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The Decline of Penicillin: The Modern Day Crisis of Antiobiotic Resistance

As antibiotics began treating a widening range of formerly fatal infectious diseases in the 1960's, the medical community grew progressively more complacent. Reassured by clinical progress, prominent scientists were convinced that modern medicine had triumphed over its bacterial adversaries. In particular, U.S. Surgeon General William H. Stewart claimed that the time had come to "close the book on infectious diseases and declare the war against pestilence won" (NLM, 2006). Nobel laureate Sir Frank MacFarlane Burnet likewise considered "the middle of the twentieth century [to be] the end of one of the most important social revolutions in history, the virtual elimination of the infectious diseases" (Burnet, 1962, p. 18). Notwithstanding the convictions of these experts, their statements are in retrospect erroneous and certainly premature; they underestimated the appreciable adaptability of bacteria, and were thus unable to foresee the impending perils of microbial resistance.

The first widespread antimicrobial compound, penicillin, was isolated from fungi of the Penicillium genus in 1928 by Sir Alexander Fleming (Sherwood, Willey, & Woolverton, 2011). Made commercially available after the end of World War II, it was swiftly adopted as the comprehensive treatment for bacterial infections (Lerner, 2004). Recognizing the probability that "mutant forms" of bacteria could develop, Fleming advocated for prudent antibiotic use in a 1945 interview with The New York Times (Levy, 2002). His apprehension was justified only three years later by the emergence of penicillin-resistant strains of Staphylococcus aureus (Sherwood et al., 2011). The following decades witnessed the launch of several more potent antibiotics, but bacteria remained quick to retaliate, developing unprecedented and increasingly commonplace drug-resistant mutations (Alanis, 2005). Even penicillin, the model antibiotic, was progressively losing its efficacy in countless species of infectious bacteria (Levy, 2002). Alexander Fleming was right: indiscriminate antibiotic use is an indisputable element in the advent of "superbugs", multidrug-resistant bacteria that pose a significant – but often understated, – threat to human health.

Bacteria have evolved to occupy and thrive in every ecological niche of the planet—a true testament to their adaptability. Similarly to many hostile environments in nature, antibiotics suppress microbial growth by limiting favorable growth conditions. A select few microorganisms have successfully acclimatized to these harsh regions, showing that bacteria are inherently capable of reproducing such evolutionary success with antibiotics. There is, in fact, a primeval precedent for antibiotic resistance: microorganisms have produced β-lactam class antibiotics and the antagonistic β-lactamase enzyme for over two billion years. (Hall, Salipante, & Barlow, 2004; Hall & Barlow, 2004) Humans have simply repurposed such natural antibiotics for their own survival. Nevertheless, since bacteria have already demonstrated the ability to develop drug resistance, cautionary pharmaceutical practices are necessary, as "antimicrobial effectiveness . . . [is] a precious, limited resource" (Spellberg et al., 2008, p. 157).

In accordance with Charles Darwin's theory of evolution by natural selection, selective antibiotic pressure is intrinsically linked to drug resistance in bacteria. "[The] pressure exerted by the presence of an antibiotic is a potent stimulus to elicit a bacterial adaptation response" (Sefton, 2002, p. 699). Whereas antibiotics are effective in eradicating normal bacteria, genetically mutated cells are often unresponsive to the drug and survive to repopulate the infected organism (McGowan, 1983). The occurrence of resistance in a bacterial population has also been shown to have strong correlations with the amount of antibiotic exposure (Mulvey & Simor, 2009).

As "the most common cause of bacterial resistance to antibiotics" (Sefton, 2002, p. 699), selective antibiotic pressure results from the interaction of multiple risk factors, notably unnecessary and excessive drug use. In the host, suboptimal concentrations of antibiotics (due to an insufficient dosage or incomplete regimen) can promote the growth of mutated strains (Sherwood et al., 2011). With hasty patient evaluations leading to an often partial and imprecise diagnosis, the current commercially driven healthcare system is putting "physicians . . . under tremendous pressure to prescribe an antibiotic even when this may not be appropriate" (Alanis, 2005, 201). Doctors are wont to prescribe broad-spectrum antibiotics, which, although effective against multiple types of bacteria, are more likely to give rise to resistance than their narrow-spectrum counterparts (Sefton, 2002). Ideally, a proper diagnosis is made first and, if necessary, narrow-spectrum antibiotics are prescribed to target the specific pathogen (Alanis, 2005). This restricts superfluous antibiotic use in outpatients and conserves the effectiveness of broad-spectrum drugs as a last resort option (Sherwood et al., 2011).

