Plagues, Policy, & Patents: Addressing Overuse of Antibiotics

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ABSTRACT

In response to the intensive use of antibiotics since their discovery in the 1930s, bacteria increasingly have evolved resistance to these critical medications. Because of this evolutionary process, antibiotics have an unusual characteristic that gives rise to a negative externality: current use erodes their future usefulness. Society is squandering the limited supply of this precious resource for low-value uses, such as treating minor infections. The price of this profligacy? Patients in the future may die from bacterial infections that become resistant to all antibiotics.

This negative externality is a market failure, calling for governmental measures to rationalize antibiotic use. Applying the economic literature on exhaustible resources, this article argues that the state should grant infinite-term patents on antibiotics. In addition to encouraging pricing that will prolong the useful life of antibiotics, infinite-term patents may create incentives for drug makers to hold some antibiotics in reserve to meet the extraordinary demand that will arise if and when there is a bacterial plague. The government also should subsidize the use of tests to determine the nature and resistances of infections, increase subsidies and research spending on vaccinations, and gather more information about the extent and nature of the threat posed by resistant bacterial pathogens.

CONTENTS

I. Introduction

The discovery and widespread use of antibiotics stand as perhaps the most important medical advance of the 20th century. These 'miracle' drugs, starting with penicillin, made many previously fatal bacterial infections curable with a few pills or injections. It was unsurprising that over the latter half of the century we continuously intensified our use of these potent, cost-effective substances.

An inevitable (with the benefit of hindsight) result of unleashing this powerful attack on our bacterial foes did come as a surprise: bacteria evolved defenses to antibiotics, often with astonishing speed. Doctors continue to detect these resistant strains of bacteria (resistant to one or more antibiotics) in greater and greater numbers. In 2000, the World Health Organization warned that "the world could be plunged back into the 'preantibiotic era' when people commonly died from diseases that in modern times have been easily treated with antibiotics …"[1] In Britain, the government estimates that over 5,000 hospital patients a year die from bacterial infections resistant to antibiotics.[2]

The trend may have intensified over the last year. Researchers at Children's Hospital in Pittsburgh reported an outbreak of resistant streptococcus (strep.) bacteria. The lead author of the study stated that "[w]e've talked about this for years and now its here."[3] Over a thousand prison inmates in Los Angeles County contracted "painful and aggressive skin infections caused by a bacterium resistant to many antibiotics …"[4] Doctors found this outbreak particularly worrisome because the bacteria spread to patients without skin wounds or other weaknesses ordinarily necessary to make people susceptible to infection. Although there were no fatalities, "in some cases doctors … had to cut away diseased tissue and administer weeks of intravenous antibiotics."[5] Initial reports in

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[1]Marc Kaufman, *Microbes Winning the War*, WASHINGTON POST, June 13, 2000, at A1.

[2]http://news.bbc.co.uk/1/hi/health/646369.stm (visited March 4, 2003).

[3]Laurie Tarkan, *Outbreak of Drug-Resistant Strep Bacteria*, NEW YORK TIMES, April 18, 2002, at A12.

[4]David Tuller, *Mystery Surrounds a Virulent Skin Infection*, NEW YORK TIMES, February 4, 2003, at D6.

[5]*Id.*

March 2003 indicated that the germ has spread outside the prison population and across the nation to Boston.[6] Another recent study found that ciprofloxacin ("cipro"), the antibiotic popularized as the agent of choice against anthrax infections, has become increasingly ineffective against many germs over the last few years.[7] In short, we now face the sobering possibility of serious, even lethal, bacterial infections that are untreatable.

Despite increasing news coverage, the threat posed by resistant bacteria does not seem to have made it onto the body politic's radar screen. There is little if any concerted public pressure on leaders to take decisive measures to manage more judiciously our precious stocks of antibiotics. Inaction is all the more unfortunate because overuse of antibiotics is a classic collective action problem — precisely the sort of problem where government action and only government action can provide a solution. The purpose of this article is to outline efficient, effective measures to economize on antibiotic use, so that we have effective drugs for serious cases long into the future, and to combat any future bacterial plague that may occur.

Section II gives a brief history of antibiotics and the bacterial evolution of resistance to thm. Section III explains aspects of the biology of resistance relevant to policy choices. Two lessons stand out from these sections. First, bacteria acquire resistance much more easily than one might think: they routinely share genes encoding resistance with a wide variety of other bacteria, including very dissimilar species. Second, recent research suggests that once bacteria develop resistance to an antibiotic, they are unlikely to lose resistance even if the particular antibiotic disappears from their environment. Thus there appears to be little hope of 'reviving' the effectiveness of antibiotics by withdrawing them from use for some 'rest' period.

This last point serves as a launching point for Section IV, which draws on economics to formulate optimal policies for limiting antibiotic use. As a resource unable to regenerate itself, antibiotics are analogous to minerals in the ground, as opposed to fish in the sea: they are an

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[6]Stephen Smith, *Resistant-bacteria Reports Cause Alarm*, BOSTON GLOBE, March 2, 2003, at B1.

[7]Melinda M. Neuhauser et al., *Antibiotic Resistance Among Gram-Negative Bacilli in US Intensive Care Units, Implications for Fluoroquinolone Use*, 289 J. AM. MED ASS'N 885 (2003).

exhaustible (or depletable) resource. As such, they require special economic analysis. Within the framework of exhaustible resource economics, there is a fundamental difficulty with antibiotics: current *low-value* uses (e.g. treatment of minor infections that may not even be bacterial) will deprive us of future *high-value* uses (e.g. treatment of life-threatening bacterial infections). This happens because there is no way for future potential users to pay present low-value users to forego consumption. As such, antibiotic consumption has a negative external effect on future consumption. *The fundamental motivation driving the policy discussion in this article is to identify measures that will discourage current low-value use, to preserve effective doses of the antibiotic for future high-value uses*.

Previous work has either focused on this negative externality without drawing on exhaustible resource economics, or has used such economics but assumed that all infections are equally harmful, making it impossible to analyze what this article takes as the fundamental question — trading off current low-value uses for future high-value uses. In addition, this article studies at length the policy implications of measures not previously examined. Section IV.C.3 shows that there is a strong case for the government to subsidize tests that can identify both the germ responsible for an infection and the drugs to which the germ has resistance.

Section IV.D then introduces patents (in economic terms, time-limited monopolies) into the analysis and studies their effect on antibiotic policy, stressing that patents serve a *property-right creation* function in this context, independent of their usual innovation-inducing role. This section makes a novel and radical argument that patent terms for antibiotics should be unlimited. Trying to encourage pharmaceutical companies to stockpile drugs to deal with potential plagues, the subject of § IV.E, buttresses the case for infinite-term patents.

Finally, Section V addresses jurisdictional questions raised by state borders in America (§ V.A), and distributional issues raised by the necessity of worldwide efforts to curb overuse of antibiotics. Given the extent of international travel and trade, overuse of antibiotics in any nation likely will spread resistant bacteria around the globe. Any policy, then, is only as good as its "weakest link." Under such conditions, it is in the self-interest of wealthy nations to subsidize the efforts of poorer nations.

II. A Brief History of Antibiotics & Bacterial Resistance

Predating our scientific age, some cultures seem to have stumbled across effective naturally-occurring antibacterial agents. At least one study indicates that members of an ancient culture ingested therapeutic doses of tetracycline, an antibiotic 'rediscovered' in the 20th century.[8] Other folk remedies, such as ingesting moldy bread, may have delivered effective doses of antibiotics.[9]

Although there were a number of earlier scientific observations and findings, the antibiotic age began in earnest when Alexander Fleming noticed that a mold contaminating one of his bacteria cultures had killed off all the germs in its neighborhood.[10] Later research revealed that the mold produced a chemical, penicillin, that could cure bacterial infections in humans. Since this discovery, scientists have identified and pharmaceutical companies have produced over 100 different antibacterial compounds that are effective against human (and animal) infections.[11]

These antibiotics have had a dramatic positive impact on human health. Formerly untreatable bacterial infections, some lethal or seriously disabling, have ceased to pose any threat. In conjunction with improved public health (e.g. water supplies free of cholera and other microbes), antibiotics increased the median life span by 8 years, from 62 to 70, during their first 20 years of use (1935 to 1955).[12]

Yet almost from the beginning of their widespread use, doctors noticed that bacteria developed countermeasures to antibiotics. Researchers reported significant levels of penicillin resistance in staph. infection (short for staphylococcus aureus, a common species of bacteria that normally does not cause serious infections, but can if it enters the

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[8]Everett J. Basset et al., *Tetracycline-labeled Bone from Ancient Sudanese Nubia*, 209 SCIENCE 1532 (1980).

[9]MADELINE DREXLER, SECRET AGENTS: THE MENACE OF EMERGING INFECTIONS 146 (2001) (available online at: http://www.nap.edu/books/0309076382/html/).

[10]http://www.time.com/time/time100/scientist/profile/fleming.html

[11]MICHAEL T. MADIGAN ET AL., BROCK BIOLOGY OF MICROORGANISMS 426 (8th edition 1997).

[12]David Schlessinger, *Biological Basis for Antibacterial Action*, in MECHANISMS OF MICROBIAL DISEASE 77 (M. Schaechter, G. Medoff & B. I. Eisenstein, eds., 1993).

bloodstream or vital organs) as early as 1945.[13] Over 95% of staph. bacteria today are resistant to penicillin and related compounds.[14]

Multiply resistant staphylococcus aureus (MRSA) strains have successively evolved resistance to almost every class of antibiotics: synthetic variants of penicillin such as methicillin; cephalosporins, penems, and carbapenems. There was great hope in the 1980s that a new class of antibiotics, fluoroquinolones such as ciprofloxacin ("cipro" for short), would remain effective because they used a relatively novel mechanism, that does not occur in nature, to attack bacteria. This unnatural, or "synthetic" characteristic, however, made little difference. "A study by the Centers for Disease Control showed that ciprofloxacin resistance of MRSA went from less than 5% to greater than 80% within 1 year …"[15]

Today, some strains of MRSA are resistant to all mainstream antibiotics except vancomycin, which has become a critical antibiotic of "last resort."[16] Even more ominously, there have been sporadic appearances of staph. infections exhibiting moderate resistance to vancomycin (labeled VISA — vancomycin intermediate staph. aureus).[17] Summing up staph.'s repeated ability to defeat almost all antibiotics deployed against it, one scientist said that these episodes "illustrate the rapid ability of bacteria to become resistant to virtually all antibacterial agents whether of natural origin … partially synthetic … or totally

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[13]Wesley Spink & Victor Ferris, *Quantitative Action of Penicillin Inhibitor from Penicillin-Resistant Strains of Staphylococci*, 102 SCIENCE 221 (1945).

[14]Harold C. Neu, *The Crisis in Antibiotic Resistance*, 257 SCIENCE 1064 (1992), citing Bruce Lyon & Ronald A. Skurray, *Antimicrobial Resistance of Staphylococcus aureus: Genetic Basics*, 51 Microbiology Rev. 88 (1987).

[15]*Id.*, citing Henry M. Blumberg et al., *Rapid Development of Ciprofloxacin Resistance in Methicillin-susceptible and -resistant Staphylococcus aureus*, 163 J. Infectious Diseases1279 (1991).

[16]U.S. CONGRESS, OFFICE OF TECHNOLOGY ASSESSMENT, IMPACT OF ANTIBIOTIC-RESISTANT BACTERIA 72 A-H-629 (Washington, D.C., U.S. G.P.O., 1995) (hereinafter, OTA).

[17]*See* http://www.cdc.gov/ncidod/hip/aresist/visa.htm (visited March 5, 2003) (documenting cases of VISA in eight states).

synthetic, such as fluoroquinolones."[18]

Some strains of another family of bacteria, enterococci, have developed complete resistance to vancomycin along with all other mainstream antibiotics.[19] The mechanism developed by the bacteria

> completely changes the ingredients it uses to make its cell wall, ingredients that are normally targeted by vancomycin. … "That's a real *tour de force*," says David Hooper, an infection control director at Massachusetts General Hospital. "What they tells me is: No matter what we come up with, over time bugs are going to figure out a way to get around it."[20]

Fortunately, enteroccoci cause many fewer serious infections than staph. As discussed in the next section, however, unrelated bacteria frequently share genes encoding resistance to antibiotics. MRSA acquiring complete resistance to vancomycin would constitute "an unstoppable killer … the latest twist in an international public health nightmare: increasing bacterial resistance to many antibiotics …"[21]

There is nothing particularly special about staph. or enterococcus; virtually all infectious bacteria have developed resistance to some antibiotics. Strep. bacteria responsible for many throat infections developed significant resistance to the antibiotic erythromycin in only two years.[22] Moraxella, a source of middle ear and chest infections, was virtually 100% vulnerable to ampicillin in the 1970s; within 20 years, over 75% of such infections were fully resistant to it, and to chemically similar antibiotics.[23]

The threat posed by antibiotic-resistant bacteria is greater because of a sort of whipsaw effect in the pharmaceutical industry. By the early 1980s, there were over 100 antibiotics and resistance was not yet a

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[18]Neu, *supra* note 14, at 1065.

[19]OTA, *supra* note 16, at 72.

[20]Drexler, *supra* note 9, at 146.

[21]Stuart B. Levy, *The Challenge of Antibiotic Resistance*, 278 Scientific American 46, 46 (1998).

[22]Neu, *supra* note 14.

[23]Richard J. Wallace Jr. et al., BRO *ß-Lactamases of Branhamella catarrhalis and subgenus Moraxella*,33 ANTIMICROBIAL AGENTS CHEMOTHERAPY 1845 (1989).

serious problem. Thus drug makers invested relatively little effort in developing new antibacterial agents. When MRSA and other resistant strains began to pose a serious public health problem in the 1990s, there were no new drugs to deploy. Perhaps worse, given the long period required to develop new drugs, there were few drugs in the pipeline. Although pharmaceutical companies seem to be gearing up their antibiotic R&D efforts, society will not reap the benefits from these efforts for years.[24]

The speed with which bacteria build up resistance suggests a need for a steady stream of new treatments. Recall that MRSA became largely resistant to cipro after only three years. Early experience with linezolid, a novel type of antibiotic approved in 2000, is no more promising: doctors detected strains of staph. resistant to this new drug in 2001.[25]

The threat posed by antibiotic-resistant bacteria has caught the attention of the medical establishment. The Centers for Disease Control launched a "Prevent Antimicrobial Resistance Campaign" in 2001[26]; the World Health Organization has a similar program.[27] Before discussing the efficacy of these and other policies designed to deal with the threat of resistant microbes (§ IV *infra*), the next section lays out some basic biological facts about bacteria and resistance that are important in assessing policy responses.

III. The Biology of Antibiotics & Resistance

There seems little doubt that heavy use of antibiotics has driven the rapid spread of resistant strains. Bacterial foes such as molds and fungi have fought such biochemical wars bacteria for ages, but apparently never with the intensity that humans have employed antibiotics over the last 60-odd years. Tests on bacteria preserved from before the age of antibiotics show that bacteria had evolved some resistance to naturally occurring antibiotics, but most remained vulnerable to the vast majority of the antibiotics discovered and developed since Fleming's discovery of

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[24]OTA, *supra* note 16, at 28.

[25]DREXLER, *supra* note 9, at 120.

[26]*See* http://www.cdc.gov/drugresistance/healthcare/default.htm (visited March 5, 2003).

[27]http://www.who.int/csr/drugresist/en/ (visited March 5, 2003).

penicillin.[28]

Heavy use does not necessarily mean overuse; e.g. if every dose of every antibiotic administered saved a life, it would be difficult to argue that we are wasting this valuable resource. Use, however, has not been so limited. Doctors routinely prescribe antibacterial drugs to treat infections that are likely viral — in which case (i) the treatment has absolutely no therapeutic benefit for the patient, and (ii) the use of the antibiotic still fosters the spread of resistance in other bacteria present in the patient. Some estimate that half of all antibiotic prescriptions are written for patients who will experience no benefit from the medication.[29]

In fairness to doctors and patients, it is often expensive and time-consuming to determine if an infection is viral or bacterial.[30] If, however, the infection is not serious, then there is a good argument that antibiotics simply should not be used. If the infection is viral, the drugs are worthless to the patient; even if the infection is bacterial, frequently antibiotics do not even shorten the duration of the illness.[31]

Although these may be the largest categories of overuse, there are other significant prodigal misuses of antibiotics. Many surgeons use them far earlier than necessary as prophylactic measures to prevent infection after surgery.[32] In a slightly different vein, doctors often prescribe "wide-spectrum" antibiotics — those that are active against many types of bacteria — when a narrower-spectrum drug would suffice. This, of course, accelerates the spread of resistance to those antibiotics that are useful in the greatest variety of cases, in effect wasting the effectiveness of a more valuable drug.

The livestock industry may be frittering away the usefulness of antibiotics by using large quantities of the drugs, at low doses, as growth

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[28]V. Hughes & Naomi Datta, *Conjugative Plasmids in Bacteria of the "Pre-Antibiotic" Era*, 302 Nature 725 (1983).

[29]OTA, *supra* note 16, at 73-74.

[30]*Id.* 127-29, 134; *see infra* § IV.C.3.

[31]Jerome.O. Klein, *Otitis externa, Otitis media, Mastoiditis,* in GERALD L. MANDELL, R. GORDON DOUGLAS JR., & JOHN E. BENNETT, PRINCIPLES AND PRACTICES OF INFECTIOUS DISEASES 579-585 (1994).

[32]Richard P. Wenzel, *Preoperative Antibiotic Prophylaxis*, 326 NEW ENGLAND J. MED. 337, 337 (1992).

enhancers; up to 70% of the antibiotics used in the United States each year may be for this purpose.[33] This steady exposure to low doses creates an ideal environment for the evolution of resistant bacteria. The low doses mean that strains with only an initial, modest resistance can survive exposure to the drug, and continual exposure places pressure on all bacteria present to evolve greater resistance.

Although there is no positive proof that resistant strains that evolved in animals have jumped the species barrier to humans, there appears to be a widespread belief that such a path of transmission exists. Based on the fear of this link, Sweden has banned the large-scale use of antibiotics for animal growth enhancement. Denmark banned the use of avoparcin, a close relative of the important 'last resort' antibiotic vancomycin, after studies showed its use increased presence of vancomycin-resistant enterococci (VRE) in Europe. Similar legislation is presently before the U.S. Congress.[34]

Use of antibiotics in all of these inappropriate ways placed extraordinary pressure on bacteria to change (or die). The first, necessary step in the appearance of resistance to a new antibiotic is simple random mutation. Just as humans evolved from apes based on a series of small, random "errors" in DNA replication that gave individuals more strength or cunning, any bacteria that mutates in a way that reduces the effectiveness of an antibiotic will have a competitive advantage in the presence of such (to the bacteria) poison. Bacteria, however, evolve much more rapidly. Humans have roughly five generations a century; bacteria have up to 100,000 generations a year.[35] Every instance of reproduction offers another opportunity for mutation. Moreover, bacterial genetic material is less stable than that of more complex organisms, further increasing the number of mutations. The vast majority of these random alterations to its genetic material undoubtedly harm the bacteria, but a small percent are useful — such as mutations that provide a defense against antibiotics.

Unfortunately, mutations are not the end of the processes by which

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[33]Drexler, *supra* note 9, at 139.

[34]HR 3804, the "Preservation of Antibiotics for Human Treatment Act of 2002," which would prohibit the nontherapeutic use in feed animals of eight specific antimicrobial drugs that could select for resistance to drugs used in human medicine. *See* http://www.asmusa.org/pasrc/browncom.htm (visited March 5, 2003).

[35]OTA, *supra* note 16, at 41

bacteria develop resistance to antibiotics. Bacteria are surprisingly sexual: they continually swap bits of genetic material ("plasmids"), and sometimes these strands of DNA contain codes for resistance.

