could also kill, *in vitro*, the organism responsible for tuberculosis (“TB”): *Mycobacterium tuberculosis*. Subsequent studies at the Mayo Clinic confirmed the value of the drug against TB. Medical societies in the United States and Great Britain immediately organized large-scale clinical trials of Streptomycin, whose results were published between 1944 and 1948.²⁸ The results were almost too good to be true. Streptomycin could cure tuberculosis – the “white plague” – without causing serious harm to patients. One of humanity’s oldest scourges appeared defeated.

Doctors soon discovered that *Mycobacterium tuberculosis* rapidly acquired resistance to mono-therapy with Streptomycin.²⁹ The solution to this potentially devastating problem was provided by a compound that the Swedish physician Jorgen Lehmann (in concert with the Swedish chemical company Ferrosan) had developed

²⁵See AMYES, *supra* note 1, at 43.

²⁶See WAINWRIGHT, *supra* note 1, at 121.

²⁷See AMYES, *supra* note 1, at 46.

²⁸See BALDRY, *supra* note 1, at 136-37; WAINWRIGHT, *supra* note 1, at 127.

²⁹See WAINWRIGHT, *supra* note 1, at 138.

between 1941 and 1945.³⁰ This was para-amino-salicylic acid (“PAS”), which was much less effective against TB than Streptomycin. However, studies in 1949-1950 demonstrated that the combination of Streptomycin and PAS was maximally effective against the disease, primarily because it prevented the development of mycobacterial resistance.³¹ Combination therapy immediately became the mainstay of treatment for tuberculosis. Isoniazid – a synthetic molecule simultaneously developed by three different pharmaceutical firms (Bayer, Hoffman-La Roche, and Squibb) – was frequently substituted for PAS starting with Isoniazid’s introduction in 1951.³² Streptomycin itself, as Waksman had hoped, was also used to treat a variety of gram-negative bacterial infections, including urinary tract infections, certain types of pneumonia, brucellosis, and the plague.³³

The extraction of penicillin from the fungus, *Penicillium notatum*, and of Streptomycin from the actinomycete, *Streptomyces griseus*, spurred scientists around the globe to search the natural world for other types of organic “bug juice.” In 1947, a research team from Parke, Davis discovered another species of *Streptomyces* – from a sample of soil taken from a mulched field in Venezuela – that produced a substance with activity against both gram-positive and gram-negative bacteria. Researchers at the University of Illinois simultaneously discovered a similar organism and substance in a compost heap in Urbana, Illinois.³⁴ The substance in both cases was Chloramphenicol, which proved efficacious against commonly occurring pathogens ranging from gram-positive staphylococci and streptococci, to gram-negative *Haemophilus influenzae* and *E. coli*.³⁵ Due to its activity against Rickettsial organisms – unique types of intracellular bacteria – Chloramphenicol

³⁰See AMYES, *supra* note 1, at 17-18.

³¹See WAINWRIGHT, *supra* note 1, at 137.

³²See AMYES, *supra* note 1, at 20.

³³See BALDRY, *supra* note 1, at 134.

³⁴See AMYES, *supra* note 1, at 49-50; BALDRY, *supra* note 1, at 148-49.

³⁵See BALDRY, *supra* note 1, at 151.

was also able to treat infections like Rocky Mountain Spotted Fever and typhus fever (an outbreak of which in Bolivia was halted by the drug in 1947). In addition, Chloramphenicol was lethal to the *Salmonella* species responsible for typhoid and paratyphoid fever.³⁶

Streptomyces yielded yet another broad-spectrum antibacterial agent in 1948: Chlortetracycline, the first of a group of drugs now known as the tetracyclines. Researchers at Lederle Laboratories isolated the *Streptomyces* species that produced this substance from a soil sample from Columbus, Missouri.³⁷ Like Chloramphenicol, Chlortetracycline was active against both gram-positive and gram-negative bacteria, as well as Rickettsial organisms.³⁸ Both broad-spectrum drugs could also be taken by mouth, a great advantage over Streptomycin and the original Penicillin G (though Lilly introduced Penicillin V, which was stable orally, as early as 1948).³⁹ By 1950, physicians had five powerful weapons at their disposal against infectious disease: penicillin, sulfonamides, Streptomycin, Chloramphenicol, and Chlortetracycline. In the space of fifteen years, starting with the introduction of Protonsil in 1935 and extending through the studies of TB combination therapy in 1949-1950, the tables had turned against many natural pathogens. Gram-positive and gram-negative bacteria, mycobacteria (TB), and Rickettsial organisms suddenly found humans – at least the ones in developed countries – most inhospitable hosts. The new wonder drugs had given man's immune system a significant boost.

As the antibacterial agents discussed thus far emerged, science struggled to give them a name. In 1942,

³⁶See *id.* See also WAINWRIGHT, *supra* note 1, at 152-53.

³⁷See BALDRY, *supra* note 1, at 150-51; WAINWRIGHT, *supra* note 1, at 152-53.

³⁸See AMYES, *supra* note 1, at 49.

³⁹See BALDRY, *supra* note 1, at 150-51 (discussing the oral formulations of the new, broad-spectrum antibiotics); WAINWRIGHT, *supra* note 1, at 86 (relating the development of Penicillin V).

Selman Waksman proposed the term “antibiotic” to refer to a “compound produced by one microorganism which is capable of killing or inhibiting another.”⁴⁰ This name derived from the word “antibiosis,” which the Frenchman Vuillemin had coined in 1889 to refer to the antagonistic effects of microorganisms on each other.⁴¹ Some authors still restrict use of the word “antibiotic” to substances of microbial origin, excluding chemical compounds like sulfonamides and PAS not found in nature. In keeping with Waksman’s definition, others apply the term to agents active against any type of microorganism (not just bacteria), including viruses and fungi. This paper uses “antibiotic” to refer to any chemical substance – whether found in nature or not – active against bacteria (including mycobacteria). This usage is consistent with much modern scientific writing as well as common parlance. The terms “antimicrobial” and “antibacterial agent” (or “antibacterial”) are used synonymously with antibiotic.

The golden age of antibiotic discovery revolutionized the world for both humans and bacteria. This paper considers the fall-out from this era. It is organized into four sections. Section II seeks to establish the significance – for human health – of antibiotics. Though it seems almost self-evident that antibacterial agents save lives from infection, it is important to establish the magnitude of any benefit in order to appreciate the dangers of a return to a pre-antibiotic age. Section III focuses on the “counterrevolution:” the emergence of resistance to antibiotics among bacteria. It uses the examples of three specific microorganisms to illustrate this evolutionary phenomenon. Section IV assesses the human response to the increasing threat of antimicrobial resistance. It judges the efforts of pharmaceutical companies and biotechnology firms to develop new drugs against “bad bugs.” Section V considers what more can be done to promote the development of such drugs. Through an analysis of the commercial costs and revenue associated with antibiotics, it arrives at

⁴⁰WAINWRIGHT, *supra* note 1, at 6-7.

⁴¹See BALDRY, *supra* note 1, at 63.

one possible plan to maintain mankind’s present advantage in its ceaseless battle against bacteria.

II. The Measure of Antimicrobials

It is generally accepted that the golden age of antibiotic discovery – the 1930s through the 1950s – played a central role in the “epidemiologic transition” from an “age of pestilence” to the current “age of degenerative [chronic] diseases.”⁴² This section of the paper aims to quantify the benefits conferred by antibiotics on Americans. In particular, it seeks to estimate the decrease in infectious disease mortality in the United States from 1936 to 1952. Quantification at this juncture will help predict the potential harm that would follow from a return to the pre-antibiotic era: as a result, for example, of increasing antimicrobial resistance and a dearth of new antibiotics (described in later sections).

The dates 1936 and 1952 have been carefully chosen. The earlier date represents the last year in which antibiotics were essentially unknown in America; the use of Protonsil to treat President Roosevelt’s son that year was extraordinary not only because of the identity of the patient, but also because of the nature of the treatment. Thereafter, sulfonamides and subsequent antibiotics became standard parts of a physician’s armamentarium. The year 1936 also marks a time when the benefits of other great measures to control infectious disease – unrelated to antibiotics – had already been realized. In particular, the disinfection of drinking water with chlorine, begun in Boonton, New Jersey, in 1908 (and mandated by Congress in 1914),⁴³

⁴²See Abdel Omran, *The Epidemiologic Transition: A Theory of the Epidemiology of Population Change*, 49 MILBANK Q. 509-538 (1971).

⁴³Chlorine Chemistry Council, *Chlorine Through the Ages*, at http://c3.org/chlorine_what_is_it/index.html# (accessed

had virtually eliminated waterborne carriage of cholera and typhoid fever by the late 1920s.⁴⁴ In addition, refrigeration had largely penetrated the food industry and household kitchen by the middle of the 1930s, reducing the incidence of disease due to foodborne pathogens.⁴⁵ Although factors unrelated to antibiotics undoubtedly continued to reduce infectious disease mortality between 1936 and 1952 – and are included as part of the “natural” rate of decline in the analysis below – there does not seem to have been another advance on the order of water chlorination during this fifteen-year period.

The year 1952 has other compelling reasons for its selection. By that date, antibiotics existed to treat infections due to all major types of bacteria: gram-positive, gram-negative, mycobacterial, and even Rickettsial organisms. Combination therapy with Streptomycin and PAS had established itself as effective therapy against TB, and Isoniazid had just emerged as an alternative to PAS. Of course, the discovery and development of new antibiotics did not stop in 1952. Indeed, that year witnessed the introduction of Erythromycin: the first of the macrolide antibiotics (and yet another product of a *Streptomyces* actinomycete).⁴⁶ Fermentation of yet another *Streptomyces* species yielded Vancomycin, a glycopeptide antibiotic, in 1956.⁴⁷ The cephalosporins – produced by a fungus found in sewage effluent in Sardinia – followed in the 1960s.⁴⁸ And work on penicillin never stopped; pharmaceutical companies introduced special anti-staphylococcal and extended-spectrum penicillins throughout the 1950s and 1960s.⁴⁹ Antibiotics introduced after 1952 were increasingly “invented” in the laboratory (and thus not true “antibiotics,” according to Waksman’s definition),

March 26, 2005).

⁴⁴See Chlorine Chemistry Council, Drinking Water Chlorination White Paper, at http://c3.org/chlorine_knowledge_center/whitepapercl.html (accessed March 26, 2005).

⁴⁵See U.S. Dep’t of Agric., *Refrigeration and Food Safety*, at http://www.fsis.usda.gov/Fact_Sheets/Refrigeration.&Food.Safety/index.asp (accessed March 26, 2005).

⁴⁶See BALDRY, *supra* note 1, at 152-53.

⁴⁷See AMYES, *supra* note 1, at 67-68.

⁴⁸See BALDRY, *supra* note 1, at 151-58; WAINWRIGHT, *supra* note 1, at 153-55;

⁴⁹See AMYES, *supra* note 1, at 57-60.

even if scientists modeled them after naturally occurring substances.

Despite all of this later research and invention, the antibiotics in place in 1952 were mostly adequate to the task of fighting pathogenic bacteria, especially given the lower levels of antimicrobial resistance at that time compared to later dates. They may not have been consumer-friendly – for example, Streptomycin was injection only with multiple, toxic side effects – but they were still widely employed. It also seems important to cut off the “antibiotic era” in the early 1950s to avoid overlap with other advances in medicine that may also have decreased mortality from infectious disease. For example, thoracic surgery to remove lung abscesses has likely saved the lives of numerous people with pneumonia. Many such advances in surgery are products of the past fifty years. The year 1952 seems safely on the “antibiotic-only” side of the line.

A. Methodology

The *Vital Statistics of the United States* (as it was long known) – initially compiled and published by the Bureau of the Census, then later by the Department of Health, Education, and Welfare (Health and Human Services) – contains a wealth of information about causes of death in this country. The *Vital Statistics* for 1930, 1936, 1952, 1960, and 2002 were examined for this paper. Causes of death due to bacterial or mycobacterial illness were identified for 1930 and 1936, and then followed forward to subsequent years.

Bacterial causes of mortality traced in the *Vital Statistics* – with the organisms now known to be responsible for them in parentheses – included: typhoid and paratyphoid fever (*Salmonella*); typhus fever (Rick-

ettsial organisms); scarlet fever (Group A *Streptococcus*); whooping cough (*Bordetella pertussis*); diphtheria (*Corynebacterium diphtheriae*); all forms of tuberculosis (*Mycobacterium tuberculosis*); pneumonia (*Streptococcus pneumoniae*, *Haemophilus influenzae*, others); diarrhea and enteritis (*E. coli*, *Salmonella*, *Shigella*, *Vibrio cholera*, *Clostridium perfringens*, others); appendicitis (enteric organisms); and puerperal septicemia (Group B *Streptococcus*). Starting in 1936, the *Vital Statistics* also included information on the following classic, bacterial illnesses: rheumatic fever, meningitis, acute endocarditis, lung abscess, and septic abortion. The 1930 statistics subsumed these diseases under larger headings (like “diseases of the heart” for acute endocarditis).

It is true, of course, that pneumonia can be viral in nature, and that both viruses and protozoa (like *Giardia lamblia* and *Entamoeba histolytica*) can cause diarrhea/enteritis. However, pneumonia and diarrhea are often bacterial in nature, and the *Vital Statistics* do not distinguish between bacterial and viral causes of these diseases (since physicians for most of the past century largely lacked the knowledge or ability to do so). Inclusion of cases of viral pneumonia or protozoal diarrhea in this analysis will do nothing to affect the absolute number of lives saved due to antibiotics, and only lead to an underestimation of the benefits of antimicrobials (because such cases will inflate the number of “bacterial” infections that did not respond to antibacterial agents). It should be mentioned that exclusively viral illnesses – such as influenza and measles – were excluded from the analysis.

For each of the five years mentioned above, a number of important calculations were made. These included 1) the total number of deaths due to bacterial illness; 2) the percentage of all deaths (from any cause) due to bacterial illness; and 3) the rate of deaths due to bacterial illness per estimated 100,000 population. For 1936 through 2002, the total number of deaths – and death rates – due to the separate conditions listed

above for those years (rheumatic fever, meningitis, etc.) were also calculated.

B. Results

1930: Approximately 300,000 Americans died of bacterial illnesses in 1930, representing an impressive 22% of all deaths that year.⁵⁰ This number excludes people who died of bacterial conditions like meningitis and acute endocarditis, as these diseases were not listed separately in 1930 (as mentioned above). The single most common bacterial cause of death was pneumonia, which killed almost 100,000 people.⁵¹ Tuberculosis (all forms) killed close to 85,000 Americans. Diarrhea/enteritis was a distant third with 30,000 deaths. Over 5,000 women died in childbirth due to septicemia.⁵² The death rate from bacterial infections, per estimated 100,000 population, was 250. See also Table 1 at the end of this subsection.

1936: Approximately 280,000 Americans died in 1936 of the same bacterial illnesses that felled 300,000 people in 1930.⁵³ Once again, this number accounted for about one-fifth (19%) of all deaths. Pneumonia was still the major killer (115,000 deaths), followed by TB (70,000 deaths).⁵⁴ The death rate for bacterial infections, per estimated 100,000 population, was 216.

⁵⁰See U.S. DEP'T OF COM., 1931 MORTALITY STATISTICS 11 (1935).

⁵¹*Id.*

⁵²*Id.* The relatively small number of such deaths is testimony to the strict antiseptic techniques practiced in maternity wards across America and Europe since the end of the 19th century. See WAINWRIGHT, *supra* note 1, at 11-12 (relating the influence of the 19th-century Viennese doctor Ignaz Semmelweis, who insisted that all health care providers in his maternity wards disinfect their hands with chlorinated substances before attending to patients).

⁵³See U.S. DEP'T OF COM., 1936 MORTALITY STATISTICS 12-15 (1938).

⁵⁴*Id.* at 12-13.

The death rate of 216 in 1936 represented a 13% decline from 1930 (250). In other words, the death rate from bacterial illness fell by 2% per year between 1930 and 1936.⁵⁵ This could be considered the “natural” rate of decline in deaths due to bacterial infection, from factors other than antibiotics (which had yet to appear on the scene). That is, bacterial causes of death would have been expected to decline by 2% per year even had antibiotics never been discovered. The “natural” rate of decline was calculated for starting years other than 1930, with similar results reached in each case.⁵⁶

The total number of deaths in 1936 from acute rheumatic fever, meningitis, acute endocarditis, lung abscess, and septic abortion was approximately 12,000.⁵⁷ This represented a rate of 9 deaths per estimated 100,000 population from these quintessential and highly treatable bacterial illnesses. To put these numbers in some perspective, approximately 14,000 Americans died of HIV/AIDS in 2002, representing a rate of 4.9 deaths per estimated 100,000 population.⁵⁸

1952: Fewer than 95,000 Americans died in 1952 of the same bacterial illnesses that killed 280,000 people in 1936 (and 300,000 people in 1930).⁵⁹ This number accounted for only about 6% of all deaths in 1952.