The non-therapeutic and rampant use of antibiotics in the agricultural industry contributes to the aforementioned selective pressure (Spellberg et al., 2008) Employed primarily as a preventative measure to increase meat yield and decrease infections in livestock, careless antibiotic use in animals has grave repercussions for public health. One study, led by James R. Johnson at the University of Minnesota (Johnson et al., 2006), concluded that "bacteria are developing resistance to antibiotics on poultry farms and that these resistant bacteria are colonizing humans" (Kuehn, 2007). Transmission of bacterial species between animals and humans carries detrimental effects, particularly when both are treated for infectious diseases with the same antibiotic. For example, because resistant bacteria have crossed over from pigs to humans, sulphonamides are no longer effective antibiotics in the Danish population and must be replaced with stronger drugs (Kuehn, 2007). Excessive nontherapeutic antibiotic use in livestock will also continue to generate an increase in drug-resistant foodborne illnesses of animal origin (Alanis, 2005).

Although selective antibiotic pressure greatly influences the likeliness of resistance, the occurrence relies on the "heterogeneous" composition of a bacterial colony. (Levy & Marshall, 2004) In addition to susceptible cells, the colony must contain a few bacteria with genetic mutations (either innate or acquired) conferring the ability to counteract a drug's specific mechanism (Sefton, 2002). Antibiotics function by inhibiting basic metabolic processes, such as synthesis of DNA, proteins, and the cell wall (Levy & Marshall, 2004). By subjecting the aforementioned colony to antimicrobial drugs, the mutated bacteria survive by virtue of their evolutionary adaptation and continue to proliferate inside the host.

Antibiotic inactivation is an adaptation often observed when investigating β-lactam antibiotic-resistance. Before the drug can reach the membrane, it is rendered ineffective by β-lactamase, an enzyme secreted by the bacteria (Levy & Marshall, 2006). Another resistance strategy consists of regulating the access of

drugs to the appropriate binding site. This is accomplished by expelling intracellular antibiotics through efflux pumps integrated in the cell membrane (Alanis, 2005). In contrast to the specific enzyme interaction for antibiotic inactivation, these non-specific transport structures, acting simultaneously on different antibiotic compounds, grant the bacteria multidrug-resistance (Sherwood et al., 2011). Genetic mutations are also capable of modifying a drug's intended target site, thereby interfering with its mechanism of action. A prime example is the alteration of penicillin-binding proteins in certain penicillin-resistant strains of Streptococcus pneumonia (Alanis, 2005). Some types of bacteria are even resistant to antibiotic classes by virtue of their physiology. For example, gram-negative bacteria, which have two plasma membranes, are inherently resistant to penicillin class drugs (Sherwood et al., 2011).

From an evolutionary perspective, antibiotic resistance genes confer a competitive advantage and, as a result, are frequently exchanged amongst bacteria. Derived from spontaneous – albeit scarce – genetic mutations, genes encoding for drug resistance are generally located within an R (resistance) plasmid—a mobile circular element of DNA (Sherwood et al., 2011). Through various mechanisms of gene exchange, the R plasmids are quickly transferred to surrounding bacteria and, to the detriment of the host, often contain several genes, each encoding for a different antibiotic resistance (Sherwood et al., 2011). The apparition of these multidrug-resistant pathogens (MDR)—defined as resistant to more than two classes of antibiotics (Sherwood et al., 2011)—is assuredly an indication that bacteria are becoming increasingly resilient to efforts at eliminating them.

"Superbugs", as these bacteria are commonly termed, are slowly dragging modern medicine back to the pre-antibiotic era, since "for patients infected with multidrug-resistant bacteria, there is no magic bullet." (Arias & Murray, 2009) As antibiotics are currently plentiful, it is difficult to fathom that at the beginning of the last century an open wound could have led to a serious and potentially fatal infection. In the same manner, given the physician's seeming arsenal of antimicrobial drugs, it is much to the public's bewilderment that bacteria are making resurgence. The Center for Disease Control estimates that since 2000, nosocomial antibiotic-resistant pathogens account for approximately 70,000 deaths per year in the United States alone (IDSA, 2004). The consequent health care costs are believed to total several tens of billions of dollars annually in the U.S. (GAO, 1999).