> The bacterium itself is the focus, if the resistance trait is linked solely to that bacterium and cannot be shared by others. This is, however, not the case with most resistant traits in the majority of bacteria. They have evolved extrachromosomal replicating genes called plasmids and their associated transposons which allow rapid and very broad dissemination of genes. … Gene transfer crosses species and genus barriers … The genetic flexibility and versatility of bacteria have therefore contributed largely to the efficiency by which antibiotic resistance has spread among bacteria and among environments globally.[36]

Note well Professor Levy's statement that these strands of DNA can "cross[] species and genus barriers." Absent such transfers, every individual species of bacteria would have to hit on a lucky mutation to gain resistance. With such transfers, it takes only one mutation in one species to spread resistance across a broad swath of bacteria. Worse, plasmids frequently contain the code for resistance to multiple antibiotics; thus in a single exchange, a bacteria can become immune to more than one drug.[37]

The ability of bacteria to pass around genes raises a new dimension to the problem of growing resistance to antibiotics. As discussed *infra* § III, most models assume that resistance increases with doses used and only with doses used. The idea is that resistant mutations confer an evolutionary advantage only in the presence of the antibiotic. Bacteria, however, may pass around plasmids conferring resistance in the absence of an antibiotic. Thus bacterial exchange of plasmids means that resistance can spread with the *pure passage of time*, even if no additional doses are being used. As discussed *infra* § IV.B.3, this possibility can significantly alter the optimal policy for employing antibiotics.

There is some evidence that the effect of doses prescribed, especially doses recently prescribed, dominates any such time effect. A number of

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[36]Stuart B. Levy, *Antibiotic Resistance: An Ecological Imbalance*, in ANTIBIOTIC RESISTANCE: ORIGIN, EVOLUTION, SELECTION & SPREAD 5 (Ciba Foundation 1997).

[37]Stuart B. Levy et al., *A Multidrug Resistance Regulatory Chromosomal Locus Is Widespread Among Enteric Bacteria*, 168 J. INFECTIOUS DISEASE 484 (1993); *see also* OTA, *supra* note 16, at 43.

studies (discussed immediately below) have shown that when a hospital or a nation ceases use of a particular antibiotic, the percent of bacteria resistant to that antibiotic declines. These observations raise the possibility of restoring the potency of antibiotics by suspending their use for a sufficient interval. With enough antibiotics, then, we could simply 'cycle' between them. When resistance reaches some critical level, we would 'rest' that drug until bacteria lost their resistance to it.

The biological theory behind such a loss of resistance is that, like any other biological function, resistance imposes a cost on bacteria. Microbes expending energy and genetic storage space on resistance have less resources to thrive and replicate. In the presence of the antibiotic, the benefits of resistance exceed these costs and thus resistant strains have an advantage. Withdraw the drug and the "*fitness cost*" of resistance (i.e. the disadvantage a bacteria experiences when it shifts resources to fighting antibiotics, necessarily depriving other functions of resources) has no offsetting benefit. The hope is that non-resistant strains will then outgrow and displace their resistant cousins.

Five years ago, Stuart Levy, a leading scholar on antibiotic resistant, expressed optimism about this possibility: "the evidence suggests that, given a 'ready and willing' susceptible flora [i.e. non-resistant strains of bacteria], a resistance predominance can be overturned if antibiotics are removed."[38] The basis for his optimism, apparently, was a series of studies showing reduced presence of resistant bacteria on cessation of use of a given drug. Here are some examples:

- when Czechoslovakia's hospitals cut antibiotic use from 20-50%, the percent of staph. infections exhibiting resistance fell significantly;[39]

- when Mt. Sinai Hospital imposed strict controls on the use of some antibiotics, mortality from infectious diseases fell;[40]

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[38]Levy, *supra* note 36, at 6.

[39]Zdenek Modr, *Statutory Control of Antibiotic Use in Man Versus Voluntary Restriction*, in THE CONTROL OF ANTIBIOTIC-RESISTANT BACTERIA 211, 214-19 (Sir Charles H. Stuart-Harris & David M. Harris eds., 1982).

[40]Salom Z. Hirschman et al., *Use of Antimicrobial Agents in a University Teaching Hospital*, 148 ARCHIVES OF INTERNAL MED. 2001 (1988)

! when the University of Massachusetts Hospital imposed strict regulations on the use of vancomycin, they eliminated vancomycin-resistant enterococci (VRE infections) for an extended period.[41]

Not all such studies, however, have offered grounds for optimism:

! when doctors decreased antibiotic use by over 30% in a number of Alaskan villages, "[n]o sustained decrease in carriage of penicillin-nonsusceptible strains was observed;"[42]

! when a hospital decreased antibiotic use on patients using ventilators (which can spread pneumonia easily), the percent of the staph. population exhibiting resistance fell only from 60% to 40%;[43]

! similarly, when doctors in Taiwan completely stopped prescribing penicillin for gonorrhea, resistance did drop somewhat but leveled off at 60% of isolates.[44]

Moreover, none of these studies, encouraging or discouraging, address the key question: even if the resistant population does decline after society shelves an antibiotic, if any resistant bacteria remain, how quickly will they reproduce and again become omnipresent? "[T]hough resistant strains can drop in number if they lose out in competition with drug-sensitive strains, they seldom disappear completely. That means

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[41]Paul P. Belliveau et al., *Limiting Vancomycin Use to Combat Vancomycin-Resistant Enterococcus faceum*, 53 AM. J. HEALTH-SYS. PHARM. 1570 (1996).

[42]Thomas W. Hennessy et al. , *Changes in Antibiotic-prescribing Practices and Carriage of Penicillin-resistant Streptococcus pneumoniae: A controlled Intervention Trial in Rural Alaska*, 34 CLINICAL INFECTIOUS DISEASES 1543 (2002).

[43]Didier Gruson et al., *Rotation and Restricted Use of Antibiotics in a Medical Intensive Care Unit. Impact on the Incidence of Ventilator-associated Pneumonia Caused by Antibiotic-resistant Gram-negative Bacteria*, 162 AM. J. RESPIRATORY & CRITICAL CARE MED. 837 (2000).

[44]Mong-Ling Chu et al., *Epidemiology of Penicillin-Resistant Neisseria Gonorrhoeae Isolated in Taiwan, 1960-1990*, 14 CLINICAL INFECTIOUS DISEASE 450 (1992).

there's always a residue of resistant bacteria around, ready to multiply if the right antibiotic rains down on them."[45]

Over five years ago, Richard Lenski argued that the same evolutionary forces that gave rise to resistance would also make that resistance persistent. "[E]volving populations of bacteria tend to compensate for the deleterious side-effects of their resistance genes … "[46] Lenski cited a study from 1977 showing that although the first strains of gonorrhea resistant to penicillin were unstable, the plasmids encoding resistance became stable within a few months.[47]

Additional research over the last few years seems to strengthen Lenski's argument. There is a growing body of evidence demonstrating that (i) the fitness costs of resistance are often small, and (ii) further evolution quickly reduces or eliminates these costs.

> [C]hromosomal drug resistance mutations studied often had only a small fitness cost; compensatory mutations were not involved in low-cost or no-cost resistance mutations. When drug resistance mutations found in clinical isolates were considered, selection of those mutations that have little or no fitness cost in the in vitro competition assay seems to occur.[48]

Another study similarly found that although the first mutations conferring resistance are often unstable, subsequent mutations frequently stabilize the change.[49] A recent study identified a specific second-stage mutation that reduces or eliminates the fitness cost of resistance to penicillin without reducing the resistant capability at all. The authors speculated that "[t]his pattern of stability loss and restoration may be common in the

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[45]DREXLER, *supra* note 9, at 150.

[46]Richard E. Lenski, *The Cost of Antibiotic Resistance — From the Perspective of a Bacterium*, *in* ANTIBIOTIC RESISTANCE: ORIGIN, EVOLUTION, SELECTION & SPREAD 131 (Ciba Foundation 1997).

[47]*Id.* 138, citing Marilyn C. Roberts, Louis.P. Elwell & Stanley Falkow, *Molecular Characterization of two β-lactamase-specifying Plasmids Isolated from Neisseria Gonorrhoeae*, 131 J. BACTERIOLOGY 557 (1977).

[48]Peter Sander et al., *Fitness Cost of Chromosomal Drug Resistance-conferring Mutations*, 46 ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, 1204 (2002).

[49]Ivan Nagaev et al., *Biological Cost and Compensatory Evolution in Fusidic Acid-resistant Staphylococcus Aureus*, 40 MOLECULAR MICROBIOLOGY 433 (2001).

evolution of new enzyme activity."[50] Another study finding that "adaptation to the fitness costs of [resistance] occurs by mitigation of the deleterious effects of the resistance mutations (compensatory evolution) rather than through reversion to the drug-sensitive state," further found that there is "no obvious association between the magnitude of ... resistance and its allied cost."[51] In other words, there is no grounds to hope that the most radical mutations — the ones that confer the most novel and effective resistance to antibiotics — are less stable and thus less likely to persist. To sum up, "[t]he data available from recent laboratory studies suggest that most, but not all, resistance-determining mutations and accessory elements engender some fitness cost, but those costs are likely to be ameliorated by subsequent evolution."[52]

Lenski identified one effective means by which a bacteria can minimize the fitness cost of resistance: "repression," or turning off the resistance function when it is not necessary (i.e. when the antibiotic is not present), with the ability to "switch on" resistance if and when the antibiotic re-enters the microbe's environment.[53] Again, subsequent research has bolstered this theory. A study of staph. resistance to the antibiotic gentamicin demonstrated that

> the emergence of [a resistant strain of staph. bacteria] following exposure to gentamicin results from a rapid switch and that bacteria exposed to cycles of [the antibiotic] gentamicin followed by antibiotic-free medium repeatedly switched between a resistant [strain] and a sensitive [i.e. non-resistant] parental phenotype (revertants). [This result] suggests that [staph.] has evolved an inducible and reversible resistance mechanism that circumvents a permanent cost to fitness.[54]

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[50]Xiaojun Wang, George Minasov and Brian K. Shoichet, *Evolution of an Antibiotic Resistance Enzyme Constrained by Stability and Activity Trade-offs*, 320 JOURNAL OF MOLECULAR BIOLOGY 85 (2002).

[51] Mary G. Reynolds, *Compensatory Evolution in Rifampin-Resistant E. coli*, 156 GENETICS 1471, 1478 (2000).

[52]Dan I. Andersson & Bruce R. Levin, *The Biological Cost of Antibiotic Resistance*, 2 CURRENT OPINION IN MICROBIOLOGY 489 (1999).

[53]Lenski, *supra* note 46, at 133.

[54]Ruth C. Massey, Angus Buckling, and Sharon J. Peacock, *Phenotypic Switching of Antibiotic Resistance Circumvents Permanent Costs in Staphylococcus Aureus*, 11 CURRENT BIOLOGY 1810 (2001).

Even more troubling, when an antibiotic triggers such a switch, it may turn on repressed resistance to *multiple* antibiotics. "A single antibiotic to treat an infection can provoke resistance to other drugs … One reason may be a master switch — dubbed MAR, for Multiple Antibiotic Resistance — on the cell's chromosome. Its almost as if bacteria strategically anticipate the confrontation of other drugs when they resist one …"[55]

Another reason that resistance often persists even when the antibiotic is not present is that the plasmids that confer resistance on their host bacteria often provide other beneficial functionality. "Over time, plasmids and their bacterial hosts can enter a symbiotic relationship, in which the growth of the host depends on the plasmid — one reason that the drug resistance bestowed this way is hard to reverse."[56]

These and related evolutionary mechanisms may well explain what is perhaps the most discouraging evidence that we cannot restore usefulness to antibiotics rendered impotent by past overuse: "the surprising persistence of resistance to tetracycline and streptomycin" — two antibiotics that have not been used heavily for decades.[57]

> Analyzing the fragrant contents of diapers from a daycare center, [Emory Professor Bruce] Levin found that a quarter of the *E. coli* lurking between the folds resisted streptomycin, a drug rarely used in the last 30 years. Although in evolutionary theory resistant bacteria are presumed to be more genetically weighed down and therefore less fit to compete, Levin suspects that after *E. coli* gains drug resistance, it evolves a second compensatory mutation that keeps it from backsliding to a state of drug sensitivity.[58]

Spanish doctors quit using tetracycline and chloramphenicol in the early 1980s, yet after 15 years the percent of strep. pneumoniae bacteria resistant fell only by half.[59] Similarly, in East Germany, tetracycline-resistant *E. coli* bacteria responsible for urinary tract infections fell only from 46% to 28% five years after termination of the use of tetracycline.

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[55]DREXLER, *supra* note 9, at 150 (citation and quotation omitted).

[56]*Id.* 149.

[57]Lenski, *supra* note 46, at 138.

[58]DREXLER, *supra* note 9, at 149-50.

[59]Ciba Conference, *supra* note 36, at 147 (comments of Baquero).

Lenski found no comfort in these numbers.

> While it may seems impressive that in five years the prevalence of resistance drops from 46% to 28%, if you put the bacteria back under positive antibiotic selection you have probably only bought yourself an extra week! It seems to be much easier to get resistant 'bugs' than to get rid of them.[60]

Summing up, Lenski notes that none of these discouraging findings should be surprising.

> [A] reduction in the cost of antibiotic resistance is not some mysterious or unexpected phenomenon. Instead, cost-reduction is a simple and general manifestation of the tendency for organisms to undergo genetic adaptation by natural selection. Just as organisms may adapt to overcome adverse aspects of their external environment (e.g. by becoming resistant to antibiotics), so too may they adapt to overcome adverse aspects of their internal physiology (e.g. by reducing harmful side-effects of resistance). … Unfortunately, this trend implies that it will become increasingly difficult over time to control the spread of resistant strains simply by suspending the usage of a particular antibiotic.[61]

Other concur, finding that recent research "argue[s] against expectations that link decreased levels of antibiotic consumption with the decline in the level of resistance."[62]

In some sense, we missed our chance by not withdrawing antibiotics when resistance first appeared. "You would have to quit using penicillin when you saw the first resistant strain, because once it has spread too far you're never going to be able to return to complete susceptibility."[63] Even such a stringent policy might not restore usefulness indefinitely; "if you can go 'cold turkey' right away, you may buy another 10 years of susceptibility…"[64] We may have missed another chance presented by the plethora of novel antibiotics available in past decades, as it is more feasible to hold back new antibiotics when there are numerous

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[60]Lenski, *supra* note 46, at 149.

[61]*Id.* 132.

[62]Sander et al., *supra* note 48.

[63]Lenski, *supra* note 46, at 148.

[64]*Id.*

alternatives. "We have had more classes of antimicrobial agents available to us in the 1980s than we are likely to have in the foreseeable future."[65] Our overuse of antibiotics seems to have made the bacterial population irreversibly more threatening. "The real problem is that it may be too late to react, in the sense that our normal flora is now the normal *resistant* flora."[66]

In the end, we are fighting a battle against the most powerful force in biology: evolution. The development of resistance is not limited to microbes; Europeans developed enough of a resistance to smallpox that it did not pose a genocidal threat by the 1600s. Unfortunately, American Indians did not.[67] Australians employed the myxomatosis virus to decimate a rabbit population threatening to overrun the continent. Initially the virus killed 99% of the rabbit population, but the successors of the few survivors are now 50% resistant despite the introduction of successively more virulent strains of the virus.[68] No matter how lethal a future bacterial plague might be, some humans likely would survive. By managing the use of existing, and especially of newly-developed antibiotics, we may have the power to reduce the mortality rate far below the 99% decimation suffered by Australia's rabbits. The remainder of this article explores optimal use of antibiotics given the biological constraints discussed in this section.

IV. Economic Analysis of Resistance to Antibiotics

A plague is one of our greatest public health fears — an untreatable infection caused by a lethal mutant bacterial strain that passes easily between persons (and perhaps other hosts). We already are experiencing isolated deaths due to untreatable bacterial infections. More generally,

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[65]Ciba Conference, *supra* note 36, at 150 (comments of Bennish).

[66]*Id*. at 11 (comments of Baquero) (emphasis added).

[67]*See* COLONEL P.M. ASHBURN, THE RANKS OF DEATH: A MEDICAL HISTORY OF THE THE CONQUEST OF AMERICA (Frank. D. Ashburn ed., 1947); Dean R. Snow & Kim Lanphear, *European Contact & Indian Depopulation in the Northeast: The Time of the First Epidemics*, 35 ETHNOHIST. 15, 17-24 (1988); JARED DIAMOND, GUNS, GERMS, AND STEEL: THE FATES OF HUMAN SOCIETIES 195-214 (1997).

[68]http://rubens.anu.edu.au/student.projects/rabbits/myxo.html (visited March 5, 2003).

resistance makes treating many infections more expensive. For example, curing a patient of penicillin-resistant gonorrhea costs 12-15 times as much as treating non-resistant cases.[69]

Before commencing the analysis of antibacterial medication, it is worth discussing why this article does not consider substances for treating other infections, e.g. viral or fungal. The reason for ignoring viruses is simple: there are basically no broadly effective antiviral medications. Without use, overuse cannot pose a problem. That said, if and when scientists identify effective antiviral drugs, we will face the same issues that we face today vis-a-vis bacteria. Viruses mutate frequently and reproduce rapidly, and so are likely to develop resistance to such medications.[70] Drugs to treat other sorts of infections have induced resistant mutations; one example is the malaria protozoa. Unlike bacteria, however, anti-malarials are not used to treat a range of conditions, both low-value and high. Malaria is always a serious disease, and thus it is less clear that we gain anything by adopting policies to limit current use. It might be, however, that too many people travel to malarial zones, and that we need policies to discourage such 'marginal' travelers who would not be willing to pay a price for anti-malarial medication that reflected the extent to which current use erodes future efficacy of the drug.

A. The Fundamental Problem

As intimated in the previous paragraph, what makes antibiotics an unusual good is that their very use undermines their future usefulness, as bacteria evolve resistance. Clem Tisdell was first to point out this problem, in an article inexplicably ignored by subsequent scholarship.[71] Unless there is some mechanism to force consumers to bear this cost when they buy antibiotics, they will ignore it and the populace will overuse antibiotics relative to the socially optimal level. To put this in stark terms, cheap and easy access to antibiotics today means that people will use them for very minor infections, and even for conditions that are likely caused by a virus or other microbe. Bacteria will develop

[69]OTA, *supra* note 16, at 60.

[70]LESLIE COLLIER & JOHN OXFORD, HUMAN VIROLOGY 87 (2000).

[71]Clem Tisdell, *Exploitation of Techniques That Decline in Effectiveness With Use*, 37 PUBLIC FINANCE/FINANCES PUBLIQUE 428 (1982).

resistance, and the drug will then be unavailable to treat life-threatening and seriously debilitating infections in the (possibly near-term) future.

A simple example helps illustrate this problem. A patient goes to the doctor with ear pain. Based on an initial examination, the doctor concludes that the patient has an infection, and that there is a 75% chance that it is viral, and only a 25% chance that it is bacterial. In either case, the infection is not serious; the patient is likely to experience two-three days of moderate discomfort and then recover. A culture test, to determine whether the infection is bacterial or viral, takes a couple days and costs more than an antibiotic prescription. Weighing the modest cost of the drugs against a couple days of discomfort, the patient is willing to pay for the antibiotics even though she realizes that there is only a 25% chance that they will provide any relief. Under these facts, the patient will press her doctor for the prescription and likely obtain it: making patients happy is good for business, and the spectre of a malpractice suit if the infection turns out to be bacterial and serious provides further impetus to write the prescription.[72] The long-term cost of such episodes (multiplied by millions of doctor visits a year) is lost lives in the future due to untreatable bacterial infections. The patient is not assessed for this cost, however, and so makes a personally rational decisions that is socially undesirable.

There are many equivalent ways to characterize the problem. Perhaps most intuitively, the very use of antibiotics imposes an external cost on later potential consumers. There is no easy way to establish a market to mediate these conflicting uses. First and foremost, there is no way to identify the set of future potential consumers — basically a random collection of individuals who will contract serious bacterial infections years in the future. Even if we could identify these future buyers, it is difficult to conceive of how they could pay present low-value users to refrain from using antibiotics. They certainly could not proceed individually; some sort of group action would be necessary on both sides.

Remedying this externality is even more difficult when future

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[72]Many claims arise from cases involving infections. OTA at 75, citing St. Paul Fire & Marine Insurance Co., 1994 Annual Report to Shareholders 4-5 (1995). *See also Nelson v. Hammon*, 802 P.2d 452, 457 (Colo. 1990) (holding that given American Heart Association guidelines and testimony by infectious disease specialists, surgeon had duty to patient to prescribe antibiotics to prevent possibility of serious bacterial infection entering patient's bloodstream); *Hellwig v. Potluri*, No. 90-C-55, 1991 WL 285712, at *1 (Ohio Ct. App. Dec. 27, 1991) (holding physician liable for failing to prescribe antibiotics to patient who stepped on a rusty nail).

generations will bear the cost of their predecessors' overuse of antibiotics. If bacteria develop resistance within the expected lives of most citizen living today, they have personal incentives to support policies eliminating the externality. If the process takes more than a generation, however, their incentives are second-order — the welfare of their children. Will the living give sufficient weight to the welfare of their progeny? The base problem is that there is no way for future generations to pay their predecessors to economize on antibiotic use.[73]

As Tisdell notes, current buyers are unlikely to refrain from use out of the goodness of their hearts. "[E]ven if users are aware of the unfavorable externality, acting individually they are unlikely to restrict the use of the technique for the collective good. … [it] is akin to the prisoners' dilemma problem."[74] This is another way to view externalities: as a collective action problem. Although everyone knows that using antibiotics in many cases is irrational in the long run, without some mechanism to ensure that others will behave, no one refrains.