The single most common bacterial cause of death was still pneumonia (40,000 people, down from 115,000 in

⁵⁵To use more exact figures: death rate from bacterial illness in 1930=247.7. Death rate in 1936=216.3. Absolute difference=31.4 (deaths per estimated 100,000 population). Percentage change in death rate between 1930 and 1936=31.4/247.7=(-)12.7%. Annual decline in death rate=12.7/6 years=2.1%.

⁵⁶See, e.g., 1931 MORTALITY STATISTICS, *supra* note 50, at 11 (giving data from 1931, from which the “natural” rate of decline between 1931 and 1936 was calculated).

⁵⁷See 1936 MORTALITY STATISTICS, *supra* note 53, at 12-13.

⁵⁸CENTERS FOR DISEASE CONTROL AND PREVENTION, NATIONAL VITAL STATISTICS REPORTS 29, 33 (Oct. 12, 2004).

⁵⁹See U.S. DEP’T OF HEALTH, EDUC., AND WELFARE, 1952 VITAL STATISTICS OF THE UNITED STATES (VOLUME II) 36-41 (1955).

1936), followed by tuberculosis (25,000 people, down from 70,000 in 1936).⁶⁰ The death rate from bacterial infections, per estimated 100,000 population, was 59.7.

The predicted death rate due to bacterial illness in 1952, based on a “natural” rate of decline of 2% per year, and starting with a baseline rate of 250 in 1930, would have been 155.⁶¹ The difference between the predicted and actual death rates was thus 95. In other words, there were 95 fewer deaths per 100,000 population from bacterial illness in 1952 than would have been predicted from the natural rate of decline. Given a population of approximately 155 million Americans in 1952, this translates into almost 150,000 fewer deaths.⁶² As argued earlier, it is likely that the introduction of antibiotics between 1936 and 1952 is responsible for most of these fewer deaths – that is, for most of these 150,000 lives saved.

The total number of deaths in 1952 from acute rheumatic fever, meningitis, acute endocarditis, lung abscess, and septic abortion was approximately 5,000: less than half the number of such deaths in 1936 (despite an increase in the population and the number of all deaths).⁶³ This represented a rate of 3.4 deaths per estimated 100,000 population, a 64% decline since 1936. See also Tables 1 and 2 at the end of this subsection.

⁶⁰*Id.* at 36, 39.

⁶¹This predicted rate is derived as follows (*see also supra* note 55): death rate from bacterial illness in 1930=247.7. Death rate predicted in 1931, given 2.1% annual decline= $247.7(1-0.021)=247.7(0.979)=242.5$. Death rate predicted in 1952 (22 years after 1930), given 2.1% annual decline= $247.7(0.979^{*22})=247.7(0.62)=154.7$.

⁶²*See* 1952 VITAL STATISTICS OF THE UNITED STATES (VOLUME II), *supra* note 59, at 16 (providing a table of deaths and death rates from which it is possible to calculate the 1952 American population upon which the *Vital Statistics* were based). The number of fewer deaths is calculated as follows: American population in 1952=155,758,376. Number of fewer deaths

= $155,758,376(95 \text{ deaths}/100,000 \text{ population})=147,970$.

⁶³*See* 1952 VITAL STATISTICS OF THE UNITED STATES (VOLUME II), *supra* note 59, at 38-39.

1960: Data for the years 1960 and 2002 (like 1930) were examined for the light that they shed on the period from 1936 to 1952. Roughly 90,000 Americans died in 1960 of the bacterial diseases that killed 95,000 people in 1952.⁶⁴ This represented a death rate of 50.4 per estimated 100,000 population, compared to 59.7 in 1952. Approximately 60,000 Americans died of pneumonia, and 10,000 of tuberculosis.⁶⁵

The predicted death rate due to bacterial illness in 1960, based on a “natural” rate of decline of 2% per year, and starting with a baseline rate of 59.7 in 1952, would have been 50.4.⁶⁶ In other words, the decline in the death rate from bacterial disease between 1952 and 1960 is entirely explainable by the natural rate of decline! This finding is consistent with one of the presuppositions of this section: that the antibiotics in place in 1952 were mostly adequate to the task of fighting bacterial infections, and that the discovery and development of novel antibiotics during the 1950s and 1960s contributed only minimally to further reductions in infectious disease mortality (though the new drugs may have been more consumer-friendly).

The number of deaths in 1960 from acute rheumatic fever, meningitis, acute endocarditis, lung abscess, and septic abortion was approximately 5,000, representing a rate of 2.7 deaths per estimated 100,000 population (compared to 3.4 in 1952).⁶⁷ The fact that the death rate from these classic bacterial illnesses declined more than the overall death rate due to all “bacterial” diseases – 20% versus 16%⁶⁸ – suggests that some of the

⁶⁴See U.S. DEP’T OF HEALTH, EDUC., AND WELFARE, 1960 VITAL STATISTICS OF THE UNITED STATES (VOLUME II) 5-14, 5-35 – 5-39 (1963) (including a table of deaths and death rates from which it is possible to calculate the 1960 American population upon which the *Vital Statistics* were based).

⁶⁵*Id.* at 5-35, 5-37.

⁶⁶Death rate predicted in 1960 (8 years after 1952), given 2.1% annual decline= $59.7(0.979^8)=59.7(0.844)=50.4$. See also *supra* notes 55, 61.

⁶⁷See 1960 VITAL STATISTICS OF THE UNITED STATES (VOLUME II), *supra* note 64, at 5-37 – 5-38.

⁶⁸Percentage decline in death rate due to listed conditions= $(3.4-2.7)/3.4 \times 100=20.6\%$. Percentage decline in overall death rate= $(59.7-50.4)/59.7 \times 100=15.6\%$.

reduction in the overall death rate was likely due to antibiotics (including improvements in antimicrobials, and increased access to the drugs) rather than the “natural” rate of decline. This view is supported by other evidence: for example, the fact that the death rate due to syphilis – the model of an infectious disease curable with antibiotics (penicillin) – fell from 3.67 in 1952 to 1.64 in 1960.⁶⁹ Of course, it is possible that the decrease in syphilis deaths resulted from a reduction in risky behavior and other factors unrelated to antibiotics, but it is likely that the penetration of penicillin to every corner of the country by 1960 also made a difference.

2002: Approximately 110,000 Americans died in 2002 of the bacterial illnesses that killed 90,000 people in 1960, representing a death rate of 38 per estimated 100,000 population (compared to 50.4 in 1960).⁷⁰ The predicted death rate in 2002, based on a “natural” rate of decline of 2% per year, and starting with a baseline rate of 59.7 in 1952 (after the greatest benefits of antibiotics had been realized), would have been 21.⁷¹ In other words, the actual death rate exceeded the predicted death rate from bacterial infections. This is not surprising, as the “natural” rate of decline in infectious disease mortality – in a world in which humans and bacteria interact in complex, changing ways, and the rule of diminishing returns holds sway in most societal endeavors – could not persist indefinitely (and is something of a convenient fiction anyway).

The predicted death rate in 2002, starting with a baseline rate of 250 in 1930, would have been 54.⁷² Using

⁶⁹See 1952 VITAL STATISTICS OF THE UNITED STATES (VOLUME II), *supra* note 59, at 36; 1960 VITAL STATISTICS OF THE UNITED STATES (VOLUME II), *supra* note 64, at 5-35.

⁷⁰See CENTERS FOR DISEASE CONTROL AND PREVENTION, NATIONAL VITAL STATISTICS REPORTS 5, 29-37 (Oct. 12, 2004) (including a table of deaths and death rates from which it is possible to calculate the 2002 American population upon which the *Vital Statistics* were based).

⁷¹Death rate predicted in 2002 (50 years after 1952), given 2.1% annual decline= $59.7(0.979^{*}50) = 59.7(0.35) = 20.7$. See also *supra* notes 55, 61.

⁷²Death rate predicted in 2002 (72 years after 1930), given 2.1% annual decline= $247.7(0.979^{*}72) = 247.7(0.22) = 53.7$. See

this earlier baseline, the difference between the predicted and actual rates in 2002 was thus 16. Given an American population of 290 million in 2002, this translates into 45,000 fewer deaths from bacterial illness than predicted.⁷³ However, it is very unlikely that antibiotics “only” saved 16 people per 100,000 population – or 45,000 Americans – in 2002. As indicated in the previous paragraph, the “natural” rate of decline in deaths due to bacterial disease probably plateaued at some point in the past fifty years. And antibiotics had already proven their ability to save as many as 95 lives per 100,000 population in 1952.

At the same time, however, it is unlikely that antibiotics in 2002 prevented all of the 95 deaths per 100,000 population calculated for 1952. This rate would translate into an astounding 275,000 lives saved in 2002. Advances in the past 50 years – for example, development of a vaccine against *Haemophilus influenzae*, previously a leading cause of bacterial meningitis and pneumonia in children – have rendered antibiotics superfluous in some situations. Nevertheless, the real number of lives saved by antibiotics is probably closer to 275,000 than 45,000. Bacterial vaccines are not that commonplace, and antibiotics really have virtually eliminated entire disease categories like tuberculosis (800 deaths in 2002), and acute rheumatic fever (no deaths separately reported in 2002).⁷⁴

Table 1: Deaths and Death Rates due to Bacterial Illness (Typhoid and Paratyphoid Fever, Typhus Fever, Scarlet Fever, Whooping Cough, Diphtheria, Tuberculosis, Pneumonia, Diarrhea and Enteritis, Appendicitis, Puerperal Septicemia)

Year	Deaths due to Bacterial Illness	American Population	Death Rate due to Bacterial Illness (per 100,000 population)
1930	293,623	118,708,333	247.7
1936	277,541	129,083,333	216.3

also *supra* notes 55, 61.

⁷³Number of fewer deaths=289,055,601(16 deaths/100,000 population)=46,250.

⁷⁴See CENTERS FOR DISEASE CONTROL AND PREVENTION, NATIONAL VITAL STATISTICS REPORTS 29 (Oct. 12, 2004)

1952	93,014	155,758,376	59.7
1960	90,345	179,321,462	50.4
2002	110,202	289,055,601	38.1

Sources: *Mortality Statistics, Vital Statistics of the United States, National Vital Statistics Reports*

Table 2: Deaths and Death Rates due to “Classic” Bacterial Conditions (Acute Rheumatic Fever, Meningitis, Acute Endocarditis, Lung Abscess, and Septic Abortion)

Year	Total Deaths due to Selected Conditions	Death Rate due to Selected Conditions (per 100,000 population)
1936	11,866	9.2
1952	5,224	3.4
1960	4,854	2.7

Sources: *Mortality Statistics, Vital Statistics of the United States*

D. Further Considerations

In light of the above results, it is interesting to examine trends in life expectancy in America since the introduction of antibiotics. According to the U.S. Government’s official statistics, life expectancy at birth was 58.5 years in 1936, and 68.6 years in 1952: a difference of 10.1 years.⁷⁵ By way of comparison, the sixteen-year periods before and after 1936-1952 demonstrated increases in life expectancy of 4.4 years (1920-1936), and 1.6 years (1952-1968). Indeed, it is striking that the United States only added 8.7 years to its average life expectancy in the 50 years after 1952; the life expectancy at birth in 2002 was “only” 77.3.⁷⁶

⁷⁵See CENTERS FOR DISEASE CONTROL AND PREVENTION, NATIONAL VITAL STATISTICS REPORTS 33-34 (Nov. 10, 2004).

⁷⁶*Id.*

See also Table 3 at the end of this subsection.

It is impossible to translate the decrease in death rates due to bacterial illness from 1936 to 1952 into effects on life expectancy without detailed knowledge of individuals' ages at death from infection. Still, it is hard to escape the conclusion that something special happened in the period that corresponds to the "golden age of antibiotic discovery." It does not seem too radical to suggest that antimicrobials added 5-10 years to the life expectancy of the average American. The five "wonder drugs" discussed in Section I may well have benefited public health as much as great civic measures like the construction of sewage disposal systems and the chlorination of drinking water. The much-heralded advances against chronic diseases and cancer in the past 50 years appear less impressive.

The results obtained in this section also agree with the results of similar analyses published in the medical literature. For example, Armstrong et al., in an article in JAMA, found that the crude infectious disease mortality rate fell by 2.8% per year in America between 1900 and 1937, but by 8.2% per year between 1937 and 1952. Thereafter, the rate slowed to 2.3% per year for the next 30 years.⁷⁷ Although the authors included all infectious diseases in their analysis (i.e. viral illnesses like influenza and polio as well), their numbers correlate with the steep decline in the death rate due to bacterial infections between 1936-1952 calculated for this paper. Armstrong et al. also noted that the reduction in infectious disease mortality rates in the 1930s and 1940s coincided with the first clinical uses of antibiotics.⁷⁸

It should also be remembered that the benefits of antimicrobials extend beyond their effects on mortality or

⁷⁷Gregory L. Armstrong et al., *Trends in Infectious Disease Mortality in the United States During the Twentieth Century*, 281 JAMA 63 (1999).

⁷⁸*Id.* at 65.

life expectancy. With the advent of antibiotics, military doctors in World War II no longer had to choose between life and limb with the grim regularity characteristic of earlier conflicts. Infected extremities could be treated with penicillin or sulfonamides instead of amputated, thus sparing their owners a lifetime of disability. With the introduction of penicillin, children no longer had to suffer the non-suppurative sequelae of Group A, beta-hemolytic *Streptococcal* pharyngitis (“strep throat”): in particular, rheumatic fever and attendant damage to the heart. Fleming’s discovery saved innumerable individuals from a lifetime of leaky valves and physical limitations. And penicillin – to continue with this one drug – could halt the progression of primary syphilis into tertiary forms of the disease that robbed people of their sanity or mental clarity. Mortality data largely fails to capture such tremendous achievements.

Table 3: Estimated Life Expectancy at Birth

Year	Life Expectancy at Birth (years)
1920	54.1
1936	58.5
1952	68.6
1968	70.2
2002	77.3

Source: *National Vital Statistics Reports*

III. History Repeating

If it is true that antibiotics save tens to hundreds of thousands of American lives each year – and prevent countless more cases of disability and suffering – then all would appear to be well in the antibiotics realm. But something is rotten in the kingdom. There is a fly in the ointment, and Alexander Fleming saw it back

in the beginning.

As early as 1942 and 1943, Fleming and researchers at Oxford discovered that some staphylococci were immune to the actions of penicillin.⁷⁹ Ernst Chain had already demonstrated, in 1940, that certain gram-negative bacteria produce an enzyme that destroys the drug. He had called this substance “penicillinase” (though it would later be renamed a “beta-lactamase”).⁸⁰ Chain and others confirmed that the resistant strains of staph also manufactured the enzyme. Fleming predicted that these strains would become more prevalent with the increased use of penicillin, as mandated by the principle of natural selection (operating through human agency in this case).⁸¹ He also worried about the evolution of other resistant organisms in response to antimicrobial therapy. In an interview with the *New York Times* in 1945, Fleming asserted that “there is probably no chemo-therapeutic drug to which in suitable circumstances the bacteria cannot react by in some way acquiring ‘fastness’ [resistance].”⁸²

Fleming’s predictions about the spread of resistant staphylococci soon came true. By 1948 – less than four years after the general introduction of penicillin – most staph in London hospitals were immune to the antibiotic.⁸³ It is wrong, however, to say that the bacteria had *acquired* resistance. Strains of penicillinase-producing staphylococci have apparently always existed, as evidenced by tests of bacterial isolates from the pre-antibiotic era.⁸⁴ The widespread use of penicillin simply “selected out” these pre-existing strains by

⁷⁹See BALDRY, *supra* note 1, at 119-20; WAINWRIGHT, *supra* note 1, at 85.

⁸⁰See BALDRY, *supra* note 1, at 120.

⁸¹See MADELINE DREXLER, SECRET AGENTS: THE MENACE OF EMERGING INFECTIONS 123 (2002).

⁸²*Id.* (quoting Fleming’s interview with the *New York Times*)

⁸³*Id.* See also BALDRY, *supra* note 1, at 120; WAINWRIGHT, *supra* note 1, at 85.