In 2002, outbreaks of hospital-borne Clostridium difficile infections were discovered in several Quebec hospitals. Having since spread throughout North America and Europe, the fluoroquinolone-resistant NAP1 strain caused severe diarrhea and proved to be fatal in over a hundred patients—particularly amongst the elderly (Mulvey & Simor, 2009). Still, methicillin-resistant Staphylococcus aureus (MRSA) and vancomysin-resistant Enterococcus faecium (VRE) are conceivably the most prominent examples of pathogenic nosocomial strains of bacteria (Grundmann, 2006).

After first being documented in the early 1980s, MRSA has significantly complicated inpatient treatment (Arias & Murray, 2009). It has become not only resistant to methicillin—a β-lactam antibiotic since discontinued—but also to the larger β-lactam class of antibiotics. This represents a particular area of concern, bearing in mind that in 2003, "more than 50% of S. aureus isolates recovered in U.S. hospitals were MRSA" (Arias & Murray, 2009). Following the spread of this nosocomial strain to the community setting, it has become "the leading cause of identifiable skin and soft-tissue infections seen in U.S. emergency rooms" (Arias & Murray, 2009). Likewise, since vancomycin is regularly cited as the "drug of last resort" (Sherwood et al., 2011) in MRSA infections, the emergence of

vancomycin-resistant strains of S. aureus presents a serious health care problem (Sherwood et al., 2011). Other species of bacteria, notably Enterococcus faecium, are displaying vancomycin resistance as well. In the United States, almost 90% of isolated E. faecium bacteria are VRE, and close to 100% are resistant to ampicillin (Arias & Murray, 2009), leaving no apparent therapy for VRE endocarditis (Arias & Murray, 2008)—the inflammation of the heart valves due to bacterial growth.

Perhaps the hallmark of antibiotic resistance is MDR Mycobacterium tuberculosis—the bacteria that causes tuberculosis, a debilitating potentially fatal infectious disease. Originating in the late 1970s, MDR-TB is significantly more prevalent in developing countries (Alanis, 2005). For comparison, by the World Health Organization's 2008 estimates, 9.2 million people worldwide have some form of tuberculosis, of which MDR-TB accounts for 500,000 cases. Of these, only 98 infections were reported in the United States (Sherwood et al., 2011). The effect of antibiotic resistance is evidently skewed towards developing nations, and the explanation appears to be rather simple: "antibiotics are much easier to obtain without a prescription in many of these [developing] countries whereas their access is much more limited in the developed world" (Alanis, 2005).

Even more threatening to the global population is the new, extremely drug-resistant strain of M. tuberculosis (XDR-TB). To be placed in this category, the bacteria must exhibit resistance to isoniazid and rifampin—the two drugs involved in multidrug-resistant strains—as well as fluoroquinolone and one of amikacin, kanamycin, or capreomycin. In 2010, there were an estimated combined total of 1.6 million cases of MDR-TB and XDR-TB worldwide (Sherwood et al., 2011).

Clearly, antibiotic-resistant bacteria pose an unmistakable threat to public health. Yet even with current policies seeking to curb the growth of the problem, efforts remain insufficient. Independent interventions are for the most part ineffective and should be combined to create comprehensive, multifaceted ones, which are better suited to contain a crisis of this magnitude (Foucault & Brouqui, 2007). Various studies have determined that the most effective mitigation strategies are: infection control measures like gloves, masks, and proper hand hygiene (Garner, 1996); national guidelines (Enne, 2001) and education programs (Gonzales, Steiner, Lum, & Barrett , 1995) that standardize prescription practices amongst physicians; and documentation of antibiotic prescription and instances of resistance at the community level in order to maintain drug effectiveness (Cornaglia et al., 2004). Following the implementation of a multifaceted program consisting of "screening, infection control precautions and the prudent use of antibiotics," Denmark observed a 30% decrease in prevalence of MRSA between 1970 and 1960 (Barrett, 2004).