Yet a third way to characterize the problem as an example of a common pool. Common here means the absence of property rights. When no one has property rights, and an asset is part of the great unclaimed commons, an asset grab occurs. The most common example is a fishery: if anyone can fish, a flood of participants will exhaust the stock rapidly. Given the ability of fish to regenerate if harvested judiciously (e.g. throwing back small fish; not fishing during certain times of year; generally, leaving in the water a population sufficient to regenerate itself), such hasty depletion is likely sub-optimal.

However we choose to model the problem, any solution must somehow discourage some present low-value use to preserve the potency of antibiotics for future high-value cases. In terms of the standard demand curve, we need to eliminate purchases by those at the bottom of the curve in early periods so that there are doses left to service the high part of the curve in later periods.

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[73]TODD SANDLER, GLOBAL CHALLENGES, AN APPROACH TO ENVIRONMENTAL, POLITICAL, & ECONOMIC PROBLEMS 76-82 (1997).

[74]Tisdell, *supra* note 71, at 429.

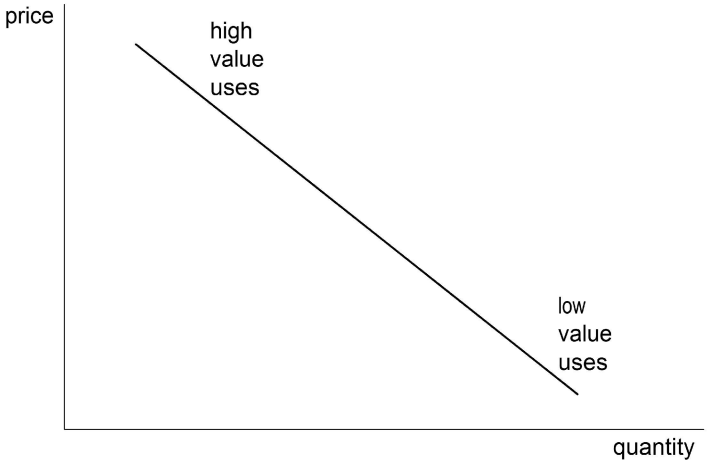

Figure 1

Gardner and Layton, apparently unaware of Tisdell's work, constructed a more sophisticated model and reached the same general conclusion: sound policy should somehow deter low-value uses and preserve effectiveness for future high-value uses.

> Essentially, the social planner saves some of the treatments for future generations. In the unregulated case, no one 'owns' the treatments, and so there is no incentive to save them … Some individuals will not now treat their disease, because it is 'too' expensive and some diseases no longer will be treated with antibiotics because the benefits do not exceed the full cost to society. The treatment will be saved for someone more sick in the future.[75]

They highlight the trade-off between (high-value) human and (low-value) animal use of antibiotics (as a growth enhancer in livestock, discussed *supra* § II) in even starker terms.

> Put provocatively to emphasize the point, when both humans and animals use antibiotics we are equating the economic value of improving human life a bit more with extra pounds of beef … how are vegetarians of any nationality compensated for the fact that we might one day in the future exhaust our miracle drugs so that others can have cheaper beef today?[76]

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[75]Gardner Brown & David Layton, *Resistance Economics: Social Cost & the Evolution of Antibiotic Resistance*, 1 ENVIRONMENT & DEVELOPMENT ECON. 349 (1996)

[76]*Id.* 355.

B. Generalizing the Problem: The Exhaustible Resource Model

The previous subsection noted that one way to conceptualize the problem of antibiotic overuse was to view the resource as a common pool in which nobody has property rights. The analogy drawn to a fishery is not quite accurate. Antibiotics do not have the ability to reproduce themselves.[77] Perhaps surprisingly, the proper analogy is to exhaustible resources, such as minerals. Although we can manufacture as many doses of penicillin as we please, over time more and more bacteria will achieve resistance. When most bacteria have such resistance, an antibiotic is 'exhausted.' Thus the number of *effective* doses of an antibiotic is limited, in almost exactly the same sense that the number of barrels of oil on the earth is limited. This subsection introduces the economics of exhaustible resources, and discusses the application of this theory to the special case of antibiotics.

1. Basic model

Exhaustible resources' defining characteristic — exhaustibility — requires a different economic analysis than conventional, reproducible goods. If there is a fixed, finite amount of some good (say, coal), then a decision to consume the good today forecloses future options: to consume that unit in a year, in ten years, or a hundred. This does not hold for more typical reproducible goods, such as paper. If demand for wheat unexpectedly rises in the future, past consumption in no way limits suppliers' ability to crank up production. Owners of exhaustible resources (public or private) thus must consider the ramifications of present use for future availability in a way that producers of reproducible goods do not.[78]

Although most explications of exhaustible resource economics stress the famous "Hotelling rule" (discussed *infra*) that the price (or "rental") of such resources will rise at the interest rate, the basic insight about the special nature of exhaustible resources is best illustrated by first ignoring the interest rate by assuming that it is zero. This in effect assumes that

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[77]Note that to the extent antibiotics could regain usefulness if shelved for some period, they would share with a fishery self-reproduction. Some models of optimal use of antibiotics rely on this analogy, *infra* § IV.F, but, as discussed *supra* § II, the most recent scientific evidence suggests that reversing resistance by pulling antibiotics from use will not work.

[78]PHILIP A. NEHER, NATURAL RESOURCE ECONOMICS, CONSERVATION & EXPLOITATION 271-86 (1990).

welfare in the present and all future periods is weighted equally.

This equality of present and future welfare would seem to obviate the need to carefully plan the timing of consumption of an exhaustible resource. If, however, producers face rising costs (as is often the case), the producer of an exhaustible resource will behave differently than the producer of a renewable good. Imagine that a large number of miners own all of the world's gold deposits. They all face the same costs, and since they are small, their output has no effect on price — they are classic competitive market "price takers." We can use the following standard supply and demand diagram to contrast the profit-maximizing behavior of exhaustible and reproducible good producers.

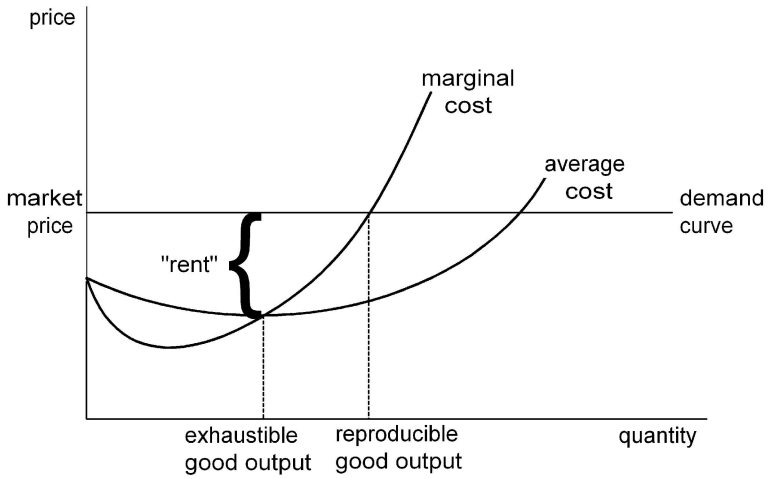

Figure 2

To maximize profits, the supplier of a reproducible good keeps making units until the market price just covers the cost of the last unit made — marginal cost. The flat demand curve means that marginal revenue equals market price. Thus we have a well-known result from the economics of the firm: to maximize profits, produce up to the point where marginal costs rise to equal marginal revenue.[79]

[79] WALTER NICHOLSON, MICROECONOMIC THEORY 358 (3d. ed. 1985).

This standard economic logic does not work for exhaustible resources. Supplying a quantity up to the reproducible output level today means that there will be fewer units to sell later. These same units could have been produced *at lower cost* in a subsequent period; this is because costs are rising at the reproducible profit-maximizing output level. The producer of an exhaustible resource could increase profits by selling less now and more in the future. Taking this cost minimization logic to its limit, the exhaustible resource seller will always produce at that level of output that minimizes average (per unit) cost in each period. Given that the price (i.e. demand) does not change over time or with variations in output, this strategy yields the maximal possible profit on the producer's fixed supply of the good.

Note that the exhaustible resource firm, despite the fact that it operates in a competitive market, earns positive economic profits — its total revenues (price × units sold) exceed its total costs (per unit cost × units sold). This difference, called *rent*, is the return on the exhaustible resource. If a firm buys a stock of an exhaustible resource, it will pay a price that reflects this future stream of rents. In that case, we can see, there are not really any true economic profits; the difference between price and average cost is just sufficient to recompense the buyer of the exhaustible resource for its purchase price.

Our assumption that interest rates are zero is unrealistic, of course. In order to focus on the effect of interest rates on the supply of exhaustible resources, we now assume costs of production are zero. This is not entirely at odds with reality; costs are a small fraction of price for many low-cost oil producers, and for drugs with patent protection.

Positive interest rates put a new pressure on exhaustible resource owners to extract and sell sooner rather than later: the asset itself is sterile (unlike fish and other reproducible resources, oil does not replenish itself), but if sold and converted to cash it can 'reproduce' itself and grow at the rate of interest.

If we assume that the exhaustible resource provides no value by its mere presence, the only thing that will induce holders to postpone converting it to cash is the prospect of rising prices. If prices are expected to remain unchanged, producers will extract every unit today.[80]

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[80]This extreme result is due to our assumption that production is costless; if there are production costs, they would place some constraint on the rate of extraction, though our analysis in general will still hold. This assumption leads to almost identical results as assuming that marginal costs are positive but constant — i.e. per unit cost does

This flood of supply will drive the price down to a very low level. Assuming the demand curve has significant slope, then any supplier wise enough to hold back his supply will be able to sell her small quantity — the only supply available — at a high price. This later price may exceed the earlier price by a percent greater than the interest rate; if so, all the suppliers who sold will wish they hadn't. Thus unchanging prices are not an equilibrium if interest rates are positive.

To go to the other extreme, it is also an unstable situation for owners to expect prices to increase at a rate exceeding the interest rate. Anyone with such a belief would never sell. Thus the only equilibrium path for prices is to increase at precisely the rate of interest; this is called the Hotelling Rule.[81] The following diagram illustrates how industry supply "creeps up" the demand curve, supplying smaller and smaller quantities at higher and higher prices; it assumes an interest rate of 10%.

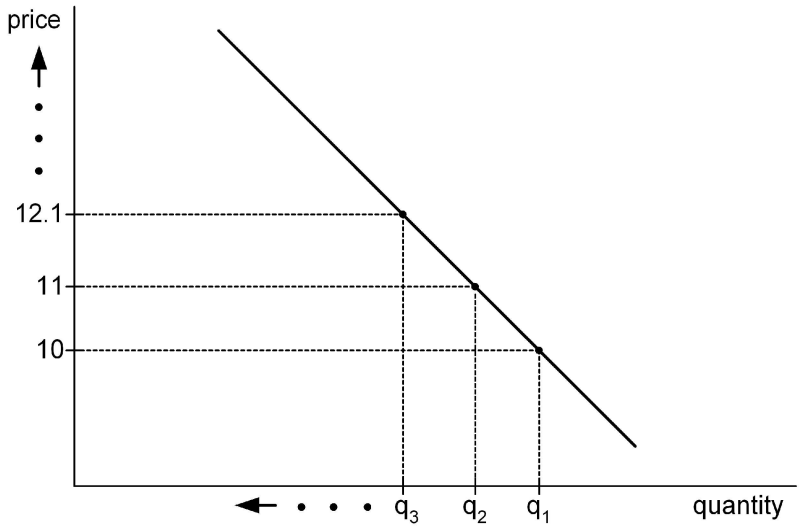

Figure 3

Where does this process, of rising prices and lower quantities, start and end? It ends at the "choke price," where demand disappears. The beginning is a little more subtle. Given this terminal point as defined by the choke price, the initial price and quantity combination from the

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not rise or fall with quantity produced.

[81]Harold Hotelling, *The Economics of Exhaustible Resources*, 39 JOURNAL OF POLITICAL ECONOMY 137 (1931)

demand curve (quantity q_1, at price of 10) is set so that, if prices rise at the rate of interest, the sequence of quantities that follow will add up to the total supply of the exhaustible resource.[82]

If we admit positive costs, the basic story still holds, but the quantity that must increase at the rate of interest is not the price, but rents on the exhaustible resource: price less cost. This embodies the return on the resource itself; the costs of production represent payments to labor and capital hired to extract the resource.

Our application of the exhaustible resource model to antibiotics in subsequent sections requires familiarity with the effect of changing some of the key variables. First, the greater the stock of the resource, (i) the lower the initial price (and greater the initial quantity transacted), and (ii) the longer it will take to exhaust the resource. Given that prices (or rents) must rise at the rate of interest, starting at the same price when the initial stock is larger would lead to the same quantities, and we'd hit the choke price before exhausting the resource. Once we start at a lower price, the requirement that prices rise at the same rate as in a world with a smaller stock implies that it will take longer to exhaust the resource. The two price paths are parallel; thus the one starting at a lower price will take longer to reach the choke price.

[82]Although the analysis is more complex, the same argument holds if there is no choke price, i.e. the demand curve approaches a zero quantity for very high prices but never actually goes to zero. Intuitively, the size of the quantities demanded at very high prices get extremely small — so small that even though we are summing an infinite number of them, the sum is finite.

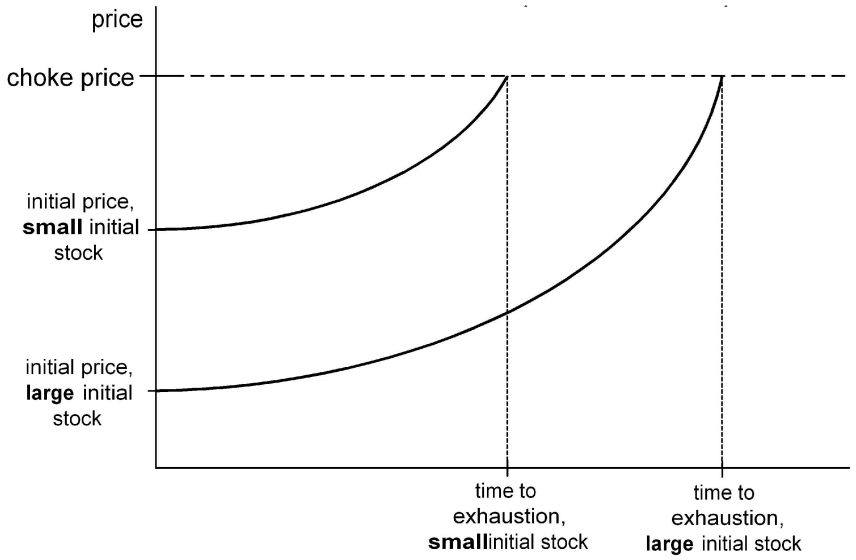

Figure 4

The picture for the two quantity paths over time is basically just the inverse of these price paths, given the inverse relationship between price and demand.

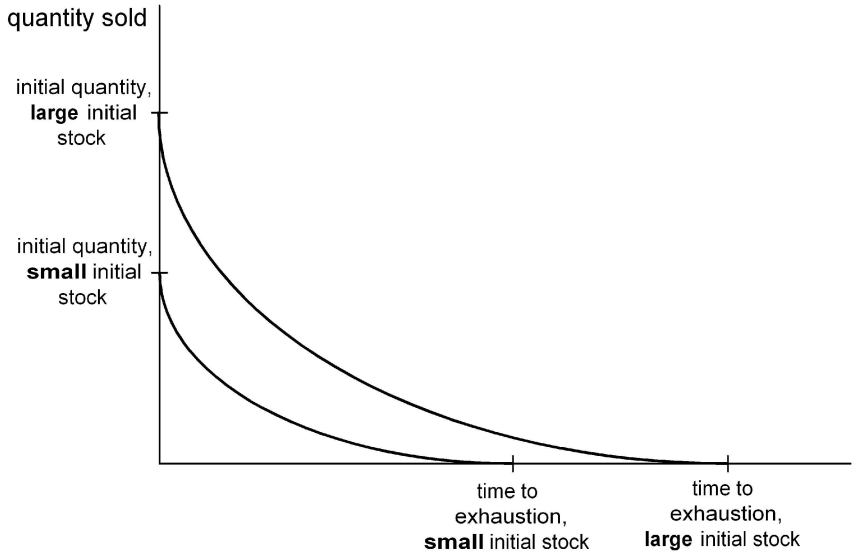

Figure 5

Next, we examine the effect of changes in the interest rate. A higher interest rate (all else remaining equal; e.g. same initial stock in both cases

here) will lead to (i) a faster increase in prices (or rents, if costs matter), and (ii) a lower starting price. Result (i) is simply the Hotelling Rule. To understand result (ii), assume that the initial price and quantity were the same as under the lower interest rate. Then, given that prices under the higher interest rate will be higher in every period, quantity sold will be lower in each period. When the choke price is hit, then, the resource will not be exhausted. In order to avoid leaving valuable ore in the ground, a higher interest rate implies a lower starting price. The following figure illustrates the effect of a change in interest rates on the path of prices for the exhaustible resource.

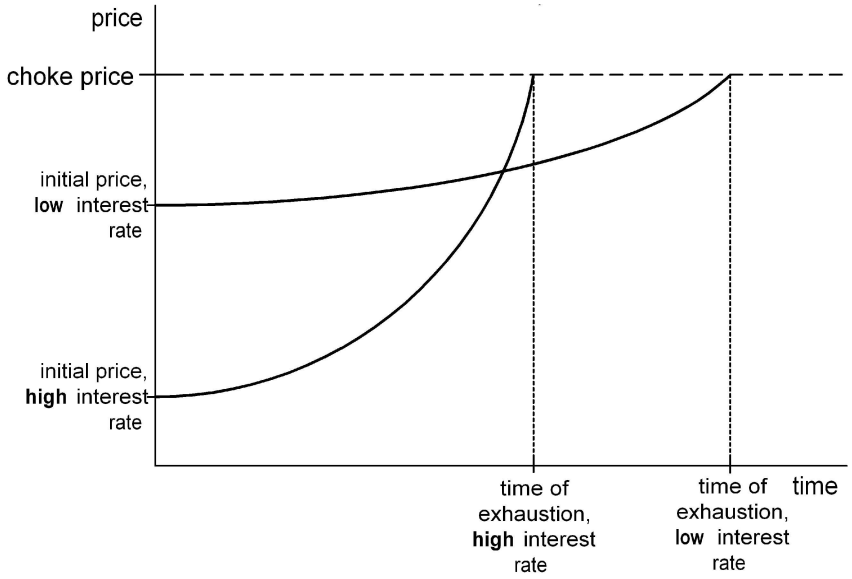

Figure 6

Here is the corresponding picture for quantity sold over time.