⁸⁴See BALDRY, *supra* note 1, at 160 (relating the recovery of penicillinase-producing staphylococci from a food poisoning outbreak in 1932, as well as the discovery of organisms from sixteenth-century plant specimens that also produced a beta-

eliminating susceptible varieties of the organism. The resistant staph suddenly found themselves with a clear survival advantage over other members of their species. It is not clear that Fleming understood this point completely, as in the same interview with the *New York Times* quoted above, he stated that microbes could be “educated” to resist penicillin, implying that staphylococci somehow acquired resistance when exposed to his wonder drug.⁸⁵ Scientists still claim that no initially sensitive organism – with the exception of *Neisseria gonorrhea* – has ever become immune to benzyl penicillin.⁸⁶

If Fleming was mistaken about the ability of staphylococci to acquire immunity to penicillin, he was right about the capacity of other bacteria to develop resistance to a host of other antibiotics. In the 1950s, researchers in Japan discovered that certain strains of *Shigella* – an organism responsible for outbreaks of dysentery in that country – were resistant to all four antibiotics used to treat the bug: Streptomycin, Chloramphenicol, Tetracycline, and sulfonamides.⁸⁷ The four separate genes that conferred resistance to the four different drugs all appeared to be new: i.e., there was no evidence that a *Shigella* organism prior to the antibiotic age had possessed them. Moreover, strains of *Shigella* were either sensitive or resistant to all four antibiotics; no strains, for example, were only immune to Streptomycin.⁸⁸ The researchers calculated that it would require 10^{28} spontaneous mutations for a bacterium to acquire all four resistance genes (given standard rates of mutagenesis). The time or space required for so many mutations would exceed the age of the earth or the surface area of the planet.⁸⁹

Struggling to explain the existence of multi-drug resistant *Shigella*, the great Japanese scientists Akiba

lactamase).

⁸⁵See MICHAEL SCHNAYERSON & MARK J. PLOTKIN, THE KILLERS WITHIN: THE DEADLY RISE OF DRUG-RESISTANT BACTERIA 35 (2002) (quoting Fleming’s interview with the *New York Times*).

⁸⁶BALDRY, *supra* note 1, at 157-58.

⁸⁷See *id.* at 163-64. See also DREXLER, *supra* note 81, at 148-49.

⁸⁸See AMYES, *supra* note 1, at 93-94.

⁸⁹See *id.* See also DREXLER, *supra* note 81, at 148.

and Ochai proposed that the organisms – and other bacteria – were able to transfer resistance genes to each other. Moreover, they and others suggested that resistance genes were located not on the bacterial chromosome, but on mobile loops of DNA that resided in the bacterial cytoplasm.⁹⁰ These loops of DNA became known as “plasmids.” Akiba and Ochai eventually demonstrated that bacteria could indeed transfer copies of their plasmids to other members of their species, and occasionally to other species, during a non-reproductive “tryst” known as conjugation.⁹¹ In addition, scientists showed that bacteria could swap genes back and forth between their chromosomes and plasmids (though not to the degree that later became evident: see below).⁹² In the Japanese example, a certain plasmid presumably traveled between bacteria, picking up resistance genes to the antibiotics mentioned above, before finally establishing residence in a grateful *Shigella* organism, which thus received immunity to the four drugs *en bloc*. Researchers have since demonstrated that commensal organisms in the human bowel (particularly *E. coli*) often act as intermediaries in the spread of immunity, serving as a reservoir of resistance genes from and for the many bacteria that pass through the gut.⁹³

Over time, scientists refined their view of the ways in which bacteria acquire immunity to antibiotics. It became apparent that classic conjugation could not explain the promiscuity of certain resistance genes, which appeared to move quickly and easily between bacterial strains and species.⁹⁴ In the 1970s, researchers discovered the existence of “transposons:” highly mobile sequences of DNA that can jump between chromosomes and plasmids, and that often enclose resistance genes.⁹⁵ Transposons explain the ubiquity of many

⁹⁰See BALDRY, *supra* note 1, at 164; AMYES, *supra* note 1, at 94.

⁹¹See DREXLER, *supra* note 81, at 148-49.

⁹²See SCHNAYERSON & PLOTKIN, *supra* note 85, at 37.

⁹³See BALDRY, *supra* note 1, at 164.

⁹⁴See AMYES, *supra* note 1, at 116-22.

⁹⁵See *id.* See also DREXLER, *supra* note 81, at 149.

of these genes across species. For example, a transposon conferring immunity against Streptomycin may initially reside on the chromosome of an *E. coli* organism. It may then jump to a plasmid in the bacterial cytoplasm. During attempted conjugation with a strain of *Vibrio cholerae*, or even during “close contact” with the foreign strain, the transposon may leap to a cholera chromosome or plasmid, even if the *E. coli* plasmid carrying the transposon cannot survive in *Vibrio cholerae* (because many plasmids are particular to certain species, and cannot exist outside them). Scientists speculate that transposons allow resistance genes to survive in austere conditions, when plasmid-free bacterial cells predominate (because plasmid DNA is burdensome for bacteria). Under such conditions, the ability of resistance genes to integrate themselves into the bacterial chromosome – which replicates as long as the bacterium lives – significantly increases the chances of their survival.⁹⁶

One other resistance element, discovered in the past decade, merits mention. This is the integron: a structure that resembles a transposon but that consists of sequences of multiple genes encoding for bacterial resistance (as opposed to the single genes enclosed in transposons).⁹⁷ As the researcher Stuart B. Levy explains: “Integrations capture and integrate cassettes of antibiotic resistance genes,” which are “joined in tandem, producing a single element mediating resistance to multiple antibiotics.”⁹⁸ It is likely that integrons played a part in the acquisition of multi-drug resistance by the Japanese *Shigella* strains discussed earlier. If the resistance genes in that case did indeed come from *E. coli*, integrons may have mediated their transfer (*en bloc*) onto a *Shigella* plasmid, from which they could have spread to other *Shigella* organisms via ordinary conjugation. As the researcher Sebastian Amyes points out, the “whole concept of integrons begs the question

⁹⁶AMYES, *supra* note 1, at 117-18.

⁹⁷*See id.* at 122-24.

⁹⁸Stuart B. Levy, *Antibiotic Resistance 1992-2002: A Decade's Journey*, in THE RESISTANCE PHENOMENON IN MICROBES AND INFECTIOUS DISEASE VECTORS 33 (Stacey L. Knobler et al. eds., 2003).

as to whether the acquisition of resistance genes is random and if Darwinian selection ensures that only those that are useful are selected.”⁹⁹ This is because a bacterium could acquire more genes than it needs to protect itself against a single antibiotic, since multiple resistance genes travel together in integrons, which appear to be all-or-nothing propositions. Perhaps the extra burden of the unneeded genes is simply the price that the bacterium pays for an increased chance of survival.

The resistance genes carried by bacterial chromosomes, plasmids, transposons, and integrons confer immunity against antibiotics in a variety of ways. Some code for enzymes that attack the essential structure of antibiotics. Beta-lactamases, for example, destroy the beta-lactam ring integral to the function (and survival) of penicillin and cephalosporin molecules.¹⁰⁰ The beta-lactamases produced by gram-positive organisms leave the bacteria and diffuse into surrounding tissue, where they attack antibiotics, whereas those manufactured by gram-negative organisms remain inside the bacteria and only disable drugs once these have entered the microbes.¹⁰¹ Other enzymes secreted by bacteria – like acetyltransferases and phosphotransferases – interfere with the biochemistry of antibiotics while leaving their structures intact.¹⁰² Organisms resistant to tetracyclines have evolved an efflux pump encoded on their plasmids. This pump removes tetracycline from the cell faster than active transport mechanisms can introduce it.¹⁰³ Certain species of bacteria (such as *Pseudomonas aeruginosa*) produce efflux pumps that can excrete a number of unrelated antibiotics.¹⁰⁴ Scientists worry that the genes for such generic pumps – which are still confined to bacterial chromosomes, and thus to the same species – will find their way onto plasmids or into integrons, spreading immunity far

⁹⁹AMYES, *supra* note 1, at 123.

¹⁰⁰See BALDRY, *supra* note 1, at 120, 165; DREXLER, *supra* note 81, at 146.

¹⁰¹BALDRY, *supra* note 1, at 165.

¹⁰²See *id.*

¹⁰³See AMYES, *supra* note 1, at 110-11.

¹⁰⁴*Id.* at 110.

and wide. Some of the antibiotics targeted by these super-pumps include ones for which no plasmid-mediated resistance yet exists.¹⁰⁵

Bacteria immune to Trimethoprim – an antimicrobial engineered to inhibit the bacterial version of an enzyme (dihydrofolate reductase) essential to most forms of life, and designed to achieve such high concentrations in tissue that no efflux pump can defeat it – produce a variant of the enzyme (encoded on plasmids) uninhibited by the drug.¹⁰⁶ A similar strategy thwarts sulfonamides. And resistance genes allow *Streptococcus pneumoniae* to rebuild the proteins in its cell wall targeted by penicillin, and *Enterococcus* species to change the composition of their own walls when these are threatened by Vancomycin.¹⁰⁷

Plasmids, transposons, enzymes, efflux pumps: all have enabled bacteria to resist the onslaught of antibiotics, even if antimicrobials have still succeeded in saving countless human lives (more on this seeming inconsistency later). Indeed, most new antibacterial agents encounter resistance almost immediately upon their clinical introduction. For example, resistance to Streptomycin was reported in 1947, while studies of the drug were still ongoing, and immunity to Linezolid was discovered in 1999, one year before the FDA approved this new compound.¹⁰⁸ And to reiterate: the spread of resistance – as occurred among staphylococci in London hospitals in the 1940s – is perfectly consistent with evolutionary principles. Confronted with the existential threat of antibiotics, those bacteria that possess traits conferring even slight immunity to antimicrobials will increase their share of the population. The natural selection of resistant strains of bacteria underlies what

¹⁰⁵*Id.*

¹⁰⁶See AMYES, *supra* note 1, at 111-16.

¹⁰⁷See DREXLER, *supra* note 81, at 146.

¹⁰⁸See Karen Bush, *Antibacterial Drug Discovery in the 21st Century*, 10 CLINICAL MICROBIOLOGY & INFECTION 11 (2004) (providing a table of dates of reported resistance to new antimicrobial agents).

Stuart B. Levy has called “the antibiotic paradox:” the observation that the more antibiotics are used, the less effective they become.¹⁰⁹

The rest of this section considers the cases of three bacteria whose increasing resistance to antibiotics has raised general alarm: the gram-positive species *Staphylococcus aureus*, and the gram-negative genera *Acinetobacter* and *Pseudomonas*. Examination of these three organisms will help to illuminate the resistance phenomenon, and permit an assessment (or partial assessment) of the need for new treatments for bacterial infections.

A. *Staphylococcus aureus*

According to the SENTRY Antimicrobial Surveillance Program, which collects data from 30 medical centers in 23 states in the U.S., *Staphylococcus aureus* (*S. aureus*) is the most common pathogen isolated in blood-stream, lower respiratory tract, and skin/soft tissue infections in America.¹¹⁰ Between 1997 and 1999, this single organism was implicated in 25%, 26%, and 42% of such infections, respectively. Similarly high rates obtain across Europe, Canada, and Latin America.¹¹¹ This is not too surprising, as *S. aureus* is ubiquitous, frequently living as a commensal organism on the skin or in the nose, and colonizing 25-30% of the American population at any given time.¹¹²

¹⁰⁹See STUART B. LEVY, THE ANTIBIOTIC PARADOX: HOW THE MISUSE OF ANTIBIOTICS DESTROYS THEIR CURATIVE POWER (2d ed. 2002).

¹¹⁰Daniel J. Diekema et al., *Survey of Infections Due to Staphylococcus Species: Frequency of Occurrence and Antimicrobial Susceptibility of Isolates Collected in the United States, Canada, Latin America, Europe, and the Western Pacific for the SENTRY Antimicrobial Surveillance Program, 1997-1999*, 32 CLINICAL INFECTIOUS DISEASES S114-S115 (2001).

¹¹¹*Id.* at S115.

¹¹²See Centers for Disease Control and Prevention, *CA-MRSA Information for the Public*, at

As discussed earlier, staphylococci (including *S. aureus*) repopulated themselves to resist benzyl penicillin almost as soon as the latter was introduced in the 1940s.¹¹³ By 1950, most nosocomial (i.e. hospital-based) staph infections around the world were penicillin-resistant.¹¹⁴ Why, one may wonder, did this not result in a return to the pre-antibiotic era, with resistant staph running roughshod over helpless humans, killing and maiming at will? There appear to be at least three reasons why this scenario did not occur. First, penicillin was not the only arrow in the physician's or pharmacist's antimicrobial quiver. Other antibiotics were available to treat infections, including those due to gram-positive organisms like *S. aureus*. In particular, Chloramphenicol, Tetracycline, and sulfonamides all had some activity against staphylococci. It was likely difficult for a single microbe to acquire resistance genes encoding for 1) a beta-lactamase (penicillin); 2) an efflux pump (Tetracycline); 3) a variant form of dihydrofolate reductase (sulfonamides); and 4) another pump or enzyme to combat Chloramphenicol. Integrons, in particular, make such multi-drug resistance possible – and even likely with the passage of time and in the face of unrelenting antibiotic pressure – but the 1950s were still early in the game.

A second possible reason for the failure of *S. aureus* to exploit its immunity fully is that resistant strains of bacteria tend to be less efficient than non-resistant strains.¹¹⁵ The metabolic burden of carrying and expressing resistance genes takes a toll on a bacterium's ability to perform other tasks – like infecting its host. In the closely fought battle between bacteria and the human body's natural defenses (integumental barriers, digestive enzymes, white cells, etc.), the extra burden on resistant microbes may tip the balance in favor of the human being. A third possible explanation is that the highest rates of penicillin resistance

http://www.cdc.gov/ncidod/hip/aresist/ca_mrsa_public.htm (accessed March 30, 2005).

¹¹³See *supra* note 83 and accompanying text.

¹¹⁴See BALDRY, *supra* note 1, at 160.

¹¹⁵See AMYES, *supra* note 1, at 111-12.

among *S. aureus* in the 1950s likely obtained in hospitals, where antibiotics were most prevalent. As is true today (and discussed below), susceptible strains of staph probably caused most community-acquired infections, which comprise the bulk of bacterial infections. And even in the hospital, rates of resistance undoubtedly varied, depending in part on the degree of penicillin use. In an intriguing yet predictable phenomenon, withdrawal of antibiotics for some period of time often leads to a precipitous drop in the proportion of resistant strains of bacteria, as these are replaced by more efficient, non-resistant strains (now at no competitive disadvantage).¹¹⁶

Despite the fact that catastrophe did not attend the relentless, forward march of penicillin-resistant *S. aureus* in the 1950s, the medical community still breathed a sigh of relief in 1960 when Beecham Laboratories introduced Methicillin: the first penicillin resistant to beta-lactamase.¹¹⁷ By adding a bulky methyl group to penicillin, Beecham scientists created steric hindrance that prevented beta-lactamases from binding (and destroying) the antibiotic. Methicillin was only 3% as efficient as benzyl penicillin in binding bacteria, but its ability to resist penicillinase more than compensated for this relative deficiency.¹¹⁸ For close to 20 years, Methicillin – and its oral analogue, Cloxacillin – were the drugs of choice to treat *S. aureus* infections. Though resistance to these agents was reported as early as 1961, significant immunity did not spread to the general bacterial population (for unclear reasons).¹¹⁹ Happy days were here again.

But this “second golden age” could not last forever. In the 1980s, a strain of Methicillin-resistant *S. aureus*

¹¹⁶See BALDRY, *supra* note 1, at 161 (describing an example of this phenomenon involving staphylococci at a London hospital in 1958).

¹¹⁷See AMYES, *supra* note 1, at 57-59, 201-202; BALDRY, *supra* note 1, at 161-62.

¹¹⁸AMYES, *supra* note 1, at 201.

¹¹⁹See Bush, *supra* note 108, at 11.

(“MRSA”) emerged that eventually swept the world. It defeated Methicillin not by synthesizing a bigger, better beta-lactamase, but by producing an additional penicillin-binding protein (“PBP”) with lower avidity for the antibiotic.¹²⁰ PBP’s are really bacterial enzymes necessary for cell wall synthesis; all penicillins work by binding these enzymes and disrupting their actions. With one functional PBP, mostly uninhibited by drug, *S. aureus* could simply ignore the presence of Methicillin. Having retained the ability to produce beta-lactamase, MRSA had freed itself from the fear of penicillins completely.