Probably the most successful multifaceted intervention to date is the "Direct Observed Therapy" (DOT) used in the treatment of tuberculosis (Sherwood et al., 2011). To insure compliance with the antibiotic regimen, patients are obliged to take the drugs only under the supervision of a health care professional. The success of the strategy is indisputable. In the United States, as the treatment of tuberculosis by DOT increased from 21% of cases in 1993 to 53% in 2005, there was a corresponding 50% decrease in the incidence of the disease (Sherwood et al., 2011).

Along with the implementation of control measures and the appropriate regulation of drugs, a new collection of antibiotics is needed to bolster the dwindling effectiveness of antimicrobial therapies. However, there is a significant economic disincentive for pharmaceutical companies to produce new antibiotics. With drug development averaging 10-14 years

(Shlaes & Moellering, 2002) to complete and costing an estimated $800 million dollars (DiMasi, Hansen, Grabowski, & Lasagna, 1991), return on this long-term investment is of paramount importance to the company. Hence, because antibiotics are often short-course treatments and prone to resistance, it is more economically sound to develop drugs for "chronic diseases [that] are treated with noncurative therapies . . . [and] are required to be taken for the life of the patient" (Spellberg et al., 2008; p. 157).

This rationale is markedly responsible for the reduction and, to some degree, stagnation in antibiotic discovery since the early 1980s. As an illustration, between 2003 and 2007, the Food & Drug Administration approved 7 new antiviral compounds targeting HIV compared to only 5 new antibiotics (Spellberg et al., 2008) Similarly, between 2004 and 2008, there were 5 antibiotics in development, only one more than for erectile dysfunction (Spellberg et al., 2004). Companies are very careful to secure reliable sources of income. In addition, vague drug safety and efficacy guidelines from the FDA (Blaser & Bartlett, 2006; Boucher, 2008), together with the current initiatives seeking to regulate and reduce antibiotic use, further deter pharmaceutical companies from undertaking antimicrobial drug design.

Antibiotic resistance presents one of the most crucial global health problems of this century. In the last few decades, the emergence of multidrug-resistant superbugs have paralleled the decrease in antibiotic development, and scientists are becoming increasingly vocal about the imminent health crisis. Unless multifaceted interventions and restricted antibiotic usage see widespread implementation, the current problem will surely intensify. Resistance will spread amongst species of bacteria and render the treatment of infectious diseases increasingly difficult and potentially even unmanageable. Humans have long been believed to be the dominant species. Yet, as these displays of bacterial resilience demonstrate, human arrogance is without basis. Having dominated the earth for billions of years, bacteria are remarkably more adaptable to adverse environments than previously expected; and, if not regulated properly, drug-resistant stains will wreak havoc on the health of the global population. In fact, Dr. Joshua Lederberg, the 1958 Nobel Prize laureate in Physiology or Medicine, sums up the current antibiotic resistance hazard succinctly in his statement: "The future of humanity and microbes will likely evolve as . . . episodes of our wits versus their genes" (Lederberg, 2000).

References

Alfonso JA. (2005). Resistance to Antibiotics: Are we in the post-antibiotic era? Arch Med Res. 36(6):697-705.

Antimicrobial resistance: data to assess public health threat from resistant bacteria are limited. (1999(. RCED-99–132. Washington D.C.: United States General Accounting Office.

Arias CA, Murray BE. (2009). Antibiotic-Resistant bugs in the 21st century—A clinical super-challenge. N Engl J Med. 360(5):439-43.

Arias CA, Murray BE. (2008). Emergence and management of drug-resistant enterococcal infections. Expert Rev Anti Infect Ther. 6:637-55.

Barrett SP. (2004). Debate-guidelines for GRE control–the case for optimism. J Hosp Infect. l57:285-9.

Blaser MJ, Bartlett JG. (2006) Letter to FDA Commissioner Andrew C. von Eschenbach, MD.: Infectious Diseases Society of America. Available at: http://www.idsociety.org/WorkArea/downloadasset.aspx?idp3384.

Boucher HW. Open public forum. In: FDA Anti-Infective Drugs Advisory Committee: Joint with Drug Safety and Risk Management Advisory Committee. Silver Spring, MD.

Burnet M. (1962). Natural history of infectious disease. Cambridge, UK: Cambridge University Press; p.18.