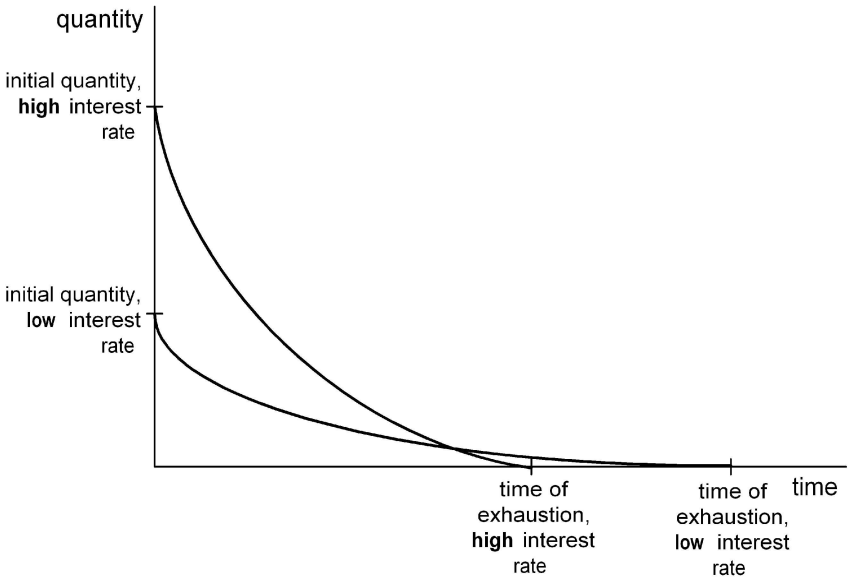

Figure 7

It is worth taking a moment to understand the economics that explains these outcomes. High interest rates mean that the value society places on pay-offs decreases rapidly as those pay-offs come further and further in the future. Thus higher interest rates "tilt" decisions toward immediate, as opposed to postponed, consumption. For an exhaustible resource like antibiotics, high interest rates indicate that competing investments (bonds, e.g.) are very attractive; to get anyone to hold the resource, rises in its price must match returns on these competing assets.

Finally, considering the effect of lower demand (with all other variables fixed, i.e. the initial supply and interest rates).

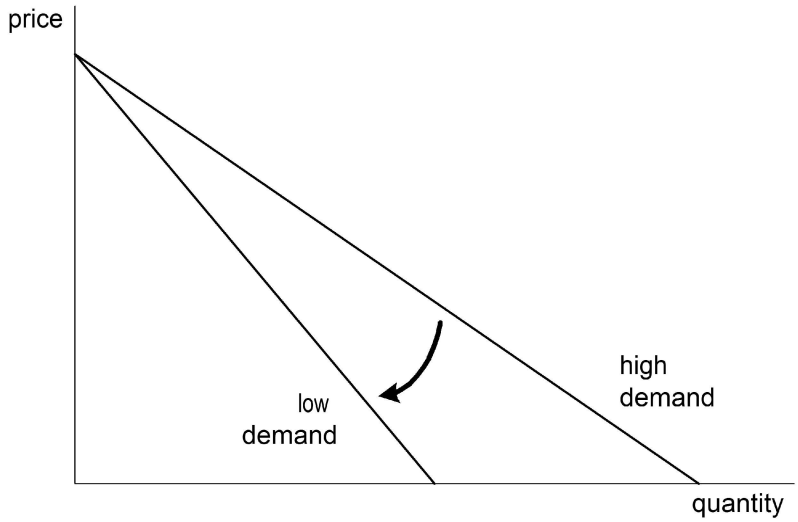

Figure 8

The series of prices that exhaust the resource under high demand are insufficient to exhaust supply given low demand; the definition of lower demand is a lower quantity purchased for any given price. In the face of lower demand, then, the initial price of the resource must be lower. Given the requirement that the rate of price increases in all cases must be equal to the interest rate (Hotelling's Rule), and that the last price is the highest point on the demand curve (the "choke" price), the paths of prices over time for the two demand curves are as follows.

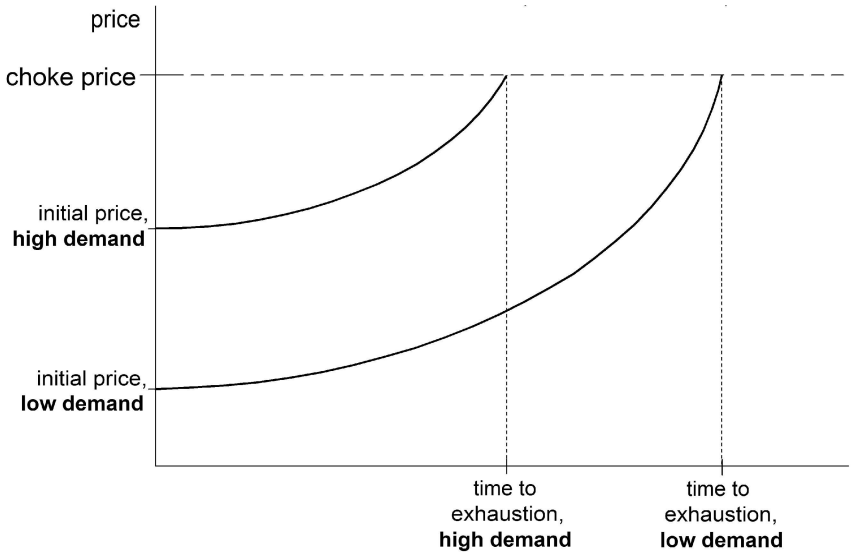

Figure 9

The pattern of quantities sold under the two different demand curves is ambiguous. The total sold in both cases, of course, is the same: the amount of the resource available. Without pinning down details about the two demand curves, however, we cannot say whether the initial quantity sold will be greater under the high or the low demand curve.

The important conclusion we can draw is that a decrease in demand will extend the time to exhaustion. The economic intuition behind this result is straightforward: lower demand means consumers desire the good less and spend their money elsewhere. The same stock of a resource can meet this lower demand for a longer term than it can satisfy higher demand.

2. Property rights problem remains

Perhaps the most surprising result in the study of exhaustible resources is that, for most exhaustible resources, the supply decisions of competing sellers leads to socially optimal use. As long as no owner or group of owners of the resource has monopoly power, their private interests will lead them to deplete the resource at precisely the same rate as a benevolent social planner. At bottom, this is simply an application of the First Theorem of Welfare Economics, which says, roughly, that a competitive market without externalities (or other distortions) leads to an

efficient allocation of all goods.[83]

There are a couple of direct implications of this market-efficiency result. First, it tells us that the behavior of monopolists generally is sub-optimal for exhaustible resources just as it is for 'normal' non-exhaustible goods. We will discuss this at some length in § IV.D *infra*, when we examine the effect of patents on the market for antibiotics.

More fundamentally, the antibiotics market does not satisfy the conditions of the First Theorem of Welfare Economics for the reason discussed *supra* § IV.A. To recap the argument, the fact that present use of antibiotics erodes future usefulness, combined with a lack of property rights in antibiotics, creates a negative externality. There is in effect a missing market, between future sufferers of serious bacterial infections and present sufferers of mild and possibly non-bacterial infections. Without some mechanism to discourage current low-value uses, it is not surprising that we cannot count on private ordering to produce socially optimal results.

3. The 'pure time' effect

So far we have assumed that the only process by which antibiotics lose their efficacy is use, i.e. that there is a fixed number of effective doses and no more, but also no less. Tisdell's overlooked article contains another possible effect ignored in subsequent scholarship: it might be that antibiotics become less useful by the mere passage of time.[84]

Tisdell finds that "[i]t is difficult to imagine relevant processes that are solely quantity-dependent or solely time-dependent … In practice, the quantity of exposures to a new control technique and their time-pattern need to be simultaneously considered."[85] The microbiology scholarship discussed *supra* § III suggests that Tisdell was on to something. Recall the frequency with which bacteria swap snippets of genetic material (plasmids). Once a bacteria has developed resistance, then, it can pass this characteristic on to other bacteria *even if the antibiotic is not in use.* It is quite possible that a single plasmid encodes resistance to multiple

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[83]DAVID M. KREPS, A COURSE IN MICROECONOMIC THEORY 199 (1990). Efficiency here means pareto optimality: nobody can be made better off without reducing the welfare of someone else.

[84]Tisdell, *supra* note 71, at 430.

[85]*Id.*

antibiotics, say two: A and B. Then administering antibiotic A will create an environment favoring transfer of immunity to both antibiotics, even though nobody is receiving doses of antibiotic B.

Thus it seems reasonable to assume that both the number of doses and the passage of time play a role in determining the effectiveness of antibiotics. Indeed, other factors likely matter as well, e.g., the geographic spread of use. Resistance to an antibiotic used in many cities with frequent travelers likely develops more rapidly than if the same number of doses are used intensively in only one relatively isolated city. For expository clarity, however, we first will consider examples that focus on the 'pure passage of time,' and ignore all other factors. We will then consider a simple example combining the time effect with the dosage effect.

Consider an antibiotic that remains useful for, say, 5 years, regardless of the number of doses administered. If we discount future benefits, then optimal use pattern is obvious: start using it immediately and price the drug at marginal cost. Any delay reduces net social benefits on a present value basis. Thus if antibiotic resistance increases with time from first use, instead of doses delivered, there is no externality from a lack of property rights: private ordering will produce the socially desirable outcome, high production (down the demand curve all the way to marginal cost) immediately.

In his pure time model, Tisdell arbitrarily assumed that demand for an antibiotic would increase over time. He gave no justification — and indeed, made no such assumption in his dosage model. Unsurprisingly, given this assumption he shows that if demand is increasing rapidly enough, it is efficient to delay use of the drug.[86] This approach is unfortunate, as it masks the impact that a pure time effect has on the optimal policy: in the absence of expanding demand, it strongly favors use sooner rather than later. Further, it makes pricing at marginal cost, the market outcome, socially optimal.

A pair of examples contrasting a dosage model with one combining dosage and time effects helps further illustrate these tendencies. Say that we have 10 brand new antibiotics (label them A-J), and that each is good for 100 doses. The socially optimal level of antibiotic supply each period is 100 total doses, in any combination of the ten drugs. In a world where only the number of doses matters for the development of resistance, we

[86]Tisdell, *supra* note 71, at 433-35.

could use the antibiotics in any pattern we wish, and still be able to depend on 100 doses for ten periods. At one extreme, we could use 100 doses of A in period one, 100 doses of B in period two, and so on through 100 doses of J in period 10. At the other extreme, we could use 10 doses of each antibiotic A-J in each period. In addition, we can use any averaging of these two extreme cases (e.g. 20 doses of antibiotics A-E in periods one to five; 20 doses of F-J in periods six to ten).

Now assume that, in addition to the effect from doses administered, the number of effective doses of each of the ten antibiotics, once used, declines with time according to the following formula: you lose ten dose to the passage of time after one period, twenty doses after two periods, etc … The following table summarizes the total number of doses of all ten antibiotics available if, in each period, we administer *ten doses of each of the ten antibiotics* (100 per period, as in the previous paragraph).

period	Stock at start of period	loss due to doses administered	loss due to time passing	Stock remaining for next period
0				1000
1	1000	100	100	800
2	800	100	200	500
3	500	100	300	100
4	100	100	–	0

Table 2

Under the combined influence of dosage and time effects, we will exhaust each of the ten antibiotics after 4 periods if we use all ten drugs simultaneously.

If, instead, we use one drug per period, exhausting all 100 doses before any time effect kicks in, we can still supply the desired level of doses for ten periods. Given that the pure passage of time detracts from the usefulness of the drugs, we want to use each in an intense burst; a pure time effect makes 'blitzkrieg' use of individual antibiotics desirable as opposed to the simultaneous, modest use of all. Note that intense use of the drugs in seriatim fashion does not cost us anything if it turns out that only doses delivered matters. If, then, there is a reasonable

possibility of a pure time effect, this insight provides a robust reason for seriatim, intense use of each antibiotic in turn.

The market, unassisted, is unlikely to lead to this 'burst' use pattern. Even if all ten drugs have equal, level marginal cost, the optimal use is only one of a continuum of equilibrium outcomes, and all other possibilities involve the suboptimal simultaneous use of more than one drug. Society likely would need central coordination to deploy one drug at a time. If the costs of making each drug rise with quantity produced, then it is very likely that the market outcome involves the use of multiple drugs. Competitive pressure will lead firms to produce each drug up to the point equating the marginal costs of all in use.[87] The government would need to discourage use of all but one antibiotic, either by regulatory fiat, by imposing a sufficient tax on all but one drug in each period, by using its power of eminent domain to force patent owners to sell their rights to drugs that the government wishes to shelve, or some other policy measure to ensure seriatim use of antibiotics.

Reductions in antibacterial efficacy due to the passage of time, independent of doses administered, may be very important, then, in determining the optimal pattern of antibiotic use. Even if policy makers solve this part of the problem, they will face dosage constraints — which in a sense are more fundamental. Thus, the remainder of this article focuses on simple dosage constraints.

4. Differing focus in applying the exhaustible resource model

The basic (dosage effect only) exhaustible resource models provides a more sophisticated setting in which to study the root problem identified by Tisdell, the externality that exists because use of antibiotics erodes future usefulness. Other recent scholarship using this approach has focused on a different set of issues. Borrowing methods from epidemiology, these more detailed models factor in effects not contained

[87]If separate firms have new patents on each drug, the problem is worse. Each firm will want to produce immediately for two reasons. First, the time value of money makes profits earned sooner more valuable than profits earned later. Second, the limited term of the patents may make waiting even more undesirable. The government will need to compensate patent holders to induce them to delay production, with cash and perhaps also with extensions of their patents' terms. This article discusses the role of patents in the antibiotic market at length *infra* § IV.D.

in our simple models.[88] First, they account for the fact that antibiotics confer a positive external benefit: cured patients are less likely to spread the disease. Second, they explicitly examine the issues raised by the existence of multiple antibiotics, with differing levels of resistance to each.

In other ways, these models are more limited. Of paramount importance, they do not distinguish between high-value and low-value uses of antibiotics. By assuming that cures to all infections are of equal value, these models cannot study the fundamental trade-off in antibiotic use policy.[89] They are instead designed to model the course of a specific infection in a closed environment such as a hospital; this article, following Tisdell, focuses on the more general, worldwide problem.

This article ignores the positive externality of antibiotic use (reduction in spread of bacterial infections) as a second order effect. Patients will often spread the disease before they are diagnosed and given antibiotics, and they can continue to spread the infection even when taking antibiotics, up to the time they are cured (free of the infectious agent). This positive externality is much more significant for vaccines, since those vaccinated can never become a breeding ground for a particular infection. The bottom line is that, in the long run, this paper assumes that the negative externality stemming from excessive use far outweighs any positive externalities antibiotics offer.

C. Policy Alternative One: Pigovian Tax & Related Mechanisms

Maintaining our focus on this fundamental trade-off between current use and future usefulness, this section and the next analyze the efficacy of government policies designed to curb present use so that antibiotics retain their efficacy for serious infections in the future. This section first casts serious doubt on the medical community's 'command and control' proposals to deal with overuse of antibiotics. It then discusses the classic solution to negative externalities, a tax on the undesirable conduct (here, use of antibiotics), and some related subsidies for goods that reduce the

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[88]Sebastian Bonhoeffer, Marc Lipsitch, & Bruce Levin, *Evaluating Treatment Protocols to Prevent Antibiotic Resistance*, 94 PROC. NAT'L ACAD. SCI. 12,106 (1997); Ramanan Laxminarayan, *Bacterial Resistance and the Optimal Use of Antibiotics*, Discussion Paper 01-23, Resource for the Future (June 2001).

[89]Laxminarayan explicitly values the cure of all infections equally. Laxminarayan, *supra* note 88, at 7. Bonhoeffer et al. use a number of welfare measures that implicitly do the same. Bonhoeffer et al., *supra* note 88, at 12,106-08.

need for antibiotics (tests to determine the cause of infections; vaccines that obviate the need for antibiotics). The following section, IV.D, discusses the pros and cons of patent rights as a solution to the lack of property rights in antibiotics.

1. The medical community's command/control response

With the crumbling of the iron curtain and the economic reforms in China, command and control as a means to allocate scarce resources (i.e. run an economy) is generally on the wane. It retains a rather shocking vitality, however, in proposed solutions to the overuse of antibiotics. Major medical organizations, medical researchers, and legal commentators all have focused exclusively on regulatory command, along with education and jawboning (trying to persuade people to act selflessly and refrain from the anti-social overuse of antibiotics), as the proper tools for reducing low-value uses of antibiotics.

A major congressional study of the overuse of antibiotics conducted in 1995 contains not one significant discussion of using prices or other economic levers to address overuse of antibiotics, perhaps because the expert panel that authored the study included not a single economist or social policy expert.[90] In discussing the costs of controlling emergence of resistant strains, the report discusses various aspects of hospitals' financial incentives with nary a word about imposing a tax to alter those incentives.[91] It suggests, *inter alia*, detailed rules and 'formularies' to regulate the use of antibiotics.[92]

Three years later, in 1998, the Center for Science in the Public Interest suggested the following measures to deal with the problem:

- national funding for programs to educate health professionals and the public on the problem of antibiotic overuse;

- require tests to identify infectious agents before prescribing antibiotics;

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[90]OTA, *supra* note 16. This report does mention extending patents for manufacturers of new antibiotics willing to limit sales to resistant strains, *id*. 18.

[91]*Id*. 93.

[92]*Id*. 11-12.

- ! use government hospitals as "showcases" for the prudent use of antibiotics;

- ! require hospitals receiving federal Medicare/Medicaid dollars to offer vaccinations; and

- ! limits or bans on some agricultural and husbandry uses of antibiotics, along with education for farmers.[93]

Just last year, the high-powered Interagency Task Force on Antimicrobial Resistance, composed of all the major governmental agencies with an interest in health policy, listed as its top priority items

- ! a society-wide education campaign, and

- ! "educational and behavioral interventions" to assist doctors in curbing antibiotic use.[94]

Not one of these large-scale policy documents authored by sophisticated governmental and private institutions, so much as contemplates using taxation or other mechanisms to alter private incentives.

The same criticism applies to policy proposals from the medical academy. A recent editorial in the leading American medical journal advocated the use of traditional and computerized practice guidelines and education (of both doctors and their patients) to discourage overuse of

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[93]Center for Science in the Public Interest, *Protecting the Crown Jewels of Medicine, A Strategic Plan to Preserve the Effectiveness of Antibiotics* (1998), available at http://www.cspinet.org/reports/abiotic.htm (visited March 5, 2003).

[94]Interagency Task Force on Antimicrobial Resistance, *Recent Comprehensive Effort: Public Health Action Plan to Combat Antimicrobial Resistance* (Progress Report, June 5, 2002). The Task Force consisted of the Centers for Disease Control (CDC), the Food and Drug Administration (FDA), the National Institutes of Health (NIH), the Center for Medicare and Medicaid Services, the Health Resources and Services Administration, the Department of Agriculture, the Department of Defense, the Department of Veterans Affairs, the Environmental Protection Agency (EPA), the U.S. AID, and the Agency for Health Research and Quality.

antibiotics.[95] Another study made much the same recommendations, along with advocating restrictions on some uses of antibiotics.[96] Legal commentators similarly have focused their recommendations almost exclusively on regulation and education.[97]

The efficacy of such measures is very questionable. Education will not lead a *self-interested* patient to refrain from requesting antibiotics. Indeed, full knowledge of the private benefits of indiscriminate antibiotic use may lead to more rather than less antibiotic use. Jawboning seems best understood as attempting to instill a new norm that people will obey based on either an internal moral voice, or on the disapproval and informal sanction of others. Ingraining a new norm may take a long time, as this is best done with children. Relying on social disapproval and informal sanctions seems unlikely to work well, as the use, and especially the overuse of antibiotics is largely secret. Attempting to recruit doctors to express disapproval of patients who request antibiotics excessively also is problematic, both because physicians have special duties to their patients, and because competition among doctors means that patients can simply switch doctors if refused a desired prescription.

The case against direct command-and-control regulation is subtler. Regulating antibiotics entails a strict limit on the number of doses administered, or strict guidelines on use. For a government with complete information, these measures might be sensible. If, however, doctors and their patients have better information on the costs and benefits of the various uses of antibiotics, top-down regulation in effect prevents them from using this information in deciding when to use antibiotics and when to refrain from use. A tax or subsidy, on the other hand, by its very nature, will eliminate only lower-value uses. It permits

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[95]Benjamin Schwartz, David M. Bell, & James M. Hughes, *Preventing the Emergence of Antimicrobial Resistance: A Call to Action by Clinicians, Public Health Officials, & Patients* (Editorial), 278 J. AM. MED. ASS'N 944 (1997).

[96]Rosamund J. Williams & David L. Heymann, *Containment of Antibiotic Resistance*, 279 SCIENCE 1153 (1998).

[97]*See* Scott B. Markow, Note, *Penetrating the Walls of Drug-Resistant Bacteria: A Statutory Prescription to Combat Antibiotic Misuse*, 87 GEO. L.J. 531 (1998) (advocates using Medicare and Medicaid rules layered on top of state regulation); Michael Misocky, Comment, *The Epidemic of Antibiotic Resistance: A Legal Remedy to Eradicate the "Bugs" in the Treatment of Infectious Diseases*, 30 AKRON L. REV. 733 (1997) (similar regulatory approach).

the parties 'on the ground' dealing with the problem to draw on their superior information when they decide where and when to economize on the use of a taxed resource.