According to reports of the National Nosocomial Infections Surveillance System (“NNIS”), which monitors infectious diseases in 300 hospitals in the United States, the proportion of *S. aureus* isolates in American hospitals today that are resistant to Methicillin is nearly 60%.¹²¹ This compares to about 45% in 1998.¹²² The highest hospital rates of resistance are found in intensive care units, followed by other inpatient areas, followed by outpatient areas (where “only” about one-third of *S. aureus* is Methicillin-resistant).¹²³ The use of penicillins in inpatient areas is virtually ubiquitous, with combined mean usage rates exceeding 100% of patients (some of whom apparently receive different types of penicillin during the same admission).¹²⁴

If MRSA were merely resistant to Methicillin (or all penicillins), it would scarcely pose a problem for clinicians. As in the 1950s, physicians have a number of antibiotics in their armamentarium active against *S. aureus*, including older drugs like macrolides (e.g. Erythromycin), Vancomycin, and aminoglycosides (e.g. Gentamicin), and newer agents like fluoroquinolones (e.g. Ciprofloxacin). MRSA, however, is better characterized as *multi-drug resistant S. aureus*. According to the SENTRY Program survey, over 90%

¹²⁰See AMYES, *supra* note 1, at 201-204.

¹²¹NNIS System, *National Nosocomial Infections Surveillance (NNIS) Report: Data Summary from January 1992 through June 2004*, 32 AM. J. INFECTION CONTROL 475 (2004).

¹²²*Id.*

¹²³*Id.* at 482.

¹²⁴See *id.* at 479.

of MRSA isolates in U.S. hospitals are resistant to Erythromycin, almost 90% to Ciprofloxacin, and 36% to Gentamicin.¹²⁵ In addition, some isolates are only susceptible to the glycopeptides: Vancomycin and Teicoplanin (which have very similar profiles).¹²⁶ As mentioned earlier, Vancomycin was first introduced in 1956, but was disfavored for decades because of its narrow spectrum, tepid activity, and toxicity.¹²⁷ Its utility against MRSA revived the drug's fortunes in the 1980s. Today, Vancomycin is one of the most commonly prescribed antibiotics in the hospital. NNIS reports indicate that the vast majority of patients in intensive care units receive the compound, and that fully one-third of all inpatients are prescribed the agent at some point during their hospitalization.¹²⁸

Vancomycin has thus emerged as the go-to drug for serious *S. aureus* infections. Clinicians prescribe it both for confirmed cases of MRSA, and as initial antibiotic therapy when *S. aureus* is a possible pathogen (because it may be Methicillin-resistant). It therefore came as a shock to the health care community when strains of *S. aureus* with intermediate resistance to Vancomycin – so-called Vancomycin-intermediate *S. aureus* (“VISA”) – were identified in America starting in 1997. As of 2003, eight cases of VISA had been confirmed in this country.¹²⁹ Researchers believe that intermediate resistance develops from pre-existing strains of MRSA in the presence of Vancomycin.¹³⁰ It should be emphasized that the VISA isolates studied to date have each remained susceptible to at least three different antibiotics, including sulfonamides.¹³¹ Contrary to popular belief, they have not escaped the reach of available antimicrobials.

¹²⁵Diekema et al., *supra* note 110, at S119.

¹²⁶*Id.* at S129.

¹²⁷See AMYES, *supra* note 1, at 67-68.

¹²⁸See NNIS System, *supra* note 121, at 479-81.

¹²⁹See Centers for Disease Control and Prevention, *VISA/VRSA Fact Sheet*, at <http://www.cdc.gov/ncidod/hip/ARESIST/visa.htm> (accessed March 31, 2005).

¹³⁰Scott K. Fridkin, *Vancomycin-Intermediate and -Resistant Staphylococcus aureus: What the Infectious Disease Specialist Needs to Know*, 32 HEALTHCARE EPIDEMIOLOGY 108, 110-12 (2001).

¹³¹See *id.* at 111.

If physicians and scientists were spooked by the discovery of VISA in this country, imagine their fear when the first two – and, to date, only two – cases of Vancomycin-resistant *S. aureus* (“VRSA”) were reported in America in 2002. The VRSA isolates were recovered from patients in Michigan and Pennsylvania.¹³² Researchers determined that *S. aureus* in both instances had acquired a Vancomycin resistance gene from another gram-positive organism: *Enterococcus*. They also concluded that the two VRSA isolates were unrelated; the bacteria had evolved independently of each other.¹³³ It was unclear whether this was good or bad news. On the one hand, it was good to know that an epidemic VRSA clone was not loose in the land. On the other hand, it was – and is – frightening to think that *S. aureus* can acquire Vancomycin immunity from *Enterococcus* with some frequency. Once again, it is important to note that the VRSA strains remained susceptible to multiple antibiotics. The strain from Pennsylvania, for example, was sensitive to Chloramphenicol, Rifampin, and sulfonamides (among others).¹³⁴

Though the emergence of VISA and VRSA may have caught physicians and patients unawares, pharmaceutical companies were in many ways prepared for it. Since 1999, drug houses have introduced three antibiotics as alternatives to Vancomycin in the treatment of *S. aureus* infections. The first, Quinupristin/Dalfopristin, is a combination of two streptogramins: drugs discovered in the 1950s and somewhat similar in function to macrolides.¹³⁵ The second, Linezolid, is an oxazolidinone, which – with Linezolid’s introduction in 2000

¹³²See *VISA/VRSA Fact Sheet*, *supra* note 129.

¹³³See Centers for Disease Control and Prevention, *Public Health Dispatch: Vancomycin-Resistant Staphylococcus aureus – Pennsylvania 2002*, 51 MORBIDITY & MORTALITY WKLY. REP. 902 (2002), available at <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5140a3.htm>.

¹³⁴*Id.*

¹³⁵See Steven J. Projan & David M. Shlaes, *Antibacterial Drug Discovery: Is It All Downhill From Here?*, 10 CLINICAL MICROBIOLOGY & INFECTION 18-19 (2004). See also AMYES, *supra* note 1, at 72 (describing the features of the streptogramins).

– became the first new class of antibiotic to reach the market since Trimethoprim in 1968.¹³⁶ The third agent, Daptomycin, was developed by Eli Lilly in the early 1980s but dropped due to toxicity concerns. The drug was adopted by a smaller pharmaceutical company in the 1990s and approved by the FDA in 2003. A lipopeptide, it represents another novel class of antimicrobial.¹³⁷

To date, the FDA has only approved Quinupristin/Dalfopristin for treatment of Vancomycin-resistant Enterococcal bacteremia, and Daptomycin for treatment of *S. aureus* skin infections.¹³⁸ All three new drugs, however, clearly have value as alternatives to Vancomycin in a wide variety of MRSA infections – particularly for patients who are allergic or intolerant to Vancomycin – and as potential first-line agents in VISA and VRSA outbreaks. In the SENTRY Program survey, MRSA isolates had near universal susceptibility (*in vitro*) to both Linezolid and Quinupristin/Dalfopristin.¹³⁹ The VRSA isolate recovered in Pennsylvania in 2002 was also sensitive (*in vitro*) to these two antibiotics.¹⁴⁰ Linezolid is a particularly valuable drug because it can be given orally as well as parenterally. Patients started on the intravenous formulation in the hospital can be discharged home on the pills to complete treatment for MRSA infections; it is generally considered desirable to treat a bacterial illness with a single, effective agent, in this manner. Doctors can also prescribe oral Linezolid for outpatient treatment of community-acquired MRSA infections. The same may one day be true for VISA and VRSA infections.

¹³⁶See John H. Powers, *Antimicrobial Drug Development – The Past, The Present, and The Future*, 10 CLINICAL MICROBIOLOGY & INFECTION 24 (2004).

¹³⁷See Matthew Herper, *A Better Antibiotic?*, Forbes.com (Sept. 7, 2003), at <http://www.forbes.com/2003/07/09/cx.mh.0708cbst.html>. See also Powers, *supra* note 136, at 24 (providing the class of drug and year of introduction).

¹³⁸See RxList, *Synercid: Indications and Usage*, at http://www.rxlist.com/cgi/generic2/quindal_ids.htm (accessed March 31, 2005); RxList, *Cubicin: Indications and Usage*, at http://www.rxlist.com/cgi/generic3/cubicin_ids.htm (accessed March 31, 2005).

¹³⁹See Diekema et al., *supra* note 110, at S130.

¹⁴⁰*Public Health Dispatch*, *supra* note 133.

Books, articles, and speeches on antibiotic resistance almost invariably focus on *S. aureus*: in particular, MRSA. As just discussed, *S. aureus* is indeed a major human pathogen. And over the past 60 years, the bacterium has managed to find ways to defeat benzyl penicillin and now Methicillin – with Vancomycin (its new nemesis) in its sights. However, close to 100% of MRSA in this country is still sensitive to Vancomycin and Teicoplanin. And – it bears repeating – most *S. aureus* in the community is still susceptible to Methicillin. In addition, those scattered isolates of *S. aureus* resistant to Vancomycin are still susceptible to multiple other antimicrobials, including older drugs like sulfonamides and new agents like Linezolid and Daptomycin (which represent completely novel classes of antibiotics). Reports of staph’s success at escaping the clutches of antibiotics appear somewhat exaggerated.

This is not to say that mankind should rest on its laurels. The natural selection of drug-resistant staphylococci will continue so long as drugs are used. The antibiotic paradox cannot be denied: even Linezolid will lose its effectiveness as its use increases. And the rising prevalence of MRSA outside of hospitals will present practical problems for physicians and patients. The public was alarmed when four children died of community-acquired MRSA infections in Minnesota and North Dakota between 1997 and 1999.¹⁴¹ In three of the cases, physicians did not think to cover a “hospital bug” like MRSA with their initial choice of antibiotics, as the children had arrived from home.¹⁴² This is a serious issue for doctors, who frequently prescribe antibiotics – especially in the community (but also in the hospital) – in an “empiric” manner, without knowledge of the precise

¹⁴¹See Centers for Disease Control and Prevention, *CA-MRSA Information for the Public*, at http://www.cdc.gov/ncidod/hip/aresist/ca_mrsa_public.htm (accessed March 30, 2005).

¹⁴²See Centers for Disease Control and Prevention, *Four Pediatric Deaths From Community-Acquired Methicillin-Resistant Staphylococcus aureus – Minnesota and North Dakota, 1997-1999*, 48 MORBIDITY & MORTALITY WKLY. REP. 707-10 (1999), available at www.cdc.gov/mmwr/preview/mmwrhtml/mm4832a2.html.

pathogen. Outpatient treatment of certain bacterial infections may have to change to include coverage of MRSA (perhaps with Linezolid or sulfonamides) until this organism can be excluded on the basis of gram stain or culture. This is not a pleasant prospect.

B. *Acinetobacter* and *Pseudomonas*

While *S. aureus* basks in the limelight of public attention, a poster-child for antibiotic resistance, two gram-negative bacteria inhabit the shadows of sick wards across the country, posing a more credible threat of return to a pre-antibiotic age. The first, *Acinetobacter*, has long received little respect from the medical community. *Acinetobacter* species are found in soil and water and frequently live as commensal organisms on human skin.¹⁴³ They pose little risk to healthy individuals. However, these species – in particular, *Acinetobacter baumannii* (*A. baumannii*) – have recently emerged as significant opportunistic pathogens in hospitalized patients, especially critically ill patients on ventilators.¹⁴⁴ *A. baumannii* can cause a range of diseases, from meningitis and pneumonia to surgical wound and urinary tract infections.¹⁴⁵ The bacterium is easily transmitted and resists desiccation, which allows it to persist in hospital environments for days and probably contributes to its propensity for causing extended outbreaks.¹⁴⁶

According to a SENTRY Program survey, *Acinetobacter* accounts for over 2% of respiratory and wound

¹⁴³See Centers for Disease Control and Prevention, *Acinetobacter Infection: General Information*, at http://www.cdc.gov/ncidod/hip/ARESIST/acin_general.htm (accessed March 30, 2005).

¹⁴⁴See *id.*

¹⁴⁵Ana C. Gales et al., *Emerging Importance of Multidrug-Resistant Acinetobacter Species and Stenotrophomonas maltophilia as Pathogens in Seriously Ill Patients: Geographic Patterns, Epidemiological Features, and Trends in the SENTRY Antimicrobial Surveillance Program (1997-1999)*, 32 CLINICAL INFECTIOUS DISEASES S104 (2001).

¹⁴⁶*Id.* at S105.

infections in the U.S. (though close to 10% of pneumonia in Latin America, where the organisms flourish).¹⁴⁷ Though this percentage pales in comparison to the proportion for *S. aureus* – which, as mentioned earlier, is implicated in one-quarter of lower respiratory tract infections – it still represents a huge number of patients in absolute terms. And all of these patients are at the mercy of an increasingly resistant bug. Like its fellow gram-negative bacterium, *Shigella*, *Acinetobacter* early acquired an impressive collection of resistance genes to common antibiotics, including extended-spectrum penicillins and cephalosporins, and fluoroquinolones.¹⁴⁸ For close to two decades, *Acinetobacter* has been universally susceptible to only one class of antibiotic: the carbapenems, synthetic variants of natural beta-lactam compounds with excellent penetration of gram-negative organisms.¹⁴⁹ Since their introduction in the 1980s, the carbapenems – Imipenem/Cilastatin and Meropenem – have been the last line of defense against serious, nosocomial, gram-negative infections.¹⁵⁰

In the SENTRY Program survey, 8-10% of nosocomial *Acinetobacter* isolates were resistant to carbapenem antibiotics. Of all *Acinetobacter* isolates (including ones associated with community-acquired infections), 3-4% were resistant.¹⁵¹ All of these Imipenem-nonsusceptible *Acinetobacter* (“INSA”) strains came from medical centers in New York. The only traditional antimicrobial active against the INSA isolates was the aminoglycoside Amikacin, which inhibited 96% of the bacteria.¹⁵² Aminoglycosides are notorious for their kidney toxicity, and can only be administered intravenously. The only antibiotic with universal activity against the INSA strains was Polymyxin B Sulfate (“Polymyxin”): a polypeptide produced by a bacterium (*Bacillus polymyxa*), which works as a detergent against the outer membranes of microbes.¹⁵³ Though a

¹⁴⁷*Id.* at S106.

¹⁴⁸See David Landman et al., *Citywide Clonal Outbreak of Multiresistant Acinetobacter baumannii and Pseudomonas aeruginosa in Brooklyn, NY*, 162 ARCHIVES INTERNAL MED. 1515 (2002).

¹⁴⁹See AMYES, *supra* note 1, at 66-67.

¹⁵⁰*Id.*

¹⁵¹Gales et al., *supra* note 145, at S108.

¹⁵²*Id.* at S109.

¹⁵³*Id.* at S109. See also AMYES, *supra* note 1, at 69 (providing a description of Polymyxin).

fairly old agent, Polymyxin is rarely prescribed because of its own serious toxicity problems, related to its “detergent” action on certain human cells and involving the kidneys and nervous system. It is not considered a “good” drug.

The SENTRY susceptibility data for *Acinetobacter* actually look good in comparison to results from smaller studies. For example, Landman et al. examined isolates of *A. baumannii* collected from patients at 15 Brooklyn hospitals in 1999.¹⁵⁴ They found that 33% of isolates were Imipenem-resistant, of which only half were susceptible to Amikacin. The rest of the INSA strains were only sensitive to Polymyxin, with the exception of 5 (out of 419) isolates, which were resistant to all antibiotics tested!¹⁵⁵ A retrospective review of patient charts revealed that 35% of *A. baumannii* isolates represented genuine infection (and not just hospital colonization).¹⁵⁶ It is thus conceivable that several patients died in a world without antibiotics, dependent entirely on their own bodies to fight infection.

Landman et al. included another gram-negative organism in their Brooklyn study: *Pseudomonas aeruginosa* (*P. aeruginosa*). *Pseudomonas* is a leading cause of nosocomial infections, typically involving immunocompromised or critically ill patients (particularly ventilated patients, as with *Acinetobacter*).¹⁵⁷ Physicians have viewed its increasing resistance to traditional antibiotics with concern for over two decades. Like *Acinetobacter*, *P. aeruginosa* strains have acquired resistance genes against the penicillins, cephalosporins,

¹⁵⁴Landman et al., *supra* note 148, at 1516.

¹⁵⁵*Id.* at 1516-17.

¹⁵⁶*Id.* at 1519.