Cornaglia G, Hryniewicz W, Jarlier V, Kahlmeter G, Mittermayer H, Stratchounski L, et al. (2004). European recommendations for antimicrobial resistance surveillance. Clin Microbiol Infect. 10:349–83.

DiMasi JA, Hansen RW, Grabowski HG, Lasagna L. (1991). Cost of innovation in the pharmaceutical industry. J

Health Econ. 10:107-142.

Enne VI, Livermore DM, Stephens P, Hall LM. (2001). Persistence of sulphonamide resistance in Escherichia coli in the UK despite national prescribing restriction. Lancet. 357:1325-28.

Foucault C, Brouqui P. (2007). How to fight antimicrobial resistance. FEMS Immunol Med Microbiol. 49(2):173-83.

Garner JS. (1996) Guideline for isolation precautions in hospitals. The hospital infection control practices advisory committee. Infect Control Hosp Epidemiol. 17:53–80.

Gonzales R, Steiner JF, Lum A, Barrett PH Jr. (1995). Decreasing antibiotic use in ambulatory practice: impact of a multidimensional intervention on the treatment of uncomplicated acute bronchitis in adults. J Am Med Assoc. 281:1512-19.

Grundmann H, Aires-de-Sousa M, Boyce J, et al. (2006). Emergence and resurgence of meticillin-resistant Staphylococcus aureus as a public-health threat. Lancet. 368:874-85.

Hall BG, Barlow M. (2004). Evolution of the serine b-lactamases: past, present and future. Drug Resist Update. 7:111–2.

Hall BG, Salipante SJ, Barlow M. (2004). Independent origins of subgroup Bl + B2 and subgroup B3 metallo-b-lactamases. J Mol Evol. 59:133–4

Infectious Diseases Society of America. (2004). Bad bugs, no drugs: as antibiotic discovery stagnates, a public health crisis brews. Alexandria, VA: Infectious Diseases Society of America.

Jacoby GA, Munoz-Price LS. (2005). The new β-lactamases. N Engl J Med. 352:380-391.

Johnson JR, Kuskowski MA, Menard M, Gajewski A, Xercavins M, Garau J. (2006). Similarity between human and chicken escherichia coli isolates in relation to ciprofloxacin resistance. J Infect Dis. 194(1):71-78.

Kuehn BM. (2007). Antibiotic-Resistant "Superbugs" may be transmitted from animals to humans. JAMA. 298(18):2125-6.

Lerner PI. (2004). Producing penicillin. N Engl J Med. 351:524.

Levy SB, Marshall B. (2004). Antibacterial resistance worldwide: causes, challenges and responses. Nat Med. 10:S122-9.

Levy SB. (2002). From tragedy the antibiotic era is born. In: Levy SB, ed. The Antibiotic Paradox: How the Misuse of Antibiotics Destroys Their Curative Powers, 2nd ed. Cambridge, MA: Perseus Publishing. pp. 1-14.

McGowan JE Jr. (1985). Antimicrobial resistance in hospital organisms and its relation to antibiotic use. Rev Infect Dis. 5:1033-48.

Mulvey MR, Simor AE. (2009). Antimicrobial resistance in hospitals: How concerned should we be? CMAJ. 180(4):408-15.

Sefton AM. (2002). Mechanisms of antimicrobial resistance. Drugs. 62:557-566.

Sherwood LM, Willey JM, Woolverton CJ. Prescott's Microbiology. (2011). Eighth ed. New York, NY: McGraw-Hill. Chapter 34, Antimicrobial Chemotherapy; p.826-49.

Shlaes DM, Moellering RC. (2002). The United States food and drug administration and the end of antibiotics. Clin Infect Dis. 34:420-2.

Spellberg B, Guidos R, Gilbert D, Bradley J, Boucher HW, Scheld WM, et al. (2008). The epidemic of antibiotic-resistant infections: A call to action for the medical community from the infectious diseases society of America. Clin Infect Dis. 46(2):155-64.

Spellberg B, Powers JH, Brass EP, Miller LG, Edwards JE. (2004). Trends in antimicrobial drug development: implications for the future. Clin Infect Dis. 38:1279–86

The Office of the Public Health Service Historian. (2006). Frequently asked questions. US Public Health Service, Office of the Librarian. Available at: http://lhncbc.nlm.nih.gov/apdb/phsHistory/faqs.html.