Moreover, the costs of enforcing command-style regulation of antibiotic use might be quite high. Some governmental agency would need to monitor millions of prescriptions a year and somehow ferret out cases of misuse. We should expect that most patients and their doctors would not cooperate, but rather might scheme together to circumvent laws that, in their view, unfairly deprive a patient of potentially helpful antibiotic treatment.

For these reasons, this article proceeds on the premise that 'hard' economic incentives, such as taxes, subsidies, and changes in patent rights, are much more effective measures than legislative fiat, jawboning, and education.

2. Pigovian taxation

Perhaps the most common solution to negative externalities like the one caused by antibiotic use, is the imposition of a tax that forces those creating such external costs to "internalize" (take into account) the burdens they impose on others. These are called pigovian taxes, in honor of A.C. Pigou, the first economist to discuss such a measure formally.[98] In his seminal article on overuse of antibiotics, Tisdell proposed just such a tax.[99]

Neither Tisdell nor anyone else, however, has considered the implications of the exhaustible resource model for pigovian taxation of antibiotics. For most negative externalities, such as pollution, the pigovian tax per unit remains constant — the harm from pollution, as a baseline assumption, does not vary over time. Such a constant tax, however, will not work for antibiotics. In order to induce an optimal allocation of an exhaustible resource over time, the tax imposed must rise at the rate of interest after having been set at the appropriate level in the initial period. Only such a rising tax will limit use over time efficiently, by raising the price paid by consumers and thus imposing an ever-rising disincentive to use.

There is evidence that such a price mechanism and the law of demand (quantity demanded varies inversely with price) work for

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[98] A.C. PIGOU, THE ECONOMICS OF WELFARE (1925).

[99] Tisdell, *supra* note 71, at 432.

antibiotics. When Iceland stopped subsidizing the price of antibiotics, use fell significantly.[100] Congruently, an Australian commentator has blamed the continuance of such subsidies for exacerbating antibiotic resistance in that nation.[101]

The higher prices resulting from pigovian taxation would indirectly induce many of the measures that would be difficult to implement by direct regulation. For instance, if it is true that supplementing animal feed with antibiotics to enhance growth is one of the lowest-value uses of the drugs, these will be among the first consumers taxed out of the market. As long as the cost of the tax exceeds the benefits of growth enhancement, livestock producers will discontinue their use. Similarly, higher prices would lead those with mild infections, especially when the infection is likely viral, to refrain from using antibiotics. This is precisely what the tax is supposed to do: push those valuing antibiotics the least out of the market.

3. Subsidizing tests

The higher prices for antibiotics resulting from pigovian taxation would also create greater incentives for using various tests to determine if an infection is bacterial, and, if so, whether the bug is resistant to any antibiotics. The potential value of such tests is significant. According to one panel of experts, "[t]he most powerful weapons in the arsenal directed at antibiotic-resistant bacteria are techniques for the rapid and accurate identification of bacteria and determination of their susceptibility to antibiotics"[102]

At present, most such tests are expensive and time-consuming. Culturing and identifying microbes extracted from patients can be time-consuming, taking up to six weeks for tuberculosis. If they determine that the infection is bacterial rather than viral, lab technicians must then undertake a second battery of tests to ascertain those antibiotics to which the germ is resistant. There are, however, a few new tests on the horizon that reduce testing time significantly. Tests results from a throat swab

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[100]Stephenson, *Icelandic Researchers Are Showing the Way to Bring Down Rates of Antibiotic-resistant Bacteria*, 275 J. AM MED ASS'N 175 (1996).

[101] D.P. Doessel, *The "Sleeper" Issue in Medicine: Clem Tisdell's Academic Scribbling on The Economics of Antibiotic Resistance*, 25 INTL. J. SOCIAL ECON. 956 (1998).

[102]OTA, *supra* note 16, at 24.

can determine if strep. bacteria are causing the infection in about 15 minutes.[103] Such progress, however, appears to be the exception rather than the rule: "rapid technologies that would produce useful diagnostic results during the course of an office visit are not on the immediate horizon."[104]

Past scholarship has not discussed an additional efficient policy that is just the mirror image of the pigovian tax on antibiotics: a pigovian subsidy to lower the cost of such tests. Because such tests will reduce the use of antibiotics, they confer a positive external benefit on future patients with serious infections who will need the drugs. In addition to subsidizing the cost of such tests, the state might wish to subsidize research to develop faster and more accurate tests. The remainder of this subsection explains the economics behind these policy recommendations.

Testing for the type of microbe responsible for an infection, in order to limit antibiotic use to cases involving a susceptible target, adds a second policy dimension. Our first dimension, in effect, was serious versus non-serious illnesses. A pigovian tax addresses this distinction by pricing the non-serious cases out of the market for antibiotics. Testing introduces a second dimension: illnesses caused by bacteria susceptible to a given antibiotic versus all other sources of infection for which the antibiotic would be useless (viral, other microbes, *and resistant strains of bacteria*).

	Non-serious (NS)	Serious (S)
Susceptible Bacteria	pigovian tax prices out of market	
Viral, Other Microbes, Resistant Bacteria		

Table 2

[103]http://www.childrensclinicofswla.com/laboratory.htm (visited March 7, 2003) ("If strep throat is suspected, she will swab the throat for a rapid strep test. … Within 10-15 minutes your physician will return with the lab results and continue his exam."). Note that this test does not determine what resistances, if any, the bacteria possesses.

[104]OTA *supra* note 16, at 51-52.

In a world without any tests to determine microbial susceptibility to antibiotics, there is no choice but to deploy antibiotics in all serious cases where it is even moderately likely that the drug will work — the alternative would be to never use antibiotics. This illustrates that, although a pigovian tax will price non-serious cases out of the market, it cannot address this second source of counterproductive use of antibiotics, in cases where an infection will not respond to such treatment.

If such tests[105] are available, a now-familiar issue arises: individual and societal welfare gains from such tests diverge, for reasons quite similar to the negative externality of antibiotic use. Private decisions will compare the costs of the test (defined broadly, to include items such as the psychic expense of postponing treatment until the test results are available) to the expected cost of the antibiotic, its price times the percent chance that the drug would *not* help.

To illustrate, assume that there is a 25% chance that an antibiotic will not work in a specific case, and that the antibiotic costs $10. If a test to determine the efficacy of the drug costs $1, then a risk-neutral patient would pay for the test, as the expected saving from using the test, $2.50 (25% chance it saves $10) exceeds the cost of the test. If the test costs more than $2.50, however, it is not in the patient's self-interest to use the test.

These personal calculations, however, ignore the social benefit that arises when patients use the test: reducing current prescriptions by 25%, thus preserving those effective doses for that many future serious susceptible infections. Continuing with the numerical example from the previous paragraph, assume that a future victim of a susceptible infection would be willing to pay (in present value terms) $20 to insure that present users did not exhaust an antibiotic. Then there is an additional social gain of $5 (a $20 gain in 25% of cases) from the use of the test. From the viewpoint of social optimality, then, we want patients to take the test as long as it costs less than $7.50 (private gain of $2.50 from potential saving in personal antibiotic costs, plus this $5 social gain due to preserving the efficacy of the antibiotic). In terms of the table presented above, using the test gives us additional discrimination power, beyond a pigovian tax, to economize on the use of antibiotics in serious cases where the drugs will do no good.

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[105]For simplicity, we assume that a single test both identifies the infectious agent and, if it is bacterial, determines its resistance to antibiotics.

	Non-serious (NS)	Serious (S)
Bacterial (B)	pigovian tax prices out of market	proper cases for treatment
Viral (V)		ruled out by test

Table 3

Generalizing these insights into more general economic terms, an affordable test in effect reduces the demand for the antibiotic, as illustrated here.

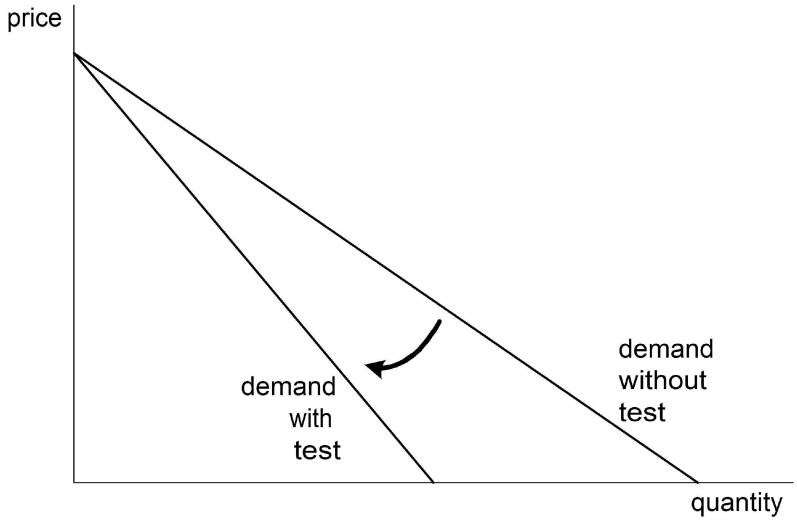

Figure 10

This is just a reproduction of Figure 8, *supra* p. 28. Recall our analysis of the effect of lower demand (all else equal): in order to exhaust a stock of the same size under conditions of lower demand, the initial price must be lower, and thus the initial quantity is higher. Since percent price increases in both cases must equal the interest rate (Hotelling's Rule), the path of prices over time for the two different demand curves is as follows.

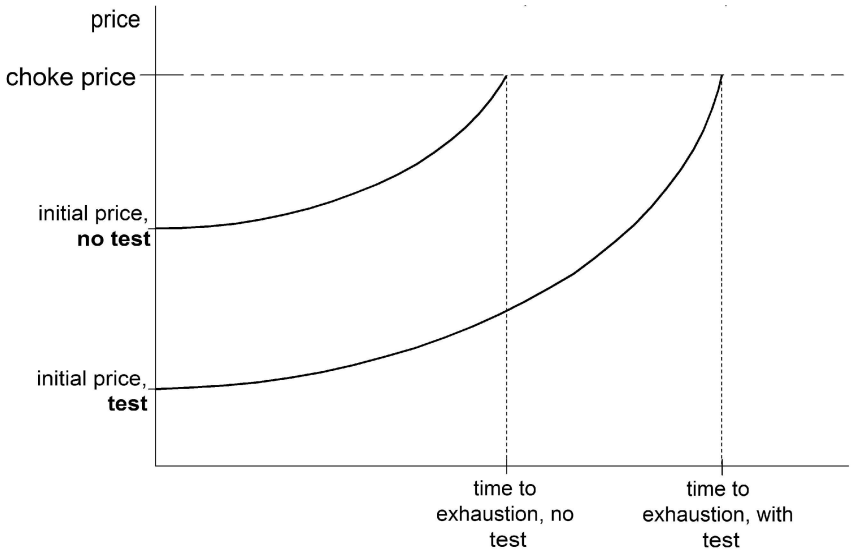

Figure 11

Based on the reasoning behind Figure 9 (*supra* p. 29), which is equivalent, we can conclude that the price path in a market with the test must lie everywhere below the price path in a market with it.

This means that, consistent with the implications of the simple numerical examples above, the test stretches out the useful life of the antibiotic. Recall from those examples that purely private incentives will lead to *less than* optimal use of tests for antibiotic efficacy. This is simply the inverse of the overuse of antibiotics in the absence of a pigovian tax. Such overuse presented a negative externality; potential users of the test provide a *positive* externality. In such cases, the state should offer a subsidy to lower the price of tests for antibiotic efficacy. A properly calibrated subsidy will increase use of the test to a level consistent with maximizing its utility to society as well as to individuals.

4. Subsidizing vaccines

Tests to determine the nature and resistance of infectious agents are not the only source of positive externalities in antibiotic policy. Vaccines (treatments that prevent infection in the first place) offer two positive externalities, one enmeshed with antibiotic policy, the other independent of our concerns. Most policy analysis of vaccines focuses on the latter: for many diseases, vaccinated individuals cannot carry the pathogen, and thus cannot serve as a vector to spread it. Unvaccinated people pose a positive threat to the community; hence laws often mandate vaccinations

(frequently at a price of zero, to spur compliance).[106]

The second, to date ignored positive external effect implicates antibiotic policy: anyone vaccinated against bacterial disease X will never need an antibiotic for the disease, as the vaccine renders them immune. If everyone is vaccinated against disease X, the disease itself may disappear, and the antibiotic can be deployed against diseases Y and Z (for which there may be no effective vaccination).

As with the use of the tests discussed in the previous section, this (with some positive probability) translates into an incremental effective dose of the antibiotic in the future. It seems very difficult, however, to find a way for a future beneficiary of this preserved effective dose to compensate the vaccinated party, and we have the now-familiar positive externality. As with the test in the previous section, the government should subsidize the price of vaccinations because, in addition to helping control the spread of disease, they economize on the use of our exhaustible supply of antibiotics.

For similar reasons, the government might want to subsidize vaccination research. Given the ready availability of many antibiotics over the last 50-odd years, the market for such vaccines may have been stunted. Now that we are beginning to realize that antibiotics are an exhaustible resources, it may be sensible to invest public funds in vaccines — and any other similar treatments that will reduce the extent to which we dip into the limited pool of effective doses of antibiotics.

5. Subsidizing or socializing information gathering

Governmental information gathering, or subsidization of private efforts, may comprise another efficient tool in societal efforts to preserve the effectiveness of antibiotics. For example, data on the statistical likelihood that various symptoms result from a given bacteria, along with data on the likelihood that each antibiotic will work against that bacteria,

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[106] Massachusetts passed the first law mandating vaccinations, requiring all school children to receive vaccination against smallpox. John Duffy, *School Vaccinations: The Precursor to School Medical Inspection*, 33 J. HIST. MED. ALLIED SCI. 344, 346 (1978). "By the 1980-81 school year, all 50 states had [mandatory vaccine] covering students first entering school." Kevin M. Malone & Alan R. Hinman, *Vaccination Mandates: The Public Health Imperative & Individual Rights*, in LAW IN PUBLIC HEALTH PRACTICE (Richard A. Goodman et al., eds., 2003). The Supreme Court ruled that mandatory vaccination programs are constitutional in *Jacobson v. Massachusetts*, 197 U.S. 11 (1905) (holding state law requiring smallpox vaccination did not violate any Due Process Clause liberty interest).

might offer a rough-and-ready, cost-effective way to decide quickly what antibiotic, if any, to prescribe. Similarly, data on the geographic spread of resistant strains could enable doctors to target antibiotic usage more narrowly and effectively.

Here, as is common for the production of information, private incentives to construct the data may be suboptimal. First, it is difficult to exclude anyone from obtaining the information; once it is revealed, controlling its spread is problematic. Moreover, use of the information is non-rivalrous: unlike a hamburger, "consumption" of the information to treat patient X in no way makes the information unavailable or useless to patient Y. Under such circumstances, the optimal price for this public good is zero. Private markets cannot provide efficient amounts of such goods.[107]

Admittedly, in some cases private parties may have incentives to produce some of this information. For example, a firm that has developed a new antibiotic (over which it has a patent-created monopoly)[108] might find it profitable to garner data demonstrating to doctors and their patients that this new drug works where existing antibiotics do not. There is indeed such private data-gathering.[109] In general, however, it seems unlikely that private parties will have incentives to produce all of the wide variety of data useful in economizing on the use of antibiotics.

At present, there is no national program for compiling data on the prevalence and types of resistant bacteria. Some states collect relatively limited data; even this has proved productive. For example, one such database enabled the state of Washington to pinpoint quickly the cause of an outbreak of e.coli infections. Nevada, without a reporting and monitoring apparatus, had a similar outbreak that lasted much longer, and for which the state never did identify the source of the infection (making recurrence more likely).[110] Unfortunately, the trend over the last decade

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[107]NICHOLSON, *supra* note, at 706-16.

[108]Patents are discussed at length in the following section, IV.D.

[109]*Antimicrobe Spy Network*, 277 SCIENCE 185 (1997). Note that the government cannot compel private information owners to disclose data without paying just compensation. Ruckelshaus v. Monsanto, 467 U.S. 986 (1984) (trade secret compensable property interest for purposes of Takings Clause).

[110]OTA, *supra* note 16, at 63.

or so has been less, rather than more, governmental surveillance of the resistant bacteria threat.[111]

D. Policy Alternative Two: Patents

In sketching the regime of public information gathering, subsidies for tests, and taxes on antibiotics necessary to deter inefficient overuse of antibiotics, the discussion in the previous section was notably silent on the magnitude of the information gathered, the subsidies given, or the taxes imposed. This was a dodge, for calibrating these measures is extremely difficult.

Thinking about the optimal tax rate illustrates the problem. In order to mimic the efficient price path over time for an exhaustible resource, the tax on an antibiotic must rise over time. This alone is not unduly complicated; all the taxing authority need do is select the proper interest rate and raise the tax by that percent each period. What is difficult is determining the appropriate *initial level* of the tax. This depends critically on both supply (the cost structure for making a given antibiotic) and demand. Public officials do not have very good information about either, and obtaining even crude estimates could be quite expensive. An error in setting the initial tax rate will result in suboptimal tax rates for the entire working life of the antibiotic. Finally, note that because the supply and demand for each antibiotic differs, often substantially, the state would need to select a different initial tax rate for each antibiotic.

Pharmaceutical firms likely have better information on costs of making antibiotics, and on the structure of demand for each drug. It would not be to their financial advantage, however, to provide the government with honest estimates. There is another way, however, to draw on this knowledge: give firms monopoly rights in antibiotics. This, of course, is already done, at least for limited terms, via the patent system.

It should not be surprising that patents offer at least a partial solution to the problem of excessive use of antibiotics. As discussed in the introduction, absence of property rights in effective doses of antibiotics is one way to conceptualize this problem. A patent creates a legally-protected monopoly on the right to produce, and a legal monopoly is a very powerful property right — the power to exclude the world from

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[111]See R.L. Berkelman et al., *Infectious Disease Surveillance: A Crumbling Foundation*, 264 SCIENCE 368 (1994); David P. Fidler, *Legal Issues Associated with Antimicrobial Drug Resistance*, 4 EMERGING INFECTIOUS DISEASES (http://www.cdc.gov/ncidod/eid/vol4no2/fidler.htm) (1998).

selling the product. The remainder of this section analyzes the benefits, and the costs, of using patents instead of taxation to curb overuse of antibiotics.

1. Traditional benefits and costs of patents

The usual justification for rewarding inventors with monopoly rights, called patents, is "a practical utilitarianism: reward the creator of a useful thing, and society will get more useful things … this mode of thought … is the core of all patent systems."[112] The patent system is thus part and parcel of a market economy, harnessing the inventiveness of self-interested individuals to share their discoveries with society by offering a reward in the form of a monopoly over the invention for some term (today, typically 20 years).[113]

It is important to emphasize that, in the context of antibiotics, we are studying a second, distinct facet of a patent monopoly that is not relevant for most other goods. The traditional purpose of the patent system, encouraging innovation, remains relevant for antibiotics, but we are focusing on the fact that a patent monopoly creates property rights that help mitigate overuse.

For most products, the fact that the government grants a monopoly is an evil for the usual reason: monopoly sellers restrain supply below the optimal level, raising prices above marginal cost, in a manner that maximizes their private profits at the expense of social loss (the so-called "deadweight loss" attributable to monopoly).[114] Patent monopolies, however, are *necessary* evils, since they provide the incentive to invest in innovation.

For antibiotics, it is not clear that monopolization is less desirable

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[112]PATRICK P. MERGES & JOHN F. DUFFY, PATENT LAW & POLICY: CASES & MATERIALS 2 (3d ed. 2002).

[113]35 U.S.C. § 154(a)(2). The Drug Price Competition & Patent Term Restoration Act of 1984 gives patent holders partial compensation for patent time lost in the drug approval process. 35 U.S.C. § 156.

[114]JEAN TIROLE, THE THEORY OF INDUSTRIAL ORGANIZATION 66-68 (1988) If the demand curve is horizontal, and in rare other cases (e.g. a good with constant elasticity of substitution), monopoly prices (and quantities) will equal the competitive outcome. *Id*. For antibiotics effective against both some serious conditions and some minor irritants, the demand curve will have a downward slope, reflecting the fact that people will pay more to treat more serious illnesses.

than a free market, which suffers from the negative externality caused by a lack of property rights. Because of this externality, prices above marginal cost are desirable: these higher prices will constrain demand by discouraging low-value uses, and preserving doses for more serious cases. Note that it is in the self-interest of the patent holder to serve this social end.