¹⁵⁷See Michael J. Richards et al., *Nosocomial Infections in Medical Intensive Care Units in the United States*, 27 CRITICAL CARE MED. 887-992 (1999) (identifying *P. aeruginosa* as the leading cause of nosocomial pneumonia in intensive care units in the U.S.).

and fluoroquinolones. According to the NNIS report, 18% of *P. aeruginosa* in U.S. intensive care units is resistant to “anti-Pseudomonal” penicillins (which were specially developed to fight this bacterium), 14% to third-generation cephalosporins (also designed with this organism in mind), and 35% to Ciprofloxacin.¹⁵⁸ In outpatient areas, rates of resistance range from 5% (cephalosporins) to 23% (Ciprofloxacin).¹⁵⁹

Like *Acinetobacter*, *Pseudomonas* was almost uniformly sensitive to carbapenems in the past. No longer. The NNIS report reveals that almost 20% of *P. aeruginosa* in intensive care units, and 7% in outpatient clinics, is now resistant to Imipenem.¹⁶⁰ In Brooklyn, Landman et al. reported an overall resistance rate of 17% in the 15 hospitals included in their study.¹⁶¹ The majority of Imipenem-resistant strains were susceptible to Amikacin, but 6 isolates were immune to all antibiotics tested.¹⁶² The researchers, however, did not test *Pseudomonas* against Polymyxin, which has now emerged as the real last line of defense against this organism (as in the case of INSA). In studies of Imipenem-resistant *P. aeruginosa* in Latin America, Polymyxin has retained universal activity against the bacteria.¹⁶³ It is sobering, however, to see a solitary “S” (“sensitive”) on an antimicrobial susceptibility profile for *P. aeruginosa* isolates from Brazil.¹⁶⁴ Will patients in North and South America one day have to depend on the highly toxic, detergent antibiotic Polymyxin to save them from a common, life-threatening nosocomial pathogen (assuming that Polymyxin even retains its activity against *Pseudomonas*)?

¹⁵⁸NNIS System, *supra* note 121, at 482.

¹⁵⁹*Id.*

¹⁶⁰*Id.*

¹⁶¹Landman et al., *supra* note 148, at 1517.

¹⁶²*Id.* at 1518.

¹⁶³See, e.g., Ana C. Gales et al., *Carbapenem-Resistant Pseudomonas aeruginosa Outbreak in an Intensive Care Unit of a Teaching Hospital*, 8 BRAZ. J. INFECTIOUS DISEASES 269 (2004).

¹⁶⁴*Id.* (reproducing the susceptibility profiles for five *P. aeruginosa* isolates sensitive only to Polymyxin).

Unfortunately, the growing resistance of *Acinetobacter* and *Pseudomonas* species to every good antibiotic is all too typical of gram-negative bacteria as a group. Perhaps most worrisome is the development of carbapenem resistance in the *Enterobacteriaceae*: an important family of highly pathogenic, gram-negative organisms responsible for a wide range of human infections. Genera in this family include intestinal pathogens like *Salmonella* and *Shigella*, the plague agent *Yersinia*, and the versatile *E. coli*. Another *Enterobacteriaceae*, *Klebsiella pneumoniae* (*K. pneumoniae*), is an especially common cause of nosocomial pneumonia, and rivals *E. coli* as a urinary tract pathogen. In the late 1990s, reports of immunity to carbapenems in this bug began to surface in Europe and Latin America.¹⁶⁵ In 2000, New York experienced a deadly outbreak of Imipenem-resistant *Klebsiella*, which infected 14 patients, of whom 8 died as a complete or partial result.¹⁶⁶ The *K. pneumoniae* isolates recovered from the outbreak were broadly immune to most antibiotic classes. Indeed, only Tetracycline was uniformly active against the organisms; even Polymyxin failed against one isolate.¹⁶⁷ The scientists who studied the episode considered the emergence of carbapenem resistance in this species of *Enterobacteriaceae* a “global sentinel event.”¹⁶⁸

In striking contrast to the three new drugs – and two new drug classes – recently introduced to fight MRSA, not a single new antibiotic to treat resistant, gram-negative bacteria has reached the market in over a decade.¹⁶⁹ Carbapenem resistance, in particular, has received little attention from the pharmaceutical industry, despite the fact that doctors dread the prospect of having to prescribe Polymyxin for patients on

¹⁶⁵See, e.g., Fiona M. MacKenzie et al., *Emergence of a Carbapenem-Resistant Klebsiella pneumoniae*, 350 LANCET 783 (1997) (reporting isolation of an Imipenem-resistant strain of *K. pneumoniae* during an outbreak of multi-drug resistant *Klebsiella* in Scotland).

¹⁶⁶See Neil Woodford et al., *Outbreak of Klebsiella pneumoniae Producing a New Carbapenem-Hydrolyzing Class A Beta-Lactamase, KPC-3, in a New York Medical Center*, 48 ANTIMICROBIAL AGENTS & CHEMOTHERAPY 4795 (2004).

¹⁶⁷See *id.* at 4796.

¹⁶⁸*Id.* at 4793.

¹⁶⁹See AMYES, *supra* note 1, at 53-91 (surveying the various classes of antibiotics, of which the carbapenems and third-generation cephalosporins, introduced in the 1980s, appear to have been the last designed to target resistant, gram-negative bacteria).

any regular basis. And despite the fact that many infectious disease experts believe that the pre-antibiotic era, if it does return on a wide scale, will begin again with bacteria like Imipenem-resistant *A. baumannii* and *P. aeruginosa*. As a microbiologist at the United Kingdom’s Antibiotic Resistance Monitoring & Reference Laboratory has written: “If [carbapenem resistance] does spread widely we will face a situation where many nosocomial gram-negative infections become effectively untreatable. It is here, against gram-negative opportunists, that the medical need for new agents is most acute.”¹⁷⁰

There is a small glimmer of hope on the horizon in the form of Tigecycline, an antibiotic by Wyeth Pharmaceuticals that has just completed Phase III trials (and that the FDA has granted priority review status).¹⁷¹ Though Tigecycline is often described as the first in a new class of antibiotics (the glycylcyclines), it is really a semi-synthetic derivative of Tetracycline, engineered to defeat the infamous Tetracycline efflux pump (and one other type of bacterial resistance).¹⁷² In support of its New Drug Application, Wyeth conducted studies comparing Tigecycline to Imipenem in the treatment of nosocomial pneumonia and intra-abdominal infections.¹⁷³ Preliminary data from the intra-abdominal trial – presented by Wyeth at a conference last fall – suggest that Tigecycline is comparable to Imipenem in microbiologic eradication rates.¹⁷⁴ *In vitro*, Tigecycline has also demonstrated enhanced activity against the *Enterobacteriaceae*, and even against certain Imipenem-resistant *Acinetobacter* strains.¹⁷⁵ Whether the drug can replicate this latter success in the

¹⁷⁰David M. Livermore, *The Need for New Antibiotics*, 10 CLINICAL MICROBIOLOGY & INFECTION 7 (2004).

¹⁷¹See Wyeth Pharmaceuticals, *FDA Grants Priority Review Status to Tigecycline* (Jan. 28, 2005), at http://www.wyeth.com/news/Pressed_and_Released/pr01_28_2005.07_38_01.asp (accessed April 1, 2005).

¹⁷²See David C. Hooper, *Glycylcyclines*, ICAAC Symposium on Emerging Therapies (Dec. 17, 2001), at http://hopkins-abxguide.org/show_pages.cfm?content=F25_010302.content.html (accessed April 1, 2005).

¹⁷³See National Institutes of Health, *Tigecycline versus Imipenem/Cilastatin for the Treatment of Subjects with Nosocomial Pneumonia*, at <http://www.clinicaltrials.gov/ct/gui/search?term=tigecycline> (accessed April 1, 2005); National Institutes of Health, *Comparison Study of Tigecycline to Imipenem/Cilastatin to Treat Complicated Intra-Abdominal Infections in Hospitalized Subjects*, at <http://www.clinicaltrials.gov/ct/gui/search?term=tigecycline> (accessed April 1, 2005).

¹⁷⁴See Wyeth Pharmaceuticals, *Phase III Study Examines Activity of Tigecycline in Patients with Serious Intra-Abdominal Infections* (Nov. 2, 2004), at http://www.wyeth.com/news/pressed_and_released/pr11_02_2004.12_01_20.asp (accessed April 1, 2005).

¹⁷⁵See Caroline J. Henwood et al., *Antibiotic Resistance Among Clinical Isolates of Acinetobacter in the UK, and in vitro Evaluation of Tigecycline (GAR-936)*, 49 J. ANTIMICROBIAL CHEMOTHERAPY 484 (2002); Maria Eugenia Pachon-Ibanez et al., *Activity of Tigecycline (GAR-936) against Acinetobacter baumannii Strains, Including Those Resistant to Imipenem*,

human body is unknown. The agent is also active against MRSA, and Wyeth has apparently submitted data demonstrating its ability to cure clinical MRSA infections (as if the world needed yet another potential treatment for this bug!).¹⁷⁶ Unfortunately, Tigecycline offers poor coverage against *Pseudomonas* and similar organisms.¹⁷⁷ Once again, important gram-negative bacteria are left in the dark.

Contrary to popular belief, then, the need for new antibiotics seems most pressing to treat not *S. aureus*, but rather those gram-negative organisms – such as *A. baumannii*, *P. aeruginosa*, and certain *Enterobacteriaceae* (like *K. pneumoniae*) – that have steadily acquired resistance to most good antibiotics. This statement, however, should be qualified by two observations. First, the vast majority of the gram-negative bugs just mentioned are still susceptible to carbapenems. Indeed, most are still sensitive to cephalosporins and/or fluoroquinolones.¹⁷⁸ And the vast majority of Imipenem-resistant organisms are still susceptible to at least one “good” antimicrobial: Amikacin in the case of *Acinetobacter* and *Pseudomonas*, and Tetracycline in the case of *Klebsiella*. Although aminoglycoside antibiotics like Amikacin are not ideal drugs due to their kidney toxicity, they have been widely used for generations and are not as dangerous as Polymyxin.

Second, even if these gram-negative bacteria did escape the ambit of all good antibiotics – or even all antimicrobials (which could be the same thing for patients intolerant to a toxic agent like Polymyxin) – the

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¹⁷⁶ See Wyeth Pharmaceuticals, *supra* note 170 (mentioning the inclusion of Phase III trial data on MRSA in Wyeth’s New Drug Application for Tigecycline).

¹⁷⁷ See Hooper, *supra* note 172 (noting Tigecycline’s poor coverage of non-lactose-fermenting gram-negative rods like *P. aeruginosa*).

¹⁷⁸ See Gales et al., *supra* note 145, at S108 (finding that two-thirds of *Acinetobacter* isolates studied for the SENTRY Program were susceptible to a cephalosporin, and over three-quarters to a fluoroquinolone); NNIS System, *supra* note 121, at 482 (finding that 85-95% of *Pseudomonas* and *Klebsiella* isolates recovered by NNIS from hospital inpatient areas were sensitive to third-generation cephalosporins, and that close to two-thirds of *Pseudomonas* samples were still susceptible to a fluoroquinolone).

pre-antibiotic age would not return in all its horror. As discussed above, organisms like *A. baumannii* and *P. aeruginosa* are primarily opportunists, infecting the sickest patients in the hospital, especially those on ventilators. Indeed, these bacteria are the quintessential “hospital bugs,” rarely causing problems for healthy individuals or community dwellers. From a public health perspective, the death of an elderly, critically ill patient in an intensive care unit (from an *Acinetobacter* infection) is not nearly as significant as the death or disability of a child in the community (from, say, rheumatic fever). This may explain the obsessive concern about *S. aureus* among many health officials; even incomplete resistance among the staphylococci – which cause infections in young, healthy people – could be considered worse than complete resistance among pseudomonal organisms.

Still, it seems prudent for the human species to acquire new arms in its battle against gram-negative bacteria, even if the lives of most Americans saved each year by antibiotics do not depend on the outcome of a skirmish with hospital bugs. Bacteria have a way of evolving, and a future “public health dispatch” about four deaths from community-acquired, pan-resistant *A. baumannii* infections in Midwestern schoolchildren is not inconceivable. In addition, critically ill patients today may still want to live, and people are often attached to their hospitalized relatives. Though it seems like an excellent start, Tigecycline does not appear to be the complete answer to the problem of nosocomial, gram-negative pathogens, especially given its uncertain activity (*in vivo*) against carbapenem-resistant bacteria, and its poor coverage of *Pseudomonas*. Additional action seems needed.

IV. The Pipeline Runs Dry

Many infectious disease experts, confronted with reports of increasing immunity to antibiotics among medically important bacteria, advocate changes in clinical practice to stem the rising tide of resistance. They call, sensibly enough, for measures to reduce the incidence of bacterial infections in order to decrease the need for (and prevalence of) antimicrobials. For example, they recommend that hospitals make sparing use of invasive devices, such as urinary or central venous catheters, which often serve as portals of entry for infection. They encourage widespread vaccination against influenza, because patients hospitalized with the flu are easy targets for opportunistic bacteria.¹⁷⁹ For suspected bacterial illness, the experts advocate empiric antibiotic therapy based on the local susceptibility data of likely pathogens, with conversion to targeted therapy once a causative agent is identified by culture.¹⁸⁰ They caution against “treatment” of contamination and colonization as opposed to actual infection.¹⁸¹ They are particularly keen about public educational campaigns – and behavioral interventions for health care providers – to help stop the prescription of antibiotics for probable viral illnesses.¹⁸² In hospitals and clinics, the experts call for strict adherence to procedures to prevent transmission of bacterial pathogens, including containment of infectious body fluids and maintenance of “appropriate hand hygiene” by doctors and nurses.¹⁸³ They also support restrictions on the use of antibacterial agents in pesticides and animal feed.¹⁸⁴

¹⁷⁹See, e.g., Julie L. Gerberding, *The Centers for Disease Control and Prevention’s Campaign to Prevent Antimicrobial Resistance in Health Care Settings*, in THE RESISTANCE PHENOMENON IN MICROBES AND INFECTIOUS DISEASE VECTORS 210-12 (Stacey L. Knobler et al. eds., 2003).

¹⁸⁰See *id.* at 212-13.

¹⁸¹See *id.* at 213-14.

¹⁸²See, e.g., David M. Bell, *Development of the Public Health Action Plan to Combat Antimicrobial Resistance and CDC Activities Related to Its Implementation*, in THE RESISTANCE PHENOMENON IN MICROBES AND INFECTIOUS DISEASE VECTORS 201-204 (Stacey L. Knobler et al. eds., 2003).

¹⁸³See Gerberding, *supra* note 179, at 214.

¹⁸⁴See Bell, *supra* note 182, at 205.

All of the above measures are undoubtedly important in fighting the spread of resistance. Minimizing needless use of antibiotics will reduce the selective pressures that promote the evolution of resistant strains of bacteria (by decreasing the survival advantage enjoyed by immune microbes). Tailoring antimicrobial therapy to actual pathogens – by switching to narrow-spectrum drugs once an infectious agent is identified – will diminish the exposure of bacteria to broad-spectrum antibiotics. Although not discussed earlier, use of broad-spectrum drugs is particularly strongly associated with the emergence of resistant microbes, including organisms immune to compounds unrelated to the drugs.¹⁸⁵ Frugal use of “big-gun” antibiotics, besides limiting general resistance, will also prolong these agents’ own lives and utility as empiric therapies. Finally, frequent handwashing is certainly a sensible suggestion. Resistant bacteria do not need any enemy assistance in their campaigns against mankind.

As important as the above measures are, however, they do not cancel the need for new antibiotics. It is difficult for bacteria to lose resistance genes once acquired; plasmids and transposons are fairly permanent fixtures of bacterial cells, even if these “mobile” resistance elements frequently transfer *copies* of their DNA to other organisms.¹⁸⁶ And although (as previously mentioned) immune strains of microbes tend to be replaced by non-immune strains in the absence of antibiotics, the former seldom disappear completely. They linger in the background, lurking in the shadows, ready to return at the first slip-up – such as repeated prescription of inappropriately broad antibacterials on a certain hospital ward. In addition, even if all of the measures outlined above were adopted, Americans would still manufacture and use tens of millions of

¹⁸⁵See, e.g., Daniel Villers et al., *Nosocomial Acinetobacter baumannii Infections: Microbiological and Clinical Epidemiology*, 129 ANNALS INTERNAL MED. 182-89 (1998) (finding that previous receipt of a broad-spectrum fluoroquinolone was an independent risk factor for infection with an epidemic, multi-drug resistant *Acinetobacter* strain). See also Anthony D. Harris et al., *Risk Factors for Piperacillin-Tazobactam-Resistant Pseudomonas aeruginosa Among Hospitalized Patients*, 46 ANTIMICROBIAL AGENTS & CHEMOTHERAPY 854-58 (2002) (finding that exposure to broad-spectrum cephalosporins was associated with the emergence of Piperacillin-Tazobactam resistance in *P. aeruginosa*).