In addition to the interaction of a patent monopoly with the negative externality, we must account for the effects of a monopoly in a market for an exhaustible resource like antibiotics. If monopolization involved no deadweight loss in such markets, patents would provide an ideal solution to the problem of antibiotic overuse.

Unfortunately, as demonstrated in the following section, a monopolist controlling an exhaustible resource, like a monopolist over a regular 'reproducible' good, raises prices too much, at least initially. Thus there seems no 'perfect' market structure to address overuse of antibiotics. A free market, which is usually efficient, prices antibiotics too low because of the external effect of present use on future usefulness. A monopoly for this exhaustible resource has the same defect as all monopolies: mis-pricing that leads to misallocation.[115]

It is possible to imagine a market structure that would price antibiotics efficiently. The idea is to determine the optimal number of doses in each period (say, 100,000) , and grant licenses giving each of a large number of competing firms (say 1000) to produce a small fraction of the total (here, 100,000/1000, or 100). Selling the drug without such a license would be illegal. Since no firm would have significant market power, none would withhold supply; thus, together the firms would sell all licensed doses — by assumption the efficient outcome. The following table summarizes how this licensing regime relates to a free market and

[115]This excessive price, in addition to blocking some desirable transactions, may indirectly cause overuse of the tests discussed in the previous section that identify infective agents and their drug resistances. Recall that antibiotics priced too cheaply (not reflecting the negative externality of low-value use) led to underutilization of such tests; the test is economically desirable only if its cost is more than outweighed by the private benefit of using the test: finding out drugs won't work and saving the cost of the drug. The cheaper the drug, the less desirable the test. Monopoly, with an artificially high price, presents the flip side of this scenario. Faced with this steep price for a treatment that may not work, consumers will use the test in cases where the cost of the test exceeds its social benefits, because the artificially high price of the drug does not reflect its true social costs.

a monopoly market by separating out monopoly from property rights.

	Property Rights in Antibiotics	No Property Rights in Antibiotics
Monopoly	patent world; likely that antibiotics *under-produced*	Natural monopoly, barriers to entry, or some other force creating monopoly; *underproduction*, as in case of patent monopoly (this regime not discussed in text)
Competition	Licensing regime (large number of firms, each with license to service small portion of market); *efficient outcome*	Competitive market; anyone can produce antibiotics, they are sold at marginal cost, and thus are *over-produced*

Table 4

In order to avoid the deadweight loss associated with patent monopolies, there have been recurring calls for a "reward" or "bounty" system, under which the government, instead of granting inventors a patent monopoly, would make a one-time cash payment (reward), place the new invention in the public domain, and presumably competition would insure that it sold at marginal cost.[116] Such a system would be positively undesirable, however, for antibiotics, based on the central problem studied in this article: marginal cost pricing of antibiotics leads to excessive use. Prices in excess of cost, though perhaps not as high as

[116]Steven Shavell & Tanguy Van Ypersele, *Rewards Versus Intellectual Property Rights*, 44 J.L. & ECON. 525 (2001); Michael Kremer, *Patent Buyouts: A Mechanism for Encouraging Innovation*, 113 Q.J. ECON. 1137 (1998); Douglas G. Lichtman, *Pricing Prozac: Why the Government Should Subsidize the Purchase of Patented Pharmaceuticals*, 11 HARV. J.L. & TECH. 123 (1997). Robert C. Guell & Marvin Fischbaum, *Toward Allocative Efficiency in the Prescription Drug Industry*, 73 MILBANK Q., June 1995, at 213. For a detailed analysis of these and other proposals, *see* Michael Abramowicz, *Perfecting Patent Prizes*, 56 VAND. L. REV. 115 (2003).

monopoly prices, are positively desirable.

There is one set of circumstances under which monopolists will price efficiently: when they have the ability to price discriminate perfectly. Such a price discriminating seller has detailed information on the demand of each customer, and thus charges each the maximal price they are willing to pay. Each customer, then, pays a different price, hence the label "discrimination." This requires monopoly power, of course, for if there is competition, any attempt to charge higher prices to those with more intense desire for the good would simply drive those customers to other sellers who stand ready to undercut any price above cost.

A price discriminating monopolist can capture all possible gains from trade with her customers, and thus when she maximizes her private gain she is also maximizing social gain. In the market for antibiotics, this means that a price discriminating seller would never have the incentive to sell doses to low-value users (at a low price) because such sales would later cost her sales at a high price. This solves the basic negative externality of the antibiotic market. The ability to price discriminate means that, unlike a "regular" monopolist who must charge one price to all comers, such sellers have no need to restrict supply and charge everyone a high price; they can "creep down the demand curve" to capture efficient sales without undermining their profits from sales to those willing to pay the highest prices.

Perfect price discrimination in practice is impossible; what seller has enough information to size up individual buyers and accurately gauge the highest price each is willing to pay? The welfare implications of *imperfect* price discrimination are ambiguous. When monopolists are only able to divide up buyers into a few large groups and charge different prices to each group, the outcome may be superior to a one-price monopoly, but also may be worse.[117] Similarly, when monopolists try to separate ("screen") consumers with a menu of bundles with different prices, the result may be better or worse than the outcome under simple monopoly.[118]

Drug makers may be able to engage in fairly fine-tuned price discrimination. The holder of a patent for an antibiotic that is the sole treatment for some class of serious infections (e.g. vancomycin, discussed *supra* § II) can charge a higher price for that drug than for an

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[117] TIROLE, *supra* note 114, at 139.

[118] *Id*. 149 ("The welfare analysis of nonlinear tariffs is ambiguous.")

agent mainly used to treat minor illnesses. Patent holders may even be able to engage in price discrimination in the sales of a single substance. The owner of a drug effective against both serious infection ***A*** and mild infection ***Z*** could market the drug under two trade names, with an expensive version authorized for use against ***A*** and a cheaper version authorized for use against ***Z***.

Admittedly, price discrimination in markets for medical treatments have been politically controversial. This issue has proved a hot button in the context of a very similar product, vaccinations. For example, it may well be economically sensible (efficient) for a patent holder to charge lower prices in less wealthy nations. Yet at a congressional hearing, "Senator Paula Hawkins asked a major vaccine manufacturer how it could justify charging nearly three times as much to the United States government for vaccines as to foreign countries …"[119] Similarly, President Clinton, with a rhetorical flourish, said "I cannot believe that anyone seriously believes that America should manufacture vaccines for the world, sell them cheaper in foreign countries, and immunize fewer kids as a percentage of the population than any nation in this hemisphere but Bolivia and Haiti."[120] In response to this adverse publicity, U.S. manufacturers stopped submitting bids to UNICEF to supply vaccines to developing nations.[121] Curtailing this form of price discrimination might well have been inefficient; as long as the vaccine makers were able to charge at least marginal cost to poorer nations, and those nations presumably found such a price attractive, the pressure to charge one price to all comers destroyed some gains from trade.

2. Effect of monopolies and limits on their terms in exhaustible resource markets

If antibiotic patent holders cannot engage in effective price discrimination, and instead must select one price, we know that they will generally price above the competitive level in the exercise of their market power. This model of monopoly behavior continues to apply over time

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[119]Michael Kremer, Public Policies to Stimulate Development of Vaccines and Drugs for Neglected Diseases 24-25 (draft article).

[120]*Id.* 25 fn.10, citing MITCHELL S. VIOLAINE, NALINI M. PHILIPOSE, & JAY SANFORD, THE CHILDREN'S VACCINE INITIATIVE: ACHIEVING THE VISION (1993).

[121]*Id.*

in the dynamic context of the exhaustible resource model.[122]

To understand profit-maximizing strategy for monopoly owners of exhaustible resources, recall the discussion of competitive markets[123] in a world of zero marginal costs. Under competition, the market moved up the demand curve so that, per Hotelling's Rule, quantity decreased each period so that prices could increase at the rate of interest. Any sharper price rise cannot be an equilibrium because it would induce sellers to refrain from selling; any lower price rise conversely cannot be an equilibrium because it would induce all sellers to dump the good immediately.

In that competitive market, there were, as usual, no economic profits. A monopolist can do better. Under the simplifying assumption of zero costs, a monopolist will want to maximize discounted revenue over time. If the proceeds from the sale of a small amount of the resource (technically, *marginal revenue*) in one period exceed the discounted value of the proceeds that could be obtained by waiting to sell the same unit in the following period, the monopolist would sell her entire stock at present; holding even one unit would be inferior to selling the unit and investing the proceeds at the rate of interest. Conversely, if the marginal revenue in the next period exceeded the current marginal revenue by more than the rate of interest, the monopolist would have no incentive to sell any units today. Thus, by an argument similar in structure to that for competitive markets, we reach a similar but not identical conclusion. Instead of moving up the demand curve so that prices increase at the rate of interest, a monopolist chooses quantities so that her marginal revenue rises at the rate of interest. In other words, she moves up her marginal revenue curve instead of the demand curve.[124]

Except in unusual circumstances (e.g. when the industry demand curve is horizontal), this means that prices for an exhaustible resource

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[122]The following discussion is based on JON M. CONRAD, RESOURCE ECONOMICS 86-88 (1999)

[123]*Supra* § IV.B.1 & Figure 3.

[124]Empirically it can be difficult to calculate what portion of an exhaustible resource monopolist's price reflects market power, as opposed to rent on the resource. *See, e.g.*, Gregory M. Ellis & Robert Halvorsen, *Estimation of Market Power in a Nonrenewable Resource Industry*, 110 J. POL. ECON. 883 (2002) (finding prices above marginal cost in nickel industry stem from monopoly power, not implied rent due to owners of nickel deposits).

under monopoly will rise less rapidly than in a competitive market. The first step to understanding this result is to note that the marginal revenue curve, except in the aforementioned unusual circumstances, lies below the demand curve and has a steeper slope. Whenever a monopolist decides to sell one more unit, the demand curve dictates the price, which is average revenue (revenue per unit sold). Thus revenue on this marginal (one more additional) unit equals the new, lower price, as we move down the demand curve a bit. The drop in price, however, means that there is a negative effect on revenue: the price received for all the units except this last (marginal unit) falls. This latter negative effect makes marginal revenue decline faster than prices taken from the demand curve.

The following picture, then, illustrates the usual state of affairs, when the marginal revenue curve lies below the demand curve.

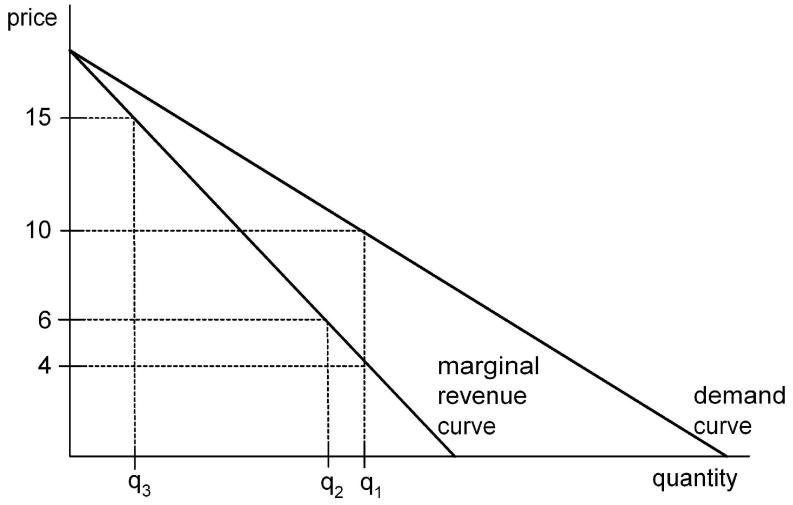

Figure 12

Consider an initial price of 10, paired with some quantity sold of q_1, and assume the interest rate is 50%.[125] In a competitive market, Hotelling's Rule dictates that the price must rise by this 50%, from 10 to 15, in the second period. This translates into only q_3 units transacted. Under a monopoly, however, the marginal revenue when q_1 units are sold is only

[125]I have used such a high interest rate to illustrate starkly the difference between the demand curve and the marginal revenue curve; the result does not depend on this choice.

4. It is this quantity, not price, that increases at the interest rate (50%). Thus the second period sales under monopoly decrease only to q_2, where marginal revenue is 6 and the price (jumping up the demand curve) is definitely less than 15. This same story repeats itself at each step; moving up the marginal revenue curve leads to gentler price increases than under competition.

There is one more step in comparing the two market structures. If a competitive market will exhaust some stock of an exhaustible resource by starting at some price p_c and reaching the choke price (a price high enough to drive demand to zero) in some time period t_c, a monopolized market cannot start at this same price, p_c. Since prices increase more slowly under monopoly, such a price path would induce greater quantities transacted in each period, and thus would exhaust the resource before the price reached the choke price. Such a path, however, cannot be optimal for a monopolist, since she could have raised her initial price (and thus, under Hotelling's Rule, all subsequent prices) by some amount and enjoyed greater profits by finishing at the highest possible price, the choke price.

This demonstrates that a monopolist in an exhaustible resource market will charge a higher initial price than would prevail in a competitive market. From this higher initial price, we can draw a further, perhaps surprising conclusion: a monopolist will take longer to sell off the exhaustible resource than would a competitive market. If this were not the case, i.e. if the monopolist exhausted in a shorter time (or the same time), we immediately reach a contradiction. We know that the competitive price path will exhaust the resource. Starting at a higher price and finishing earlier (or at the same time) means that the quantity sold under monopoly must be lower than under competition (with equality in the last period). But then the total quantity sold under monopoly will be less than under competition — i.e. such a price path will not exhaust the resource. This cannot be an equilibrium because the monopolist could earn more by selling the leftover resources in some or all periods.

Combining the three facts differentiating monopoly markets from exhaustible resources (slower price increases, high initial price, and longer time to exhaust resource), we can encapsulate the difference between monopoly and efficient (e.g. imposition of correct pigovian tax) markets for exhaustible resources in the following diagrams.

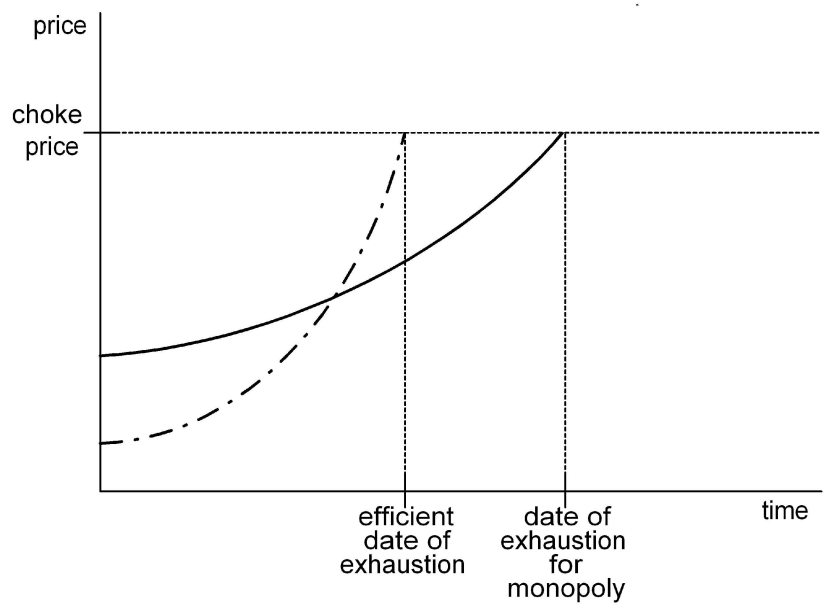

Figure 13

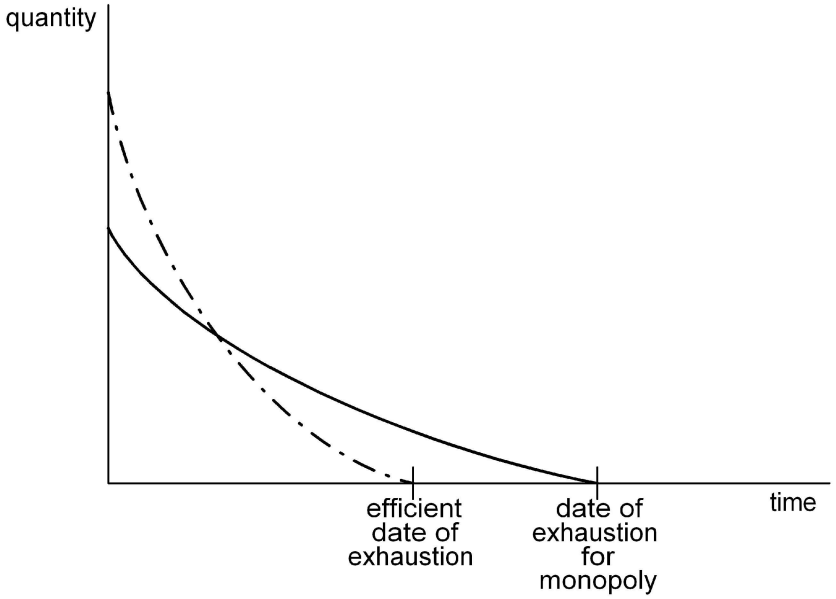

Figure 14

Monopoly is only the first half of the story. Patents do not grant

monopoly rights forever; their limited term may affect owners' behavior. The holder of a patent for a normal, non-exhaustible resource maximizes profits by producing at the same output during each period. This is not generally true for the holder of a patent on an exhaustible resource. If the patent term is longer than the period over which a monopolist facing no time constraints would exhaust the resource, the monopolist will follow the price and quantity paths shown immediately above in Figures 13 and 14. In this case, the patent's time limit isn't a binding constraint.[126]

If, however, the patent term is shorter than the unconstrained exhaustion period, the limited term will affect the way in which the patent holder behaves. Not surprisingly, the limited term works in the opposite direction of monopoly power. We have seen that monopoly power causes the owner of an exhaustible resource to raise initial prices and stretch consumption over a longer period. A limited patent term, by destroying the possibility of monopoly pricing after expiration, puts pressure on the monopolist to move sales forward in time, forcing a reduction in the initial price charged.

In most cases, the Hotelling Rule for monopolists applies: the patent holder's marginal revenue must rise at the interest rate. As long as the patent period is not "too short," a profit-maximizing monopolist will still exhaust the entire supply of the resource. In order to do so, she must start at a price lower than she would if she faced no time constraint. The curve showing prices over time for a moderately constrained monopolist illustrates such a case. If the patent period is sufficiently short, a monopolist can earn a greater profit by ignoring all intertemporal allocation issues and behaving like a monopolist in a normal (non-exhaustible resource) market, keeping price constant at the profit-maximizing level. The curve for the myopic monopolist illustrates this case.

[126]The discussion that follows is based on DANIEL LÉONARD & NGO VAN LONG, OPTIMAL CONTROL THEORY & STATIC OPTIMIZATION IN ECONOMICS 230-35 (1992).

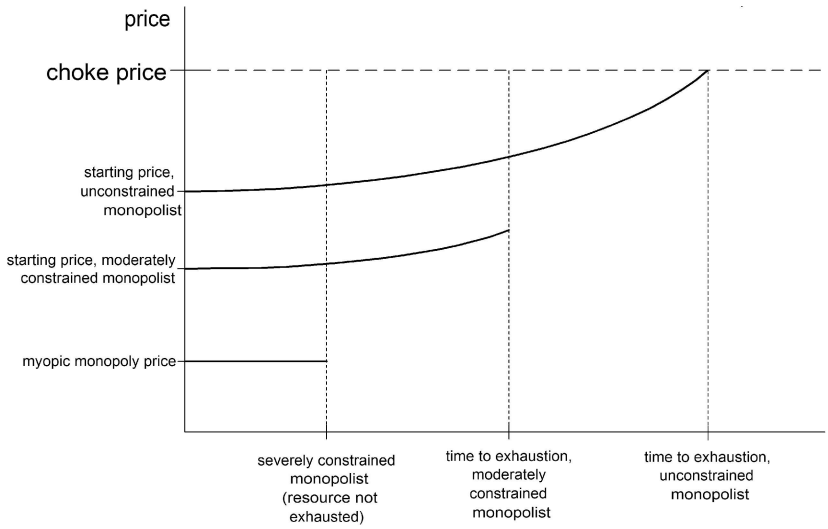

Figure 15

The corresponding figure showing quantities sold over time appears below.