¹⁸⁶See DREXLER, *supra* note 81, at 149-50.

pounds of antimicrobials every year.¹⁸⁷ It is only in a relative sense that such an amount could be considered “safe” against selection of resistant bacteria.

What, then, is the current state of antibiotic development? Spellberg et al., in a widely cited study from 2004, sought to answer this question using a two-pronged approach.¹⁸⁸ First, the researchers tracked the number of new antibacterial agents approved by the FDA over the 20-year period from 1983 to 2002 (in five-year intervals). They found that the agency approved 16 antibiotics in 1983-1987, 14 in 1988-1992, 10 in 1993-1997, and 7 in 1998-2002: a 56% decrease from the earliest to the latest periods.¹⁸⁹ Since 1998, the FDA has approved as many HIV drugs as antibiotics.¹⁹⁰

Second, Spellberg et al. examined the research and development programs of the world’s 15 largest pharmaceutical companies, and 7 largest biotechnology firms, using publicly available databases.¹⁹¹ They discovered a total of 5 antibacterials currently under development at the big drug houses, representing only 1.6% of the 418 products under investigation at the companies (which are also pursuing 12 new agents for HIV). Of 88 drugs under development at the biotechnology firms, only 1 (1.1%) was an antibiotic.¹⁹²

The six antibacterials in the pipelines of these 22 companies include Wyeth’s Tigecycline, discussed earlier, as well as Aventis’ Telithromycin, which won FDA approval in 2004.¹⁹³ Telithromycin – a ketolide antibiotic related to the macrolides – is more active than similar drugs like Erythromycin and Azithromycin against

¹⁸⁷See Levy, *supra* note 98, at 32-33.

¹⁸⁸Brad Spellberg et al., *Trends in Antimicrobial Drug Development: Implications for the Future*, 38 CLINICAL INFECTIOUS DISEASES 1280 (2004).

¹⁸⁹*Id.*

¹⁹⁰*Id.* at 1281.

¹⁹¹*Id.* at 1280.

¹⁹²*Id.* at 1281-82.

¹⁹³*Id.* at 1282, 1286.

resistant gram-positive organisms: notably, *Streptococcus pneumoniae*.¹⁹⁴ Its enhanced activity stems from the drug's ability to avoid induction of a macrolide-type resistance in bacteria. Telithromycin's activity against gram-negative pathogens appears comparable to other macrolides.¹⁹⁵

Spellberg et al. fully acknowledge one possible shortcoming of their study: their failure to include products under development at smaller pharmaceutical and biotechnology companies.¹⁹⁶ Indeed, much has been made of the supposed ability of small firms to pick up the slack in antibiotic development from big pharma; there is even a sense that investigation of new antibacterial agents has not slowed at all, but rather shifted to tiny, bleeding-edge start-ups. And it is certainly true that Daptomycin – a novel antibiotic discussed earlier in relation to MRSA – was brought to market by Cubist Pharmaceutical: a bit player in the drug industry.¹⁹⁷ In addition, the pint-sized firms of InterMune and Vicuron are presently shepherding two other antimicrobials – Oritavancin and Dalbavancin – through the new drug approval process. Oritavancin and Dalbavancin are both second-generation glycopeptides related to Vancomycin. Both reportedly met their primary endpoints in Phase III clinical trials of treatment of skin and soft tissue infections (including ones due to MRSA).¹⁹⁸ Dalbavancin is being marketed as a once-weekly injectable antibiotic, which would obviate the need for daily IV therapy in patients with resistant *S. aureus* infections (who are not candidates for oral Linezolid).¹⁹⁹ The FDA has granted the drug priority review status.²⁰⁰

¹⁹⁴See David Felmingham, *Microbiological Profile of Telithromycin, the First Ketolide Antimicrobial*, 7 CLINICAL MICROBIOLOGY & INFECTION 2-10 (2001).

¹⁹⁵See Sanjay Sethi et al., *Antibiotic Activity of Telithromycin and Comparators Against Bacterial Pathogens Isolated From 3,043 Patients With Acute Exacerbation of Chronic Bronchitis*, 4 ANNALS CLINICAL MICROBIOLOGY & ANTIMICROBIALS 5 (2005).

¹⁹⁶See Spellberg et al., *supra* note 188, at 1282-83.

¹⁹⁷*Id.* See also Herper, *supra* note 137.

¹⁹⁸See InterMune, *Oritavancin – CCSI*, at <http://www.intermune.com/wt/itm/oritavancin> (accessed April 3, 2005); Vicuron Pharmaceuticals, *Dalbavancin*, at <http://www.vicuron.com/products/proprietary/dalbavancin.html> (accessed April 3, 2005).

¹⁹⁹See Vicuron Pharmaceuticals, *supra* note 198 (claiming that Dalbavancin is the first, once-weekly injectable antibiotic).

²⁰⁰See Vicuron Pharmaceuticals, *Vicuron Pharmaceuticals Granted Priority Review of Dalbavancin NDA by FDA in Complicated Skin and Soft Tissue Infections*, at <http://www.shareholder.com/vicuron/releases.cfm> (accessed April 3, 2005).

The above small firm successes, however, are somewhat deceptive. In a curious reversal of the “normal” dynamic between big and small pharma/biotech – whereby big companies license innovative products from small firms (especially biotech start-ups) to test and market – all three antimicrobials mentioned above were discovered at large drug houses and subsequently licensed to the bit players. Both Daptomycin and Oritavancin were the brainchildren of scientists at Eli Lilly, while Dalbavancin originated at Biosearch Italia, when this company was one of the main research centers for Hoechst-Marion-Roussel (now Aventis).²⁰¹ This situation appears to be typical. A recent survey of clinical antibiotic programs at small firms concluded that the most visible efforts involved continuation of work abandoned by big pharma.²⁰² John Powers of the FDA has also found that “many of the [antibacterials] under development by biotechnology firms are products that were discovered by larger pharmaceutical companies.”²⁰³

None of this surprises drug industry experts, who maintain that few small companies can afford to pursue antibiotic research, given the unfavorable “financials” associated with antimicrobials (which are prompting even big pharma to abandon these agents, as discussed in detail in the next section).²⁰⁴ Given their lack of experience with antibacterials, small firms are especially ill equipped to develop novel classes of antibiotics, which scientists believe offer greater promise against bacterial resistance than modifications of existing drugs.²⁰⁵ This is not to say that small pharma and biotech have no role to play. Certain start-ups are pursuing important, innovative research.²⁰⁶ But as Spellberg et al. note – in defense of their exclusion of

²⁰¹See Herper, *supra* note 137 (providing information about Daptomycin); Matthew Herper, *Building an Antibiotic Powerhouse*, Forbes.com (Oct. 7, 2003), at http://www.forbes.com/2003/07/10/cx_mh_0709micu.html (accessed April 3, 2005) (providing information about Oritavancin and Dalbavancin).

²⁰²See Amy F. Boggs & George H. Miller, *Antibacterial Drug Discovery: Is Small Pharma the Solution?*, 10 CLINICAL MICROBIOLOGY & INFECTION 32-34 (2004).

²⁰³Powers, *supra* note 136, at 28.

²⁰⁴*Id.* at 32.

²⁰⁵See, e.g., Steven J. Projan, *Why Is Big Pharma Getting Out of Antibacterial Drug Discovery?*, 6 CURRENT OPINION IN MICROBIOLOGY 427 (2003) (asserting the need for truly novel antibiotics); Patrick Charles & M. Lindsay Grayson, *The Dearth of New Antibiotic Development: Why We Should Be Worried and What We Can Do About It*, 181 MED. J. AUSTRALIA 549-51 (2004) (lamenting the predominance of “me-too” antibiotics among “new” antimicrobials).

²⁰⁶See Boggs & Miller, *supra* note 202, at 34 (describing innovative approaches to antibiotic resistance being pursued at several small start-ups). See also Matthew Herper, *Antibiotics, The Next Generation*, Forbes.com (Nov. 7, 2003), at http://www.forbes.com/2003/07/11/cx_mh_0711vrtx.html (accessed April 3, 2005) (profiling innovative work involving gyrase molecules at a small research firm).

small firms from their study – the 15 largest pharmaceutical companies in the world developed 93% of the 57 new antibacterial agents approved by the FDA between 1980 and 2003.²⁰⁷ It is hard to argue with that statistic.

John Powers points out another possible shortcoming of Spellberg et al.’s study: a failure to adjust antibiotic data for general trends in drug development. If the FDA, for example, approved 60% fewer pharmaceuticals (of all types) in 2002 compared to 1983, then it could not be said that antibacterials – with a 56% drop-off in new products – have suffered special neglect.²⁰⁸ Powers presents data, from an FDA white paper, purportedly demonstrating an overall decrease in the number of new molecular entities submitted to the FDA between 1993 and 2003.²⁰⁹ However, examination of his data actually reveals little change in the number of such submissions between the beginning and end of this period.²¹⁰ Powers does show that pharmaceutical research spending has risen every year for the past decade, meaning – in the context of a flat number of new molecular entities – that drug development is becoming less productive.²¹¹ Spellberg et al. also present data that research expenditures for companies in their study rose between 1998 and 2002, which they interpret to mean that firms are spending less on antibacterials – not on drugs in general.²¹² However, without a breakdown of expenditures by drug class, this conclusion cannot be drawn (because companies could be spending a fortune to develop a single antibiotic).

²⁰⁷Spellberg et al., *supra* note 188, at 1281. Presumably, addition of antibiotics developed by the 7 largest biotechnology firms (also included in the study) would boost this percentage even higher.

²⁰⁸Of course, this statistic could mean that there is a dearth of drugs of all types.

²⁰⁹Powers, *supra* note 136, at 25.

²¹⁰The number of total new molecular entities submitted to the FDA appears to have been 28 in 1993, 45 in 1997, 33 in 2001, and 28 again in 2003. The number in 2003 is only a decrease compared to the higher numbers in the mid- to late 1990s (which may be exceptional). It is hard to describe this pattern as an “overall decrease,” as the number of submissions may normally fluctuate within some range. The number of biologic license applications, on the other hand, really did fall by over 50% between 1993 and 2003. However, antibiotics are not biologics (at least at the present time). *See id.*

²¹¹*See id.*

²¹²*See* Spellberg et al., *supra* note 136, at 1281.

Spellberg et al.’s overall results find support from other sources. For example, Joseph DiMasi studied “new chemical entities” tested in humans anywhere in the world between 1963 and 1994.²¹³ He grouped these entities into six different therapeutic categories, including “antiinfective,” antineoplastic, and cardiovascular agents.²¹⁴ DiMasi’s data derived from periodic surveys of pharmaceutical firms conducted since the 1970s by the Tufts Center for the Study of Drug Development (“CSDD”).²¹⁵ In DiMasi’s work, “new chemical entity” (“NCE”) is slightly different from the FDA’s definition of “new molecular entity” in that it excludes diagnostics. With regard to antibiotics, though, the two concepts seem identical.²¹⁶

DiMasi found that “antiinfective” agents represented close to 20% of NCEs in 1963-69, 15% in 1975-79, and 10% in 1985-89. The percentage of antiinfectives then grew to almost 20% of NCEs over the next five years, “driven almost entirely by a 3-fold increase in the number of antivirals (mostly AIDS antivirals) investigated.”²¹⁷ For all practical purposes, “antiinfectives” during the earlier periods appear to have denoted antibacterials. DiMasi provides data that demonstrate essentially no change in the total number of NCEs between 1963 and 1989, meaning that the 50% fall in the proportion of new entities that were antibiotics during this interval (from 20% to 10%) represents an absolute – not just relative – decline in the number of antimicrobials under investigation.²¹⁸ This result is consistent with Spellberg et al.’s finding of 40% fewer FDA approvals of antibiotics in 1993-1997 (when the NCEs from the late 1980s would have appeared before the FDA) compared to 1983-1987 (when the NCEs from the 1970s would have arrived at the agency).²¹⁹ The trend is also consistent with Spellberg et al.’s finding of few antibacterials in the pipelines of pharmaceutical

²¹³Joseph A. DiMasi, *New Drug Development in the United States from 1963 to 1999*, 69 CLINICAL PHARMACOLOGY & THERAPEUTICS 287 (2001).

²¹⁴*See id.* at 289-90.

²¹⁵*Id.* at 287.

²¹⁶*See* Joseph A. DiMasi, *Risks in New Drug Development: Approval Success Rates for Investigational Drugs*, 69 CLINICAL PHARMACOLOGY & THERAPEUTICS 298 (2001) (providing the researcher’s definition of NCE).

²¹⁷DiMasi, *supra* note 213, at 290.

²¹⁸*See id.* To be exact, DiMasi found essentially the same number of INDs (investigational new drugs) filed on NCEs between 1963 and 1989, with fluctuations in the number of such INDs between these two dates.

²¹⁹The FDA approved 16 antibiotics in 1983-1987, compared to 10 in 1993-1997. *See supra* note 189 and accompanying text.

firms at the present day.

It should also be mentioned that DiMasi – in another paper – buttresses Spellberg et al.’s assertion that drug houses are spending relatively less than before on antibiotic development. He presents data from the Pharmaceutical Researchers and Manufacturers of America (“PhRMA”) that the percentage of drug companies’ research expenditures devoted to antiinfective agents fell from 20% in 1980 to 15% in 1989, before growing again to 20% in 1998 – and then plunging to about 12% in 2000.²²⁰ If the upswing after 1989 mostly represented investigation of antiviral agents, the downward trend with respect to antibacterials is clear (and even more evident with the most recent decrease in percentage of expenditures). In absolute terms, however, pharmaceutical firms may in fact have spent significantly more on antibiotic research in 2000 than in 1980. According to data from PhRMA and the Tufts CSDD, inflation-adjusted research expenditures by drug companies (in 2000 dollars) totaled about \$4 billion in 1980, and \$26 billion in 2000.²²¹ Unless firms spent less than 3% of their research budgets on antibacterials in 2000, they would have exceeded the 800 million dollars expended on antimicrobials in 1980. It seems unlikely that they spent so little in 2000, as they devoted 15% of their outlays to antibiotics in 1989 (the last year before AIDS muddied the waters). As discussed in the next section, however, a clinical research dollar does not go as far today as in the past, so that increased outlays do not necessarily signify better drugs – just as they definitely do not indicate more drugs.

One general criticism of Spellberg et al.’s study is that it does not provide an estimate of the “right” number of new antibiotics. Are the five antibacterial agents presently in the pipelines of the largest pharmaceutical

²²⁰Joseph A. DiMasi et al., *R&D Costs and Returns by Therapeutic Category*, 38 DRUG INFORMATION J. 221-22 (2004).

²²¹Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 154 (2003).

and biotechnology companies too few, too many, or just right?²²² Given the fact that it takes an average of 8 years to move a drug from Phase I studies to market,²²³ one can assume that there were roughly 20 antibiotics in the pipeline in the early 1980s (because an average of 3 antibacterials were approved each year between 1983 and 1992).²²⁴ There were undoubtedly more, because a certain number of investigational drugs likely failed to win FDA approval. Five is a small figure compared to twenty, but quantity does not always equal quality. The current crop of new molecular entities could include the next penicillin, or the next carbapenem.

But that is not the case. Four of the five agents under investigation are known, and include a cephalosporin with activity against MRSA, a ketolide (like Telithromycin), a new fluoroquinolone, and Tigecycline.²²⁵ None of these drugs represents a novel class of antibiotic. And only Tigecycline seems promising as an improved therapy for nosocomial, gram-negative infections, though (as mentioned earlier) it has poor activity against *Pseudomonas*. Five definitely is too few if it leaves mankind naked against hospital bugs threatening to wreck havoc in sick wards across the country – and maybe coming soon to communities nearby. At least with respect to these gram-negative bacteria, the antibiotic pipeline does seem dangerously dry.

V. Conclusion: Prescription for Change

Since their discovery over sixty years ago in England, Germany, and America, antibiotics have saved millions

²²²This number excludes Telithromycin, which (as discussed in the text) has already been approved.

²²³Spellberg et al., *supra* note 136, at 1282 (citing a 2003 report by the Institute of Medicine).

²²⁴*See id.* at 1280 (exhibiting that the FDA approved a total of 30 new antibacterial agents between 1983 and 1992, or 3 per year).

²²⁵*See id.* at 1282. *See also* Boggs & Miller, *supra* note 202, at 34 (providing information about the new cephalosporin developed by Basilea Pharmaceutical, a spinout from Roche).

of human lives, and continue to spare possibly hundreds of thousands of Americans from death each year due to bacterial illness. Their widespread use, however, has promoted the natural selection of microbes resistant to their actions. In keeping with evolutionary principles, bacteria able to withstand antibiotics have replaced more susceptible strains of microbes lacking in “resistance genes.” These genes – often riding solo on transposons, or joined in tandem in integrons – code for enzymes and efflux pumps that are like a bird’s wings to bacteria, protecting the organisms from environmental harm. Humans have responded to repeated attempts by bacteria to slip the coils of antimicrobials with the successive development of new chemical shackles: in particular, novel classes of antibiotics to which resistance is non-existent. Against *S. aureus* – a leading cause of morbidity and mortality in humans – drug houses have recently introduced Quinupristin/Dalfopristin, Linezolid, and Daptomycin (with Dalbavancin on its way). Unfortunately, people have paid less mind to increasingly resistant “hospital bugs:” *A. baumannii*, *P. aeruginosa*, and certain of the *Enterobacteriaceae*. This inattention may partly stem from the fact that these organisms tend to afflict the sick and infirm. Of concern, the antibiotics currently under development do not seem adequate to the task of keeping some of these bacteria at bay. Even Tigecycline – one of only five antibiotics in the pipelines of the twenty-two largest drug companies, and the only one with real promise against nosocomial, gram-negative pathogens – is essentially powerless against pan-resistant *Pseudomonas*. The decline in the number of new antimicrobials, far from being a recent anomaly, has been steady over several decades. It is extremely doubtful whether small pharmaceutical companies – or “bleeding-edge” biotechnology firms – can reverse the trend.

What, then, is to be done? The rest of this paper provides one possible solution to the problem of too few antibiotics in the pipeline. It proceeds through examination of the two sides of the profit equation for

antimicrobials (or any commercial product): revenue and costs. It assumes that private, profit-maximizing pharmaceutical firms are best able to deliver on novel antibacterial agents. This is not merely some blind prejudice in favor of private enterprise. As many writers have noted, no government – regardless of its rhetoric – has developed a single new antibiotic since the time of penicillin, despite the fact that many Communist and socialist countries have tried.²²⁶ And even in the case of penicillin, it was pharmaceutical companies that were responsible for “strain optimization, compound scale-up, formulation and clinical development activities.”²²⁷ It is pharmaceutical companies – in particular, large drug houses – that possess the human and institutional resources essential for the discovery, development, and commercialization of new drugs.²²⁸ As mentioned earlier, large firms have developed over 90% of antibiotics in the past 20 years. They have proven their worth.

This is not to say that government has no role to play in preventing a return to the pre-antibiotic age. As will become clear, the solution proffered by this paper relies on government to a great extent. But it concerns itself first and foremost with the “financials” of antibacterial agents. For, to paraphrase Adam Smith, it is not from the benevolence of drug companies or biotech firms that this paper expects novel antimicrobials, but from these entities’ regard to their own interest. It therefore addresses itself not to these companies’ humanity, but to their self-love, and talks to them not of mankind’s necessities, but of their own advantages.²²⁹

²²⁶Charles & Grayson, *supra* note 205, at 549.

²²⁷Bush, *supra* note 108, at 10.

²²⁸*See id.* at 14-15.

²²⁹*See* ADAM SMITH, AN INQUIRY INTO THE NATURE AND CAUSES OF THE WEALTH OF NATIONS, Book I, Chapter II (1776) (stating that “it is not from the benevolence of the butcher, the brewer, or the baker, that we expect our dinner, but from their regard to their own interest,” and continuing that “we address ourselves, not to their humanity but to their self-love, and never talk to them of our necessities but of their advantages”).

A. Costs

In a series of studies over the past decade (some of them cited in the previous section), Joseph DiMasi and various collaborators have carefully examined drug development costs in the United States. Their findings have gained wide acceptance, including by the Office of Technology Assessment and the Congressional Budget Office. DiMasi et al.'s latest estimate of drug costs appeared in 2003, based on information obtained through 2001.²³⁰ For their updated study, the researchers secured detailed data from ten pharmaceutical firms on a randomly selected sample of 68 investigational drugs tested in humans between 1983 and 1994 (belonging to the firms). The companies – all multinationals – included four of the ten largest drug houses, and eight of the twenty largest. The researchers also collected data from the ten firms on their aggregate annual research expenditures between 1980 and 1999.²³¹ Of the 68 drugs in the study, 24 eventually won approval from the FDA, all between 1990 and 2001.²³²

DiMasi et al. found that the out-of-pocket cost per approved new drug in 2000 was \$403 million: \$121 million in preclinical, and \$282 million in clinical outlays.²³³ “Preclinical” expenses included costs associated with the discovery and initial animal testing of new compounds.²³⁴ DiMasi et al. estimated them as a percentage of a firm’s aggregate annual research expenditures (minus clinical outlays), due to the difficulty of allocating general research expenses to specific compounds, and to ensure that all costs were included in the price of new drug development (even if some research did not lead to an investigational drug tested in humans).²³⁵ “Clinical” expenses included the costs of Phase I-III trials, as well as long-term animal testing occurring

²³⁰ See DiMasi et al., *supra* note 221, at 156-58.

²³¹ *Id.* at 156.

²³² *Id.* at 171.

²³³ *Id.* at 165-66.

²³⁴ See *id.* at 155.

²³⁵ See *id.* at 160, 166.

concurrently with human studies.²³⁶ Because they were interested in companies' "expected costs" in bringing pharmaceuticals to market, the researchers assigned the costs of compounds abandoned during testing to the price of approved drugs.²³⁷

DiMasi et al. calculated the capitalized cost per approved new drug in 2000 at \$802 million: \$335 million in preclinical, and \$467 million in clinical expenses.²³⁸ As the researchers explained: "given that drug development is a very lengthy process, [its] full cost . . . should depend significantly on the timing of investment and returns."²³⁹ The researchers capitalized a drug's out-of-pocket expense to the date of marketing approval. As a discount rate, they selected average company cost-of-capital: an estimate of "the expected return that investors forgo during [drug] development when they invest in pharmaceutical R&D instead of an equally risky portfolio of financial securities."²⁴⁰ Capitalization thus accounts for the time and opportunity costs associated with the slow movement of drugs from bench to bedside.

In an earlier (1991) study on drug development costs – which was based on data obtained from 12 pharmaceutical firms on 93 randomly selected drugs first tested in humans between 1970 and 1982 – DiMasi et al. had calculated the capitalized cost per approved new drug at \$318 million (2000 dollars): less than half their updated estimate of \$802 million.²⁴¹ These two figures together yield a compound annual growth rate of 7.4% over two decades.²⁴² DiMasi et al. found that the main drivers of this phenomenal growth were clinical

²³⁶See *id.* at 155-56, 162 (including long-term animal testing in the "clinical period" if it occurred concurrent with clinical development).

²³⁷See *id.* at 159.

²³⁸*Id.* at 165-66.

²³⁹*Id.* at 160.

²⁴⁰*Id.* at 161.

²⁴¹*Id.* at 167.

²⁴²*Id.* at 168.

expenditures, which had risen between their two studies from \$104 million to \$467 million per approved drug: a 350% increase. By contrast, preclinical expenses had only risen from \$214 million to \$335 million per approved drug: a 57% increase.²⁴³ The researchers hypothesized that clinical costs had skyrocketed due to 1) increased testing of therapies for chronic disease, which “typically require more complex patient care and monitoring,” as well as larger trial sizes to establish efficacy; 2) costlier patient recruitment (as a result of increased competition for subjects); and 3) more comparative testing of drugs to satisfy insurers unwilling to pay for pricey new therapies not clearly superior to cheaper, older agents.²⁴⁴ DiMasi et al. found that Phase III trials, with a mean out-of-pocket cost of \$86 million (per investigational compound – not approved drug), were vastly more expensive than Phase I or II trials, which required outlays of \$15 million and \$24 million, respectively.²⁴⁵

But what about antibiotics? At first glance, they seem easier to test than many other pharmaceuticals, with clear-cut endpoints – like microbiologic eradication – that are measurable in days. Are they less expensive to bring to market than the average drug? DiMasi et al. addressed this question in a 1995 study that compared research and development costs for new drugs by therapeutic category. It is important to realize that the authors only considered clinical expenses in this paper, and used data from their 1991 analysis of drug development costs.²⁴⁶ The 1995 study thus focused on 93 chemical entities first tested in humans between 1970 and 1982, of which 15 were “antiinfectives,” 21 were cardiovascular drugs, and 18 were “neuropharmacological” (central nervous system, or “CNS”) agents.²⁴⁷ As mentioned in the previous

²⁴³See *id.* at 167.

²⁴⁴*Id.* at 181.

²⁴⁵*Id.* at 162.

²⁴⁶See Joseph A. DiMasi et al., *Research and Development Costs for New Drugs by Therapeutic Category*, 7 PHARMA-COECONOMICS 153-54 (1995).

²⁴⁷*Id.* at 156.

section, it is highly likely that “antiinfective” mostly denoted antibiotic in the period under consideration.

DiMasi et al. found that the out-of-pocket cost per approved antiinfective was 18% below the overall average for approved drugs.²⁴⁸ This was true despite the fact that antibiotics had slightly above-average costs for Phases I, II, and III of human testing.²⁴⁹ The high clinical success rates for antibacterials, however, more than compensated for these higher phase outlays, by burdening approved antibiotics less than other successful drugs with the costs of abandoned compounds.²⁵⁰ Over 30% of antiinfectives won FDA approval, compared to 20% of CNS drugs and 23% of all NCEs.²⁵¹ Approved antibiotics therefore only had to absorb the development costs of 70% of all antimicrobials, whereas successful CNS agents had to swallow expenses from 80% of all CNS drugs (in order to arrive at the desired “expected cost” per approved NCE).

DiMasi et al. also determined that the capitalized cost per approved antiinfective was fully 25% below average.²⁵² The improvement between out-of-pocket cost – which was already below average – and capitalized cost resulted from mean phase lengths for antibiotics that were significantly shorter than for most drugs. Antibacterials spent less time in Phases I, II, and III – and in the “NDA phase” at the FDA – than any other category of pharmaceutical.²⁵³ Indeed, “the time from the start of Phase I testing to NDA approval for antiinfectives [was] nearly 2 years shorter than average” (76.6 versus 98.9 months).²⁵⁴ Antibiotics thus had fewer “time costs” than the average drug, reducing their capitalized costs. The relative speed of antiinfectives

²⁴⁸*Id.* at 162.

²⁴⁹*See id.* at 157.

²⁵⁰*See id.* at 162.

²⁵¹*Id.* at 161.

²⁵²*Id.* at 163.

²⁵³*See id.* at 162-63.

²⁵⁴*Id.* at 163.

through Phases I-III also decreased the mean out-of-pocket and capitalized expenses of successful antibiotics considered in isolation (unburdened by the costs of abandoned compounds).²⁵⁵ However, antibacterials were still only average on these measures because of the higher phase outlays mentioned above.²⁵⁶ An approved antimicrobial may have spent less time in Phase II than a successful CNS drug, but the antibiotic had higher expenses per day in that phase (thus erasing its cost savings).

Although DiMasi et al. concentrated on clinical expenses in their 1995 study, they did include several estimates of total drug development costs for antiinfectives – inclusive of preclinical research expenditures.²⁵⁷ The authors noted that the antibiotics in their sample – 15% of the 93 drugs – appeared to account for a disproportionate share (25%) of total preclinical costs. The addition of these costs lifted out-of-pocket expenses for antiinfectives to 7% above the sample average (which was also recalculated to include research expenditures).²⁵⁸ This compares to the previous figure of 18% below average. The addition of preclinical expenses, however, still left capitalized costs for antibiotics 19% below average (compared to the previous figure of 25% below average). The lower capitalized costs resulted from the relatively short discovery period for antimicrobials: 28.9 months on average.²⁵⁹ Once again, time was on the side of antibiotics. These results call into question whether antibacterial agents remain less expensive to develop than other drugs. In a world of increasingly sophisticated methods of antimicrobial resistance, it would not be surprising if antibiotic research has slowed significantly as scientists struggle to discover new magic bullets.

It should be noted that DiMasi et al. updated their 1995 study of drug costs by therapeutic category in

²⁵⁵ See *id.* at 164-65.

²⁵⁶ See *id.* at 164-66.

²⁵⁷ See *id.* at 167.

²⁵⁸ *Id.* at 167.

²⁵⁹ *Id.* at 167.

2004 (using data from their 2003 analysis of development costs).²⁶⁰ They found that antiinfectives now had out-of-pocket expenses per approved drug that were 28% above average, primarily due to mean Phase I and Phase III outlays that were 53% and 59% above average, respectively.²⁶¹ Of note, the mean Phase III outlay for an investigational antiinfective was a staggering \$137 million.²⁶² Antiinfectives had capitalized costs per approved drug that were 6% above average. This improvement over out-of-pocket expenses resulted (once again) from development and approval times for antiinfectives that were substantially below average (total 63.0 months versus 90.3 months for all drugs).²⁶³ The overall clinical success rate for antiinfectives was 25%, compared to 30% in the 1995 study (and 21.5% for all drugs in 2004).²⁶⁴

It is difficult, however, to apply any results from the 2004 study to antibiotics due to the emergence of anti-HIV agents as the dominant form of “antiinfective” in the 1980s and 1990s. As DiMasi et al. commented: “the high out-of-pocket clinical phase costs for investigational antiinfective drugs were driven largely . . . by relatively high costs for AIDS antiviral drugs.”²⁶⁵ It is not surprising that AIDS medications have high Phase III expenses given the chronic nature of HIV, which makes testing of potential therapies similar to clinical research on other chronic diseases (requiring complex patient monitoring and large trial sizes, as mentioned earlier). DiMasi et al. did not update their 1995 analysis of preclinical expenditures associated with antiinfective agents in 2004.

The available evidence, then, suggests that antibiotics have capitalized costs of development that are 20% to 25% below the average for all pharmaceuticals (depending on the inclusion or exclusion of preclinical

²⁶⁰See DiMasi et al., *supra* note 220, at 212.

²⁶¹*Id.* at 214, 218.

²⁶²*Id.* at 215.

²⁶³See *id.* at 217.

²⁶⁴*Id.* at 215. This success rate of 25% for antiinfectives is lower than the 28% reported by DiMasi in a 2001 paper, which covered a slightly earlier period (1981-1992, instead of 1983-1994). The 28% figure may itself have been an underestimate, as the fate of certain compounds in the study was not yet known. See DiMasi, *supra* note 216, at 302.

²⁶⁵DiMasi et al., *supra* note 220, at 214.

expenses). Despite higher phase outlays – and higher discovery costs – antimicrobials spend less time in the laboratory, Phases I-III, and the NDA approval process than most other compounds. In addition, they have clinical success rates that are 5-10% above average. The speediness and successfulness of antibiotics in the pipeline more than compensate for the drugs' greater "per diem" charges. Although 20-25% of \$800 million – the mean development cost for all types of drugs – is still a very large number, antibacterials seem like a bargain compared to most other agents.

Despite the *relative* cheapness of antimicrobials, many people worried about the antibiotic shortage still focus on the cost side of the drug profit equation. They call for government grants to academia and industry for antibacterial research, and tax credits to help companies defray the costs of antibiotic development.²⁶⁶ At the FDA, they advocate automatic priority review for new classes of antimicrobials (because priority status can shave precious months off a compound's approval phase).²⁶⁷ Some criticize the agency's insistence on two well-controlled clinical trials to demonstrate a drug's efficacy for a particular indication, especially since multiple indications (and twice as many trials) are usually required for market viability.²⁶⁸ Others even question the notion of "indication" when the primary value of a new antiinfective may be against a resistant bacterium rather than any specific illness. A number of commentators have blasted the FDA's standards for proof of equivalence between two antibiotics as unduly strict.²⁶⁹ Many also support the increased use of intermediate endpoints in clinical trials – such as measurement of the absence of a bacterial pathogen as a

²⁶⁶See, e.g., INFECTIOUS DISEASES SOCIETY OF AMERICA, BAD BUGS, NO DRUGS: AS ANTIBIOTIC DISCOVERY STAGNATES ...A PUBLIC HEALTH CRISIS BREWS 24-25, 29 (2004), available at http://www.idsociety.org/pa/IDSA_Paper4_final_web.pdf (accessed April 7, 2005); Charles & Grayson, *supra* note 205, at 552; Spellberg et al., *supra* note 188, at 1284.