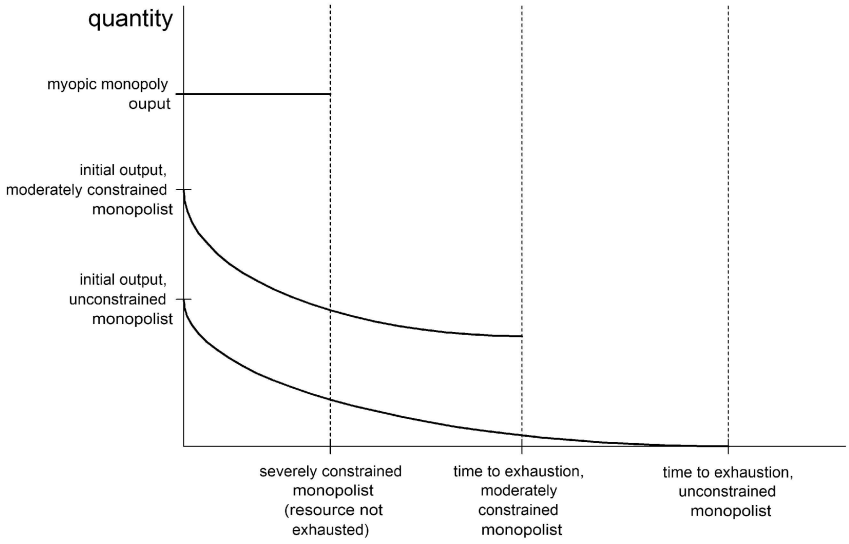

Figure 16

The socially most desirable patent term is indeterminate. We know that the consumption pattern for an unconstrained monopoly begins below the optimal path, but stretches consumption out over a longer period (Figure 12, *supra* page 54). A patent that places a binding time

constraint will induce the monopolist to charge lower prices in order to sell all units of the exhaustible resource within the constrained period. If the patent period is long enough for the monopolist to exhaust the resource, this same general result will hold: the constrained monopolist will begin with prices higher than desirable and quantities lower, but will eventually charge lower prices. It is possible, however, that the patent period will be so short that the monopolist will choose to charge the simple, fixed monopoly price and will not exhaust the resource in the patent period.

The key indisputable economic fact here is that an exhaustible resource monopolist *without any time constraint* will initially price the good higher than optimal, and will stretch out the useful life of the resource. For antibiotics, this means that a monopolist will price out of the market some moderate-value consumers , such as a patient with a painful but not serious bacterial infection. This is the cost of monopoly. The benefit is that the patent holder will maintain the utility of the drug for a longer-than-optimal time. If society is risk-averse, this is an attractive trade-off. Granting antibiotic inventors infinite-term patents trades off some short-term moderate pain in return for ensuring the ability to treat the most serious illnesses far into the future.

E. Patent Terms & Planning for Plagues

Our concern with the patent term for antibiotics stems from their exhaustibility. For most goods, the main issue surrounding the choice of a patent term is to set it just high enough to encourage desired innovation. Excessively short patent periods provide too little incentive for innovation; excessively long patent periods impose a needlessly extended run of deadweight loss due to monopolization.

In the market for antibiotics, the nature of demand, when coupled with exhaustibility, supplies another reason for a longer patent period. The demand for antibiotics is greatest when mankind faces some new bacterial plague. Such plagues, fortunately, seem to be rare events. Unfortunately, their timing is unpredictable. Economically, we can model bacterial plagues as random, sudden, short-lived explosions in demand for antibiotics. Plagues are low probability, high cost disasters, like house fires or floods. As such, some sort of insurance scheme seems like the natural way to address the threat. During good times (no plagues), we should pay premiums, in the form of refraining from the use of newer antibiotics for which resistance is rare or has not yet materialized. Society can then 'cash in' this insurance policy by using the

reserved medication to eradicate the new and deadly microbe. Note that this is almost exactly what the holder of an unlimited or long-term patent does: charges higher prices in the short term, and stretches out the useful life of the drug in the long term.

Alternatively, the government, by regulation, could place all newly-developed antibiotics in a "lock box," barring their use until this reserve contains enough drugs to address the threat of a plague. Regulation putting new antibiotics in such a lock-box, however, would wreak havoc on private incentives to develop new antibiotics.

> One of the problems is that if we were to get a new class or new type of antibiotic, then people would want to save it and would therefore be reluctant to use it. One of the difficulties for the pharmaceutical industry is looking for something which ostensibly is not going to be used.[127]

One solution to this problem would be to socialize the development of antibiotics. The government could fund research and development, and forbid manufacture of the drugs it discovers until public health experts decide that a plague exists.

The fact that governments generally have limited their funding to basic research, and have left the development of medication to private pharmaceutical enterprises suggests that the state may be a relatively inefficient drug developer and marketer. Thus it is worth exploring ways in which private ordering can create incentives for drug makers to squirrel away novel antibiotics to address the risk of a plague.

The property rights created by patents can provide such incentives. The possibility of a plague, like any sudden explosions in demand, will translate into the prospect of much higher prices for patent holders that postpone sales of a new antibiotic. It is this potential for reaping very large gains in the event of a plague that may induce private actors to preserve antibiotic effectiveness, squaring their private calculus with the public interest. There are, however, at least two problems with this solution.

First, the limited term of patents may short-circuit private incentives to postpone marketing a newly-developed antibiotic. It is quite possible that the odds of a plague within the patent period (20 years, roughly) are small, even if the odds of a plague over a longer term approach 100%, as

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[127]CIBA FOUNDATION, *supra* note 36, at 150 (comments of J.V. Copeland, SmithKline Beecham Consumer Healthcare (UK)).

seems likely. For example, assume that the odds of a bacterial plague appearing in any year are 0.5%, and that the absence of a plague in one year has no effect on the odds of a plague appearing in future years. Under this scenario, the chance that at least one plague will appear within 20 years are only 10%, but there is a 45% chance of such a plague over 120 years.[128]

The low odds of a plague within the patent period might well drive a drug patent holder to begin marketing it even though this is not socially optimal. This might seem counterintuitive: any prospective gains 20 years or more in the future will be discounted significantly under any realistic interest rate assumption. This would seem to make waiting for a plague uneconomical.

This supposition, however, is not necessarily true. For example, if we keep the assumption that the odds of a plagues are 0.5% per year, assume that an antibiotic will work against only one such plague (such intense use likely will foster resistance in bacteria), apply a 3% real rate of interest, and assume that a plague raises demand for an antibiotic by a factor of 250, then putting a new antibiotic in a lock-box and saving it until the next plague returns, on average, 7.75% more than immediately marketing the drug.[129] Even though the expected date of the next plague is very remote and thus profits from sales at that date are discounted quite heavily, the extra revenue that stems from the explosion in demand during a plague is more than enough to outweigh near-term (and thus lightly-discounted) sales in low-demand conditions. In a nutshell, it is privately rational to shelve antibiotics under these circumstances and wait for a big payday.

The upshot of this example is that patents with very long or infinite terms may induce their owners, acting in self-interest, to preserve the effectiveness of antibiotics in anticipation of a plague. One way to understand this result is to note that the usual limited-term patents create only temporary property rights; once a patent expires, the product immediately becomes a commons. For goods without any externalities,

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[128]If the odds of a plague in a given year are 0.5%, then the odds of no plague are 99.5%. The chance of avoiding a plague for N years is then $(.995)^N$. Since this probability and its converse, the odds of experiencing at least one plague, must sum to 100%, the odds of one or more plagues within the next N years are simply $1 - (.995)^N$. Using the numbers from the scenario given in the text, for 20 years we have $1 - (.995)^{20} = .095$; for 120 years, $1 - (.995)^{120} = .452$.

[129]Appendix A *infra* derives these results.

this is desirable; price falls from an artificially high monopoly level to cost, increasing the number of transactions and thus eliminating deadweight loss. For antibiotics, of course, this decline in price and increase in use is undesirable because of the now-familiar negative externality of current low-value usage. An infinite-term patent preserves property rights in the antibiotic, and the holder of this property right, free from competition over any horizon, can withhold an antibiotic until a period of extraordinary need (i.e. a plague). Strong property rights can make even a very long delay in selling a drug — i.e. putting the drug in a lock-box — attractive to self-interested patent holders.

The benefits of infinite (or very long-term) patents, however, do impose greater deadweight losses. Although there is no apparent method by which to weigh this cost against the property-rights benefits of infinite-term patents for antibiotics, there are strong heuristic grounds to believe that the benefits exceed the costs. First, precisely because bacteria develop resistance to them, antibiotics in effect have a built-in finite useful life expectancy. This sets an upper limit on the size of the deadweight loss from monopoly. Contrast this with a patent on, e.g., filters for liquids (oil; water) used in a broad array of goods. Such filters may well be used for eternity, and thus society would suffer unending losses due to monopolization.

Second, the monopoly power created by a patent over a single antibiotic may be quite limited. If the drug has effective competitors in the markets for all bacterial infections, it may confer little monopoly power. Moreover, those cases where significant monopoly power exists, i.e. where the drug is uniquely effective against a serious illness, are precisely the cases in which we value insuring usefulness most highly.

Finally, risk aversion again weighs in favor of infinite-term patents. If society is risk-averse, it will not mind paying a 'premium' (in the form of longer-term monopolization) in order to 'insure' against disastrous plagues by creating incentives for patent holders to put some antibiotics in a lock-box. The trade-off, fewer treatments for less serious cases (that in an ideal world are efficient to treat) in order to preserve usefulness for the most serious rash of cases, seems worthwhile.

Society can, in theory, reach the true optimal consumption path by imposing the appropriate pigovian tax instead of awarding patents on antibiotics. This approach, however, will largely undermine the incentives to research and develop antibiotics. In addition, as discussed

earlier, setting the proper tax rate is extremely difficult.[130] To summarize that discussion, it requires that the government obtain detailed knowledge of costs and the demand for an antibiotic in each market where it remains effective. The patent approach, on the other hand, leaves pricing issues to a manufacturer which is closer to, and an expert in, the market for drugs.

This private ordering solution to planning for plagues, via patents of infinite (or very long) duration, depends critically on not only a free market for the sale of antibiotics today, but also on the confidence that such a market will exist in the future, *especially in the event of a plague.* Can the government credibly commit to refrain from regulating prices in such dire circumstances, when voters express outrage over the high prices being charged for life-saving medication? If pharmaceutical companies believe that government will cave to popular pressure and impose price restraints or other regulations limiting their ability to reap the rewards of high plague demand, they will find shelving the antibiotic until a plague arises too risky. Instead, they will market the drugs immediately. This result is not socially desirable.

This is an example of a general phenomenon, so-called *time-consistency* problems. Actors often wish to convince others that they will follow a certain course of action in the future. A monetary authority may wish to convince private actors that it will not inflate the currency.[131] A taxing authority contemplating an 'amnesty' for those with overdue taxes will want to convince taxpayers that it is a one-time deal that the authority will never offer again.[132] Yet as time goes by, it may become attractive for the monetary and taxing authorities to deviate from their pre-announced commitments. If private actors foresee this, they will put little credence in the announced policies. Firms will expect inflation and factor that into their pricing and other decisions; taxpayers will figure that later amnesty offers will materialize and so be less inclined to pay their taxes.

Anecdotal evidence suggests that drug makers might lend little credence to a naked promise from the government to refrain from regulating drug prices when plagues strike. For example, in the face of

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[130]See discussion *supra* p. 45.

[131]Fynn E. Kydland, & Edward C. Prescott, *Rules Rather than Discretion: The Inconstency of Optimal Plans*," 85 J. POL. ECON. 473 (1977).

[132]AVINASH DIXIT & BARRY NALEBUFF, THINKING STRATEGICALLY 147 (1991).

the spread of anthrax via the mail in the fall of 2001, the makers of ciprofloxacin, the antibiotic of choice to cure such infections, were under intense scrutiny. It appears that, contrary to economic logic, they decided not to raise the price of the drug, despite an increase in production that likely raised their marginal costs.[133] Similarly, the makers of AIDs medications face ongoing pressure to reduce the price of their products.[134] How can the government *credibly* commit to resist widespread calls to place ceilings on the prices of key antibiotics if and when plagues strike?

The government could try to commit itself by contract, promising to pay a pre-determined, relatively high price for an antibiotic in return for the patent holder's agreement to keep the drug off the market until needed to treat a plague. It is not clear, however, if the government can bind itself convincingly under contract law. The general rule is that the government can take actions *as a sovereign* that may undermine the value of a contract to a party with whom the government previously contracted.[135] In *Horwitz*, the Supreme Court refused to award contract damages to a party whose contract to purchase silk from the United States was erased by a general embargo.

> It has long been held by the Court of Claims that the United States when sued as a contractor cannot be held liable for an obstruction to the performance of the particular contract resulting from its public and general acts as a sovereign. … *Jones v. United States*, 1 Ct. Cls. 383, 384 … In the *Jones* Case … the court said: "The two characters which the government possesses as a contractor and as a sovereign cannot be thus fused; nor can the United States while sued in the one character be made liable in damages for their acts done in the other. Whatever acts the government may do, be they legislative or executive, so long as they be public and general, cannot be deemed specially to alter, modify, obstruct or violate the particular contracts into which it enters with private persons. . . ." In this court the United States appear simply as contractors; and they are to be held liable only within the same limits that any other defendant would be in any other court. Though their sovereign acts performed for the general good may work injury to some private contractors, such parties gain nothing by having the

[133]http://www.guardian.co.uk/anthrax/story/0,1520,580129,00.html (visited March 2, 2003).

[134]http://www.guardian.co.uk/aids/story/0,7369,786927,00.html (visited March 2, 2003).

[135]Horwitz v. United States, 267 U.S. 458 (1925).

United States as their defendants.[136]

Thus patent holders might fear that the government could characterize its attempt to regulate antibiotic prices *in general* as a *sovereign* act which does not constitute a breach of contract. The courts do not always buy such arguments,[137] but patent holders might find the litigation risk of this issue too great.

Another candidate mechanism for the government credibly to commit itself to refraining from price regulation is the just compensation requirement. There is no question that a patent is a property interest protected by Takings Clause.[138] Existing doctrine, however, suggests that price regulation is only a taking if unreasonable. Specifically, courts have rejected landlord just compensation claims for residential rent control statutes as long as the statute provides them with a "reasonable" or "fair" rate of return.[139] What amounts to a reasonable rate of return is of course debatable, and drug makers might again decide that it is too risky to bank on the size of just compensation awards to make them whole in the face of price regulation.

In theory, consumers can address the risk of plague-induced high antibiotic prices via insurance; if most did so, there might be less pressure on politicians to regulate prices in the face of a plague. As an analogy, note that existing health insurance covers expensive procedures such as open-heart surgery by assessing affordable annual premiums to everyone and covering the costs of the unlucky few who end up needing the procedure in a given year. The same basic 'spreading' principle applies to antibiotics. Instead of a dribble of cases each year, however, plagues present a flood of cases every 100 years, say. To cover efficiently-priced antibiotics, insurers would need to accumulate reserves in those years without plagues sufficient to cover the huge expense of antibiotics

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[136]*Id.* 461.

[137]*See* United States v. Winstar Corp., 518 U.S. 839 (1996).

[138]Ruckelshaus v. Monsanto, 467 U.S. 986 (1984).

[139]*See, e.g.*, Cromwell Associates v. Newark 511 A.2d 1273, 1277 (1985) ("When the maximum increase allowable by the rent-control ordinance is insufficient to provide an efficient operator a fair rate of return, the ordinance is unconstitutional …"); *see also* Searle v. City of Berkeley Rent Stabilization Bd., 271 Cal. Rptr. 437 (Ct. App. 1990) (invalidating ordinance limiting rent increases to 40% of inflation).

warehoused for precisely this contingency.

Such a private solution to high antibiotic prices during plagues could obviate the need for any government involvement in pricing policy. It is not clear, however, that insurers operate with this amount of foresight. Similarly, consumers may lack such foresight; if so, they would be unwilling to pay for 'plague coverage,' and would flock to health insurers omitting such coverage and charging commensurately lower premia. Finally, it is possible that insurers would put pressure on the government to regulate prices in the event of a plague. Although it might seem that such firms (via management, employees, and shareholders) could not apply as much political pressure as the mass of potential plague victims, the insurance industry looks like the kind of well-organized and well-funded 'special interest group' capable of exerting considerable influence in political circles.

F. Are Antibiotics Really an Exhaustible Resource?

Even with very long patent terms that create strong property rights in antibiotics, and with some policy to insure patent holders can reap large gains when plagues strike, the premise that antibiotics are an exhaustible resource means eventually they will be gone. What measures could society take in a post-antibiotic world?

As antibiotic prices became prohibitively expensive, we could expect to see a range of responses. First, increasingly severe conditions would no longer merit the use of antibiotics. The first uses priced out of the market would be infections causing minor discomfort but without any threat of permanent disability or death. As antibiotics become increasingly scarce, bacterial infections causing significant pain and even disability would not merit the use of antibiotics.

The government might consider approving the use of antibiotic agents previously rejected for toxicity or non-trivial side effects. A drug that causes severe nausea suddenly becomes attractive when the alternative is serious illness.[140] Still, bacteria will develop resistance to

[140]In a slightly different vein, the FDA might want to rethink policy on substances so old that they are off-patent, but that have never been approved by the agency. For example, fusidic acid, an old, off-patent drug, is effective against some strains of MRSA. The FDA, however, has never approved the drug, and no firm is willing to cover the cost of sheparding the drug through the approval process when it has no patent monopoly to guarantee a return. Other firms would simply free-ride on the efforts of anyone paying the costs of obtaining approval.

such substances as well, and thus this approach is merely a stop-gap. As a world without any antibiotics approaches, people probably would seek out more vaccinations, conferring long-term protection against more serious bacterial infections. The returns to better hygiene would increase, and we might expect to see greater investments in cleanliness, both on the part of consumers and producers (e.g. restaurant employees; grocery employees).

If these measures did not work, people might limit their social interactions. Those most susceptible to sickness, especially the young and old, might risk exposure to others only when necessary. Alternatively, the vulnerable, and perhaps everyone, might wear protective gear in public. Masks covering the mouth and nose, along with gloves might be the first steps; if infectious threats become serious enough, people might don full biohazard suits, breathing only highly filtered air, drinking only highly filtered water, and never permitting any part of their skin to interact directly with the external world. Admittedly the cost of such measures in terms of inconvenience and other psychic costs are high, but in a world teeming with untreatable infectious agents, such measures could become sensible.

Perhaps, however, the premise of this article is excessively pessimistic. Although it seems undoubtedly true that individual antibiotics are exhaustible due to the evolution of resistance, the larger question is whether antibiotics as a class of drugs are exhaustible. This is as much an economic as a technical question; the key factor is the evolution of the cost of discovering novel antibacterial agents. Even if there is a unending collection of discoverable drugs, if the cost of developing successive generations of them rises extremely rapidly, then economically, if not technically, the supply of antibiotics is exhaustible.

There are some grounds to think that the cost of developing new antibiotics will rise. Scientists likely have 'picked the low-hanging' fruit over the last 60-odd years, scouring nature and finding most of the antibiotics developed naturally by molds, fungi, and other life forms that have battled bacteria for eons. There may be few such rich veins left to mine.

On the other hand, the explosion in biological knowledge and techniques (e.g., decoding bacterial DNA and determining the purpose of each gene) may reduce the cost of identifying new antibiotics. Under the best scenario, the gains from such technical process would swamp the difficulty of finding non-natural agents. In this case, antibiotics would not be exhaustible at all; they would be like any reproducible good.

Pharmaceutical companies could discover them at predictable, decreasing cost. There would be no externality from any use; pricing at marginal cost would be efficient. Government intervention would be unnecessary.

One team of economists seem to think that, if properly regulated antibiotics are more akin to a renewable fishery than an exhaustible mineral supply.[141] They build a model on the premise that antibiotics can "regenerate" their usefulness if not used too intensively.