²⁶⁷See DiMasi et al., *supra* note 213, at 293 (revealing that the average approval phase for an NDA in 1996-1999 was 1.6 years under standard review, and 1 year under priority review).

²⁶⁸See, e.g., Projan & Shlaes, *supra* note 135, at 20; Francis P. Tally, *Drug Development for Resistant Pathogens*, Slide Presentation of the PhRMA Antibiotics Working Group (Nov. 19, 2002), available at <http://www.fda.gov/CDER/present/idsaphrma> (accessed April 7, 2005).

²⁶⁹See, e.g., Charles & Grayson, *supra* note 205, at 551-52; David M. Shlaes & Robert C. Moellering, Jr., *The United States Food and Drug Administration and the End of Antibiotics*, 34 CLINICAL INFECTIOUS DISEASE 420-22 (2002).

surrogate marker for clinical cure – to reduce the length and cost of human testing.²⁷⁰ Some recommend substitution of pharmacokinetic/pharmacodynamic data for Phase II trials, arguing that appropriate dose selection for drugs is largely knowable from pharmacologic information.²⁷¹

Public grants and tax credits for antibiotic research are probably harmless, though most people consider similar provisions in the Orphan Drug Act to be of extreme secondary importance in the success of that legislation.²⁷² As for priority review, the FDA already appears to award such status routinely to promising new antimicrobials, as the examples of Tigecycline and Dalbavancin indicate. The other recommendations proposed by reformers, however, seem potentially dangerous. Biostatisticians will attest that two trials are frequently necessary to demonstrate a drug’s efficacy, and the FDA’s insistence that antibiotics prove their ability to treat an “indication” (i.e. an actual illness) seems perfectly proper. As one FDA official explained: “An oncological drug is not approved for the treatment of ‘cancer,’ but for specific forms of cancer, such as lung and breast cancer.”²⁷³ Likewise, an antibiotic should not be approved for the treatment of “infection” – or even a particular pathogen – but for specific illnesses like pneumonia or endocarditis. This is also important because “some drugs may be effective in treating a disease at one body site [but] may not be effective in treating diseases at another body site.”²⁷⁴

Further, the FDA’s standards for equivalence trials only seek to ensure that a new drug is at least superior to placebo.²⁷⁵ And surrogate markers, though sometimes useful, “are not always predictive of the ultimate

²⁷⁰See, e.g., INFECTIOUS DISEASES SOCIETY OF AMERICA, *supra* note 266, at 27; Tally, *supra* note 268.

²⁷¹See, e.g., Jerome F. Schentag & Alan Forrest, *Role for Pharmacokinetics and Pharmacodynamics in Drug Development for Resistant Pathogens*, in THE RESISTANCE PHENOMENON IN MICROBES AND INFECTIOUS DISEASE VECTORS 174-95 (Stacey L. Knobler et al. eds., 2003).

²⁷²See, e.g., John J. Flynn, *The Orphan Drug Act: An Unconstitutional Exercise of the Patent Power*, 1992 UTAH L. REV. 395 (citing findings on the relative unimportance of orphan drug tax credits to industry in the “Report of the National Commission on Orphan Diseases,” published by HHS in 1989).

²⁷³Powers, *supra* note 136, at 26.

²⁷⁴*Id.* at 27.

²⁷⁵See, e.g., John H. Powers et al., *The United States Food and Drug Administration and Noninferiority Margins in Clinical*

outcome in a clinical trial.”²⁷⁶ “In studies of the antiarrhythmic drugs, ecanide and flecanide, suppression of ventricular premature depolarizations (the surrogate) was actually associated with a poorer longer-term outcome as measured by mortality.”²⁷⁷ Finally, pharmacokinetic/pharmacodynamic data, while of undoubted utility in selecting proper doses of drugs for human testing (which can decrease the need to enlarge or repeat studies), do not strike many experts as a safe substitute for Phase II trials to assess human responses to new agents.²⁷⁸

In the end, focus on the cost of antibiotic research and development – which is largely driven by FDA regulations – seems misplaced. The FDA approval process has evolved over many decades to protect the public against dangerous and ineffective drugs. Its requirements, though expensive, appear defensible even in the case of priority agents. Antimicrobials already enjoy lower development costs than most other pharmaceuticals, and relatively short testing and approval times. Before compromising their safety and efficacy by cutting corners on standards of clinical proof, it seems sensible to turn first for help with the antibiotic shortage to the other side of the drug profit equation: revenue.

B. Revenue

In their 1995 study of drug development costs by therapeutic category, DiMasi et al. included sales information for different types of pharmaceuticals.²⁷⁹ Once again, all drugs were first tested in humans between

Trials of Antimicrobial Agents, 34 CLINICAL INFECTIOUS DISEASE 879-81 (2002).

²⁷⁶Mark J. Goldberger, *Antibiotic Resistance: Encouraging the Development of New Therapies, Preserving the Usefulness of Current Therapies*, in THE RESISTANCE PHENOMENON IN MICROBES AND INFECTIOUS DISEASE VECTORS 207 (Stacey L. Knobler et al. eds., 2003).

²⁷⁷*Id.* (citing a 1991 study by Echt et al.).

²⁷⁸See, e.g., John H. Powers, *Overview of PK-PD in Drug Development Programs: FDA Perspective*, Slide Presentation at the FDA/IDSA/ISAP Workshop (April 16, 2004), available at http://www.fda.gov/CDER/drug/antimicrobial/FDA_IDSA_ISAP_Presentation.htm (accessed April 7, 2005).

²⁷⁹See DiMasi et al., *supra* note 246, at 167-68.

1970 and 1982, and included 19 approved antiinfectives. The researchers found that the mean fifth year sales for antibiotics – to U.S. hospitals and retail pharmacies – were \$51 million (1993 dollars). The average for all pharmaceuticals was \$87 million, with CNS agents at \$79 million and cardiovascular drugs at \$175 million.²⁸⁰

DiMasi et al. updated their sales information in 2004. This time, their sample consisted of drugs approved in the U.S. between 1990 and 1994, including 25 antiinfectives and 11 antibiotics.²⁸¹ The researchers heroically calculated the worldwide sales revenue for compounds over their entire product life cycle. They discovered that peak sales for the average drug occurred in the tenth year of marketing, meaning that the fifth year sales figures presented in 1995 likely underestimated maximum annual revenue.²⁸² The 1995 data, however, were likely reliable in terms of the relative revenue position of different types of drugs (cardiovascular>CNS>antiinfectives), as the peaks of the product life cycle curves plotted for these pharmaceutical categories in 2004 roughly coincided.²⁸³

DiMasi et al. calculated the net present value of worldwide sales revenue for antiinfective drugs – over their entire life cycle – at \$2.2 billion (2000 dollars). The mean revenue for the 11 antibiotics was \$2.38 billion.²⁸⁴ This was close to the average for all drugs: \$2.43 billion. However, CNS agents had mean revenue of \$4.2 billion, including an average \$10.7 billion for selective serotonin reuptake inhibitors: popular medications used to treat depression and a variety of other psychiatric conditions. Cardiovascular drugs had mean

²⁸⁰*Id.* at 168.

²⁸¹*See* DiMasi et al., *supra* note 220, at 218-20.

²⁸²*Id.* at 218.

²⁸³*See id.* at 219 (demonstrating similarly shaped product life cycle curves for cardiovascular, CNS, and antiinfective drugs).

²⁸⁴*Id.* at 219.

revenue of \$3.7 billion, including \$5.4 billion for calcium-channel blockers (prescribed for hypertension), and an astounding \$15.2 billion for statins (used to lower cholesterol and prevent recurrent heart attacks).²⁸⁵

It appears, then, that antibiotics are profitable investments for pharmaceutical companies, with capitalized development costs of \$600-640 million,²⁸⁶ and mean worldwide sales revenue with a net present value of \$2.4 billion. This represents a potential profit of \$1.8 billion per drug, inclusive of the costs of abandoned compounds (antibacterials that never make it to market). So why are there only five antimicrobials under development at the largest pharmaceutical and biotechnology firms? The answer seems to be that antibiotics, while profitable, are less profitable than other drugs: in particular, CNS and cardiovascular agents. Extrapolating from data in DiMasi et al.'s various studies, CNS drugs have capitalized development costs of \$904 million, and mean sales revenue of \$4.2 billion: a potential profit of over \$3 billion.²⁸⁷ Cardiovascular agents have capitalized development costs of \$790 million, and mean sales revenue of \$3.7 billion: a potential profit of \$2.9 billion.²⁸⁸ Calcium-channel blockers and statins – assuming that their development costs are average for heart medications – enjoy potential profits of \$4.6 billion and \$14.4 billion, respectively. Given that the superprofitability of cardiovascular drugs was already evident in the 1980s – when their fifth year sales were more than triple those of antiinfectives – is it any wonder that the percentage of industry research expenditures devoted to these compounds rose from 20% to 28% between 1980 and 1989, while the antiinfective share fell from 20% to 15% (as discussed in the previous section)?²⁸⁹ What is surprising is that drug

²⁸⁵*Id.* at 219.

²⁸⁶This is 20-25% of the \$800 million mean development cost for all drugs. *See supra* notes 238, 252 and accompanying text.

²⁸⁷*See* DiMasi et al., *supra* note 220, at 218 (demonstrating capitalized development costs for CNS drugs that are 13% above average, or an estimated \$904 million).

²⁸⁸*See id.* (demonstrating capitalized development costs for cardiovascular drugs that are 1.3% below average, or an estimated \$790 million).

²⁸⁹*See* DiMasi et al., *supra* note 246, at 168. It should be mentioned that AIDS drugs seem exceptional in regard to their attractiveness to investment. They have higher development costs than other antiinfectives – if indeed the relative rise in development costs for antiinfectives (from 25% below average in 1970-1982, to 6% above average in 1983-1994) is attributable to antiretrovirals – but lower mean sales revenue (\$1.6 billion compared to \$2.2 billion). *See supra* notes 252, 263 and accompanying

companies have not dedicated all of their research dollars to the lucrative CNS and cardiovascular categories (though such an investment strategy would probably diversify risk poorly).

Absolute winners, antibiotics are relative losers. Though they still account for 11% of worldwide pharmaceutical sales revenue,²⁹⁰ they seem to be living off their past glory, with a diminishing share of new research dollars. The question is: is it possible to boost the revenue associated with antibacterial agents in order to increase their net present value to pharmaceutical and biotechnology companies? Without “working on” drug costs by squeezing savings out of important safety and efficacy studies, is it possible to make antibiotics – in particular, treatments for infections by resistant bacteria (like nosocomial, gram-negative pathogens) – relatively attractive investments for pharmaceutical firms? The author of this paper, after much research, reading, and rumination, believes that the answers to these questions are yes. What follows is the sketch of a three-part proposal to accomplish these aims. The three parts will be considered in turn.

1)

text. *See also* DiMasi et al., *supra* note 220, at 219 (giving mean worldwide sales revenue for HIV drugs). Despite these unfavorable financials, AIDS medications have dominated many drug companies’ antiinfective research programs for the past two decades. However, they may be losing favor, as pharmaceutical firms take a hard look at the numbers.

²⁹⁰Bush, *supra* note 108, at 15 (providing 2002 data obtained from IMS Health World Review on worldwide pharmaceutical sales of agents in various therapeutic categories).

The List. Congress should establish an independent commission to compile a list of the 5-10 most pressing needs in the antibiotic arena.²⁹¹ The commission should consist of microbiologists, pharmacologists, and epidemiologists drawn from academia, industry, and expert organizations (like the Infectious Diseases Society of America, and the Institute of Medicine's Forum on Emerging Infections). It should identify bacterial pathogens that pose a significant threat to public health, in terms of their potential effects on morbidity and mortality in this country. It should publish the criteria that it uses to reach its results. The list should take the form of bacteria – such as Vancomycin-resistant *S. aureus*, or Imipenem-nonsusceptible *Acinetobacter* – against which new drugs are urgently needed. As part of its work, the commission should consider whether current therapies for important pathogens are acceptable in terms of safety and dosing. For example, if an antimicrobial exists to treat serious infections by a certain bacterium, but is highly toxic, or only available in parenteral form, then the commission could determine that there is a pressing need for an alternative agent to cover the organism.²⁹²

2)

The Brass Ring. Congress should authorize “wild-card patent extension” for companies that win FDA approval for antibiotics to treat bacteria on the List. The “wild card” would allow these firms to extend the patent life of any drug in their portfolio (including CNS and cardiovascular agents) by 3-4 years.²⁹³ To prevent “portfolio-shopping” – whereby companies would look to sell “listed” antibiotics (whose approval is imminent or foreseeable) to the firm with the most valuable drug on the market – the wild card should only be available to entities that own the rights to an antimicrobial at the start of human testing. This restriction would undoubtedly reduce the incentive for small companies to engage in antibacterial research, as such firms likely have fewer “cash cows” in their drug stables and thus stand to benefit less from the wild card than big pharma. And the rights to a compound are worth much less at the start of Phase I trials – when small firms would have to sell their antibiotic discoveries if they planned to (and when the success rate for anti-infectives is only 30%) – than at the start of Phase III trials (when the success rate is 77%).²⁹⁴ Given that the largest drug houses have developed over 90% of new antibiotics in the past two decades, however, the loss of small companies in this scheme seems bearable.²⁹⁵

Some people have recommended extension of the patent term for new antibiotics as an incentive for their development. Terms as long as 35 years have been proposed. This idea seems weak for two reasons. In the first place, the time value of money means that revenue generated twenty or thirty years from now is only worth a fraction of present-day sales, and therefore does not substantially increase the net present value of a new drug investment. Secondly, the value of most patents declines markedly over time. Studies have demonstrated that “between-patent” competition – i.e. competition between non-identical drugs in the same class (like different third-generation cephalosporins) – destroys the worth of patents as much as or more than “within-patent” competition (i.e. competition between branded and generic drugs).²⁹⁶ This explains why most drugs do not experience generic entry upon expiration of their patents.²⁹⁷ In the case of antibiotics, long-term patent value is also destroyed by the resistance phenomenon, which may render an antimicrobial obsolete in a matter of a few years. For all of these reasons, pharmaceutical firms would almost certainly prefer to extend the present life of one of their blockbuster drugs by 3-4 years than to receive a 30-year patent on an antibiotic. The latter option, however, could be made available in case a company does in fact prefer it (because, for example, it has few good products).

3)

The Catch. Congress should authorize the FDA to regulate the use of listed antibiotics so as to minimize the chances that drug resistance will develop. The agency should strive mightily to limit the exposure of new antimicrobials – particularly novel classes of antibiotics – to bacteria, in order to maintain the drugs’ effectiveness. This will likely require a restricted distribution program (similar to the one in place for the anti-psychotic agent Clozapine),²⁹⁸ or the imposition of severe penalties on hospitals and doctors who engage in inappropriate prescription of antibacterials (as determined by periodic pharmacy and chart review). The trade-off for drug companies is clear: potentially less revenue from new antibiotics, in exchange for wild-card patent extension. The “catch” further reduces the incentive for small firms with light portfolios to pursue development of new antimicrobials, as decreased sales due to strict use regulations could possibly negate the value of even a 30-year patent term for these agents. Once again, the consolidation of antibacterial research in the largest, most successful drug houses is not necessarily undesirable.

Serious attempts to limit the prescription of new antibiotics will raise many difficult questions for the FDA. Should the agency permit the use of a listed antimicrobial as empiric therapy for an infection when the probability that a resistant pathogen is present is only 5%? 10%? Is it even possible to restrict distribution of antibacterial agents when they are usually needed immediately (unlike Clozapine), and outbreaks of infection do occur (so that requirements cannot always be predicted in advance)? And another question: how long will it take for physicians to revolt at this micro-management of medical practice? The development of tools like rapid diagnostic tests – to determine, in real time, the precise pathogen responsible for an infection – would be of considerable aid to all concerned.²⁹⁹ In any event, the FDA must not shirk its appointed task. Regulation of antibiotic use will be complicated (and expensive), but the potential benefits almost certainly outweigh the expected costs.

The three-part proposal outlined above, while imperfect, would serve to increase the net present value of investment in new antibiotic research and development. It would help to prevent – or delay – the day when bacteria reclaim the advantage in the endless battle between humans and microbes. Given the long development times for new drugs (even antibacterial agents), it is imperative that something be done quickly. Antibiotic resistance is increasing, the pipeline for novel antimicrobials is running dry, and the current financials do not look good for last century’s “miracle drugs.” Unless immediate action is taken, the enormous benefits that Americans derive from antibacterials – as much as 5-10 years of life itself – could be threatened. Even a limited return to the pre-antibiotic age is a fate best avoided. It need not happen.