> [T]he resource of resistance is much more similar to a renewable resource, in that it has the capacity to regenerate itself … so long as there is a more general population of pathogens from which to draw, the reduction of the antibiotic application will afford the capacity for the pathogen population to evolve in a less directed fashion … In this way, the resistant stock of a particular treatment may be considered as a renewable rather than an exhaustible resource.[142]

Their key assumption is that "there is a not insignificant fitness cost to carrying a trait that is not currently being selected for" — i.e. resistant strains are at a fitness disadvantage to their susceptible kin when there is no AB in the environment."[143] If so, then "[i]f the treatment is withdrawn before the pathogen population is wholly virulent [resistant], then the level of virulence [resistance] will again decline toward zero … ."[144] Based on their assumptions, and given a sufficient number of antibiotics, they construct an equilibrium in which the pressure for resistance can be counteracted by withdrawing each antibiotic after some period of use and waiting for its effectiveness to "recharge" as bacteria not exposed to it lose their resistance because of the costs imposed by maintaining such resistance.

The problem with this model is that its fundamental premise, that bacteria will lose resistance if an antibiotic disappears from their environment, does not appear to hold. As discussed at length earlier,[145]

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[141]Timo Goeschl & Timothy Swanson, *Lost Horizons: The Interaction of IPR Systems and Resistance Management*, Draft Feb. 2000.

[142]*Id.* 1.

[143]*Id.* 2.

[144]*Id.*

[145]Text accompany footnotes 45-66 *supra*.

recent microbiological research strongly suggests that (i) the costs of maintaining resistance are often small to begin with, and (ii) resistant bacteria frequently experience further evolution that eliminates these costs entirely. Further, resistance dissipates much more slowly than it spreads, based on the assumption that the costs of resistance in the absence of antibiotics are much less than the benefits of resistance in the presence of antibiotics.[146]

Thus it appears that the only way to 'escape' from the exhaustibility of antibiotics is to invent new ones continually. From a macroeconomic perspective, the relevant question is whether the costs of this development increase at a rate noticeably higher than the growth rate of the economy as a whole. If so, then in a real sense the cost of developing new antibiotics will become more burdensome and in effect they would be an exhaustible resource. If the costs of discovering a new antibiotics requires, e.g., half of GNP, the drug is effectively undiscoverable. It is like gold observed on Mars by a telescope. Conversely, if national income grows more rapidly than the cost of developing antibiotics, the burden of cranking out new ones will continuously lighten.

Goeschl and Swanson have expressed optimism on this score. "There is a virtually limitless number of methods for interfering in the basic processes of pathogen regeneration."[147] Oddly, these economists state this technical assertion without a word about cost. According to a group of biologists, even without considering cost, this technical assertion is questionable. "[T]here is more to be done than merely generating new antibiotics — the pace of which cannot keep up with microbial resistance responses."[148] If technical progress is no match for bacterial evolution, antibiotics indeed are an exhaustible resource.

It may be that eventually technical progress will outstrip the ability of bacteria to develop resistance, but any such happy era lies somewhere in the future. At present, many microbiologists seem to think that we face some non-trivial span of time over which the number of antibiotics will decrease rather than increase. Thus even if the long-run prognosis is rosy, it seems that at present we face a period of years over which

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[146]Bonhoeffer et al., *supra* note 88, at 12,107, 12,110.

[147]Goeschl & Swanson, supra note 141, at 5.

[148]Carlos F. Amábile-Cuevas, Maura Cárdenas-Garcia and Mauricio Ludgar *Antibiotic Resistance*, 83 AMERICAN SCIENTIST 320, 320 (1995).

antibiotics are effectively exhaustible. For this time span, then, it is sensible for public policy purposes to treat them as a depletable resource, so that we don't exhaust our supply of antibiotics before technology eventually comes to the rescue. Failing to take such precaution may leave us exposed to the threat of an untreatable plague.

V. National & International Dimensions of the Problem

Public policies to address the intensifying scarcity of antibiotics over the coming years cannot stop at state or national boundaries. Resistant bacteria do not politely respect such political borders. If any states or nations continue to use all known antibiotics indiscriminately, its citizens will serve as a breeding ground for resistant bacteria that, in today's highly connected world, will soon spread around the globe. The following subsections examine this problem at two levels. The first considers the legal grounds for national regulation of antibiotics among the several states of America. The second weighs the practical policy issues presented in trying to make sure that poor as well as wealthy nations rationalize their consumption of antibiotics.

A. National Dimensions

To the extent the national government decides employs longer-term patents to curb overuse of antibiotics, the Constitution's allocation of the patent power exclusively to the national government[149] affirms the federal government's power to act. Recent cases on state immunity from damage suits under the Eleventh Amendment might prevent Congress from authorizing damage suits against a states that decided to infringe an antibiotic patent, but the patent holder or the U.S. government could obtain an injunction ordering a state to cease production and distribution not authorized by the patentee.[150]

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[149]U.S. CONST., Art. I, § 8, cl. 8 ("The Congress shall have power to … To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries").

[150]U.S. CONST., Amend. XI ("The Judicial power of the United States shall not be construed to extend to any suit in law or equity, commenced or prosecuted against one of the United States by Citizens of another State, or by Citizens or Subjects of any Foreign State"); *Florida Prepaid Postsecondary Education Expense Board v. College Savings Bank*, 527 U.S. 627 (1999) (holding that 11th Amendment barred suits for monetary damages against states that infringe patents); *Ex Parte Young*, 209 U.S. 123

If Congress decided instead to rely on regulation, the Commerce Clause would seem to provide ample grounds to assert federal authority. The negative externality of low-value antibiotic use presents precisely the type of activity with cross-border, or spillover effects, for which the Constitution gives that federal government power to regulate under the Commerce Clause.

One scholar seems to disagree.

> Congress probably does not have the authority to regulate antimicrobial prescription practices directly; such authority rests with the states. The U.S. Food and Drug Administration (FDA) has authority to restrict the post-approval marketing of new drugs designed for treating serious or life-threatening illnesses and has indicated that these regulations can be used specifically in cases of new antimicrobial drugs .... Restricted distribution is, however, a disincentive to the development of new drugs, and the regulations do not address misuse of existing products.[151]

On a careful read, however, Fidler asserts only that the federal government might not be able to "regulate … *prescription practices* directly …" The grounds for even this narrow restriction on national power, however, are statutory, not constitutional. Although it is true that traditionally and at present the states have controlled most issues surrounding regulation of medical prescriptions, the Supreme Court's Commerce Clause jurisprudence suggests that Congress has the power to take over this arena.[152]

(1908) (subjecting state officials to injunctive orders of federal courts). Note, however, that the Supreme Court in some cases has refused to entertain requests for injunctive relief against the states. *Seminole Tribe v. Florida*, 517 U.S. 44 (1996); *Idaho v. Coeur d'Alene Tribe*, 521 U.S. 261 (1997).

[151]Fidler, *supra* note 111.

[152]The seminal modern cases defining the federal government's broad powers under the Commerce Clause are *United States v. Darby*, 312 U.S. 100 (1941) (upholding power of Congress to regulate hours and wages, even for employees of businesses with only an indirect impact on interstate commerce) and *Wickard v. Filburn*, 317 U.S. 111 (1942) (upholding application of national wheat marketing quota to farmer who consumed or sold locally his crop). Recent Supreme Court cases setting limits on the Commerce Clause have barred national regulation in areas that are not commercial in any ordinary sense of the word. *See* United States v. Lopez, 514 U.S. 549 (1995) (invalidating federal statute forbidding carrying firearms near schools); United States v. Morrison, 529 U.S. 598 (2000) (invalidating federal statute making gender-motivated violence a federal crime). Antibiotic use nationwide is a classic example of interstate

Fidler seems to have meant that *under existing federal law* — in the main, the Food, Drug, and Cosmetic Act (FDCA)[153] — the Food and Drug Administration (FDA, created under the Act) has no authority to regulate prescriptions in general.[154] The FDCA regulates safety, but not prescribing power. Thus, as long as it is legal under state law, physicians can write prescriptions "off-label" — for uses not covered under the "label" information approved by the FDA.

Other existing statutes might provide the basis for regulating the use of antibiotics. The Federal Controlled Substances Act (FCSA),[155] though designed to regulate addictive substances, does give the Attorney General the power to regulate any substance that poses a "risk to public health."[156] At present, unsurprisingly, no antibiotics appear on the list of controlled substances, but the "risk to the public health" standard sounds broad enough to regulate antibiotics; profligate use today can cause deaths in future years, the ultimate risk to public health.

Finally, if Congress decided to regulate via taxation (e.g. a pigovian tax), its power is almost plenary. In *McCray v. United States*, the Court upheld a very high federal tax on colored margarine even accepting that the sole purpose of the tax was to give the butter industry a decisive competitive advantage. "Since … the taxing power conferred by the Constitution knows no limits except those expressly stated in that instrument, it must follow, if a tax be within the lawful power, the exertion of that power may not be judicially restrained because of the results to arise from its exercise."[157] If an anti-competitive tax favoring one industry over another does not violate the taxing power, it seems almost certain that Congress has the power to impose an efficient tax designed to solve a collective action problem — such as a pigovian tax

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commerce, and thus these cases almost surely place no constraint on Congress' power to regulate the market for antibiotics.

[153]21 U.S.C. §§ 301-695.

[154]Markow supra note 97, at 541-43.

[155]21 U.S.C. §§ 801-904.

[156]21 U.S.C. § 811(c)(6). Under the Act, the Attorney General places controlled substances on "schedules," numbered one to five, with greater restrictions on use the lower the schedule number. 21 C.F.R. §§ 1308.11 (class I) - 1308.15 (class V).

[157]195 U.S. 27 (1904).

on antibiotics.

B. International Dimensions

As Fidler has observed, the problem is international: "An important feature of the latest chapter in mankind's struggle with infectious diseases is that the threat … is global in scope."[158] The United States cannot go it alone. To avoid squandering antibiotics requires all nations (each on its own, or in unison) to adopt policies that will induce or coerce consumers to refrain excessive use. If any nation, especially one of significant size, continues to use antibiotics indiscriminately, resistant strains will evolve there. As noted in the introduction to this section, the extent of international travel and trade virtually guarantees that resistant strains will have numerous opportunities to travel around the globe and threaten everyone.

The necessary cooperation does not seem like a significant problem for developed nations. With well-educated populations that democratically select leaders, and sophisticated bureaucracies to provide expertise, it should (if one believes in democracy, anyway) be possible for leaders to line up public support behind policies that will economize on antibiotic use and save lives down the road. An international accord to rationalize antibiotic use need not specify a single means of compliance; one nation might choose a pigovian tax specified in the agreement; another might prefer infinite-term patents. All that matters is that each nation limit key antibiotic usage to relatively serious cases.

Securing the cooperation of less developed nations, however, likely would be more difficult.[159] It will be harder to sell a less educated citizenry on the short-term pains necessary to achieve long-term gains in treating serious bacterial infections. And unpopular regimes might hold out cheap, easily-obtainable antibiotics as a 'goodie' compensating citizens in part for other policies its citizens find objectionable.

Even a willing government in a poorer nation might not possess the

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[158]David P. Fidler, *Return of the Fourth Horseman: Emerging Infectious Diseases & International Law*, 81 MINN. L. REV. 771, 774 (1997).

[159]Although antibiotics are widely available over-the-counter in many third-world nations, it seems likely that those most widely available are older ones for which there is already significant resistance.
http://www.woodrow.org/teachers/bi/2000/Antibiotic_Resistance/introduction.html (visited March 7, 2003). If so, antibiotic use in these nations poses a less significant threat to the effectiveness of the most valuable antibiotics.

bureaucratic machinery to implement a solution. These countries may lack the police and judicial systems necessary to make patents effective. Similarly, such nations have only rudimentary tax collection systems, and effectively imposing a pigovian tax might be beyond their capabilities. In addition, any significant tax will create a black market for which (again) there is insufficient legal enforcement to control.

These structural problems stand in the way of numerous beneficial policy reforms in the developing world, and there seems no easy solution for them. There are some economic problems with limiting antibiotic use in developing countries that may be tractable, however. The lack of health insurance will make it more difficult to assure the non-wealthy that they will receive expensive treatments if and when they need them. Any attempt to charge high prices in poorer economies will inevitably raise cries of unfairness, along with the concern that only the wealthy will ever receive treatment. Any notion that pharmaceutical giants from developed nations are making profits from the working classes in poorer nations will only exacerbate the perceived inequity.

There are a couple of ways to address this perception of unfairness. First, note that the price necessary to squelch inefficient low-value uses of antibiotics will be much lower in poor countries. Thus permitting or even encouraging and assisting price discrimination, with significantly lower prices charged in developing nations, would serve notions of fairness. It often will be in the financial interest of a patent holder to engage in such price discrimination. Wealthy countries also could address perceptions of injustice simply by donating (or selling at a deep discount) to poorer nations their estimated efficient level of antibiotics each year. The poor nations could then allocate the doses as they saw fit; for the purposes of the global battle to preserve the effectiveness of antibiotics, all that matters is that somehow governments limit the number of doses administered.

Summing over a number of antibiotics and a number of larger poor nations (e.g. China, India, Pakistan, Indonesia), the wealthy countries' pharmacy bill for gifting (or discounting) all this medicine likely would be significant. Is it worth it? One key point in answering this question is that such subsidies may be the best way, and perhaps the only way, to obtain the cooperation of poorer nations in the effort to control bacterial resistance and perhaps avoid a plague. If so, then the entire enterprise depends on this piece of the puzzle.

Subsidies to such participants are rational when, as with antibiotic resistance, the problem is such that a single weak component can

undermine the entire scheme. This situation is called a "weakest link" technology; if a single program to limit antibiotic use fails, the efforts of all other nations are futile.[160] In other situations, e.g. sending a man to the moon as soon as possible, it makes sense to go to the other extreme and concentrate all resources on a single program. This is called "best shot" technology. For situations involving weakest link technology, it can be rational for wealthier participants to subsidize the efforts of their poorer sisters. The wealthy might prefer a world where every nation pays its fair share, but that may be impossible or unlikely. Then the wealthier nations face a choice: subsidize and succeed, or don't subsidize and fail. As long as the subsidy is smaller than the gains from success, subsidy is preferable.

VI. Conclusion

Paying significant subsidies (in one form or another) to assist distant nations may be a difficult sell for politicians in the United States and other developed nations. Yet assistance that helps poorer nations rationalize their use of antibiotics provides tangible domestic benefits: protection of the donating nations (as well as the donee nations) from the spectre of untreatable bacterial infections. Failure to control antibiotic use in poorer countries will render futile all domestic policy measures adopted toward the same ends.

As for the optimal domestic policy measures, this article argues that patents of unlimited duration are an attractive option for creating property rights that solve the negative externality at the root of antibiotic overuse. In return for higher prices early in the life of the antibiotic (the "premium"), society benefits from the monopoly patent holder's incentive to stretch out the useful life of the drug ("insurance coverage"). Assuming that society is risk-averse about the possibility of depleting its arsenal of effective antibiotics, this trade-off is attractive. Note that making the patent term infinite creates less social loss for antibiotics than for most inventions, since bacterial evolution of resistance effectively

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[160]The pioneering study of "weakest-link" and related public goods "technologies" is Jack Hirschleifer, *From Weakest-Link to Best-Shot: The Voluntary Provision of Public Goods*, 41 PUBLIC CHOICE 371 (1983). The discussion in this paragraph also draws on Richard Cornes, *Dyke Maintenance & Other Stories: Neglected Types of Public Goods*, 108 Q.J. ECON. 259 (1993), and RICHARD CORNES & TODD SANDLER, THE THEORY OF EXTERNALITIES, PUBLIC GOODS, & CLUB GOODS 54-55,184-89 (2d ed. 1996).

limits the useful life of such drugs. Finally, infinite-term patents give private parties a planning horizon that may induce them to keep new antibiotics in reserve, in anticipation of the possibility of a bacterial plague.

In conjunction with unlimited patents, the government should (i) subsidize the cost of tests that determine the germ causing an infection and its drug resistances; (ii) continue to subsidize vaccinations, and provide additional subsidies for research to develop vaccines for serious bacterial infections; and (iii) invest more in gathering information about infections caused by resistant bacterial strains.

Without these or other measures (e.g. a pigovian tax) to curb overuse, society runs the real risk of a future in which some serious bacterial infections will be untreatable. Worse, if such infections spread easily, mankind could suffer a disastrous plague. The problem poses a fundamental test of democracy and leadership in wealthier nations. The root problem is one of collective action: what is individually rational, to use antibiotics whenever they might help even a little, is socially irrational. Governments exist in large part to solve such problems. Arguments against taking action to curb overuse of antibiotics reflect myopia ("I prefer cheap antibiotics (and meat) today, even if it puts my children at risk of death from a resistant bacteria in 20 years") or false economy ("Why should we subsidize citizens in poorer nations?"). Failure to act will reflect either deficient leaders unable to disabuse citizens of these misguided notions, or a dissolute populace unwilling or unable to make modest sacrifices now to limit grave future risks.

Appendix A
Deriving Results Comparing Immediate Sale of A Novel Antibiotic
With Shelving It In Anticipation of the Next Plague
(discussed in text, *supra* text accompany footnote 129)

First, define the following terms:

r = *real rate of iterest*

$\delta = \frac{1}{1+r}$ = *discount factor*

ρ = *odds of plague in a given year*

H = (*high*) *price of drug, during a plague* (assume H = 1 without loss of generality)

L = (*low*) *price of drug, during normal times* (some fraction of H, i.e. a fraction of 1)

V_w = Expected value of waiting to market until first plague

V_m = Expected value from marketing immediately

The usual manipulation of potentially infinite - term discounting equations us that Vw is given by:

$$V_w = \frac{\rho\left[(1-\rho)\delta^2\right]}{1-(1-\rho)\delta}$$

Under the assumption that r = 3%, ρ = 0.5%, and L = H/250, V_w computes to .14 (i.e. 14% of the value of being able to sell the drug immediately in a plague (high-demand) market).

Computing V_m is a bit more involved. The following explanation demonstrates how to compute the expected value for a given year, and then presents computation results for a 20-year period by summing up such terms.

Given our assumption that an antibiotic can be used against only one plague, for each year we must calculate the odds that a plague occurs first in that year; this is given for year t by

$f_t = (1 - \rho)^{t-1} \rho$

The expected payoff in such a year (low demand in all preceding years, then high plague demand in that year) is the sum of a discounted series of t-1 payments of L followed by a discounted payment of H:

$$\frac{\delta - \delta^t}{1 - \delta} L + \delta^t H$$

The expected payoff is then simply the sum of the product of these two terms over the number of years — in our case, the length of the patent period, which is roughly 20 years. There is a final term, beyond the sum, to reflect the possibility that no plague occurs within the 20-year period; the expected value in that case simply includes the discounted value of a stream of 20 payoffs in low-demand (non-plague) markets. Algebraically, we have:

$$V_m = \left[\sum_{t=1}^{20} f_t \left(\frac{\delta - \delta^t}{1 - \delta} L + \delta^t H \right) \right] + (1 - \rho)^{20} \frac{\delta - \delta^{20}}{1 - \delta} L$$

The following table shows the calculation of this sum for the parameters used above ® = 3%, ρ = .005, H = 1, L = 1/250).

Year	Odds that 1st plague occurs in this year	Discounted value if 1st plague occurs in this year	Product of Odds and Discounted Value	Comment
1	0.50%	0.971	0.0049	Plague in 1st period
2	0.50%	0.946	0.0047	Plague not in 1st period, but in 2nd
3	0.50%	0.923	0.0046	Plague not in 1st or 2nd period, but in 3rd
4	0.49%	0.900	0.0044	.
5	0.49%	0.877	0.0043	.
6	0.49%	0.856	0.0042	.
7	0.49%	0.835	0.0041	
8	0.48%	0.814	0.0039	
9	0.48%	0.794	0.0038	
10	0.48%	0.775	0.0037	
11	0.48%	0.757	0.0036	
12	0.47%	0.738	0.0035	
13	0.47%	0.721	0.0034	
14	0.47%	0.704	0.0033	
15	0.47%	0.687	0.0032	
16	0.46%	0.671	0.0031	
17	0.46%	0.655	0.0030	.
18	0.46%	0.640	0.0029	.
19	0.46%	0.625	0.0029	.
20	0.45%	0.611	0.0028	Plague not in 1st-19th year, but in 20th
	90.46%	0.060	0.0538	No plague within 20 years
			0.1281	TOTAL EXPECTED VALUE

The total expected value, about .129, is roughly 7% less than the expected value of simply waiting for the first plague before marketing, no matter

how long that might take. Thus, in a world without a time limit on patent monopolies, it would be privately rational for a patent owner to wait; this squares with the socially optimal result. Time-limited patents shorten the horizons of the patent holder and may make it privately rational (though socially undesirable) to market the antibiotic immediately.