A REVIEW AND ANALYSIS OF THE FALL AND HOPEFUL RISE OF AMERICAN HEALTHCARE

A dissertation submitted to the Caspersen School of Graduate Studies
Drew University in partial fulfillment of
the requirements for the degree,
Doctor of Medical Humanities

Steve Brozak
Drew University
Madison, New Jersey
May 2016

ABSTRACT

A Review and Analysis of the
Fall and Hopeful Rise of
American Healthcare

Doctor of Medical Humanities Dissertation by

Steve Brozak

The Caspersen School of Graduate Studies
Drew University May 2016

In spite of universal agreement that the American healthcare system has fallen into a broken series of disparate models that can't continue, there is little agreement in what can be done to fix them. This dissertation through a collective analysis attempts to undercut many standard beliefs about the relevance of science and medicine to major corporate decisions in the pharmaceutical and healthcare sector, detailing some of the effects of random serendipity on medical discoveries, and the growing and worrisome impact of direct influence from the financial sector on improvements in healthcare and treatments. It seeks to dispel and correct misconceptions regarding actual medical and organizational practices and offers as a potential solution to the chaos in decision-making along with the continuing cost increases. The advocacy is for the adoption of some of the large-scale innovative programs implemented by the Veterans Health Administration (VHA) that have shown success varying from cost containment, scientific innovation and quantifiable accomplishments in the treatment of both acute and chronic diseases.

CONTENTS

ACKNOWLEDGEMENTS

With compliments and my sincere thanks to the U.S. Department of Veterans Affairs for making this research possible.

With my love and appreciation to my wife and daughters for their support in allowing me to realize this endeavor.

INTRODUCTION

"Get your facts first, then you can distort them as you please." – Mark Twain

The main fact in healthcare innovation is that serendipity, tenacity and open-mindedness are the true drivers of initial discovery. But in the next stage, money and the certainty of making more money drive it from the laboratory to the patient. Hence a paradox exists that often distorts the drug and healthcare discovery process. In exploring this paradox, this body of work attempts to challenge the conventional wisdom surrounding drug development and healthcare overall. It does this by exploring various themes pervasive in the sector that affect discovery and its subsequent monetization.

The majority of significant healthcare breakthroughs began with U.S. Government support. A vast array of public sector initiatives supported by U.S. funding - performed both at academic and government institutions – germinated many of the blockbuster drugs that benefit the entire world.

For that reason, the first theme I explore in this compendium is the impact of the U.S. Government and its multifaceted support system for the sciences on the drug industry. The second theme goes beyond where the U.S. Government support ends, and discusses the involvement of the free markets, which includes private and public structures. Private structures include venture capital, private equity, or larger corporations that take interest in the promise of a technology. Public structures – more commonly referred to as capital markets – refer to companies that can be owned or traded in a public forum. As both a private and public interest, stakeholders play different roles at different stages of a technological innovation's life cycle. This is a crucial moment, because at both levels of investment important decisions are

made around the allocation of resources to technology. Private and public markets capital dictate what science and technology is funded with decisions driven by macro market forces.

For instance, PD-1-targeting technology has become passé, a mere two years after explosive investment in that branch of cancer immunotherapy that followed the initial breakthroughs that garnered extreme media and market attention. Soon every other company with a similar technology converted itself into a PD-1 player and began courting new money in search of a PD-1 opportunity.

Now that the PD-1 gold rush is over, investors are already beginning to shift their focus to another immune pathway to combat cancer, TIM-3, which may help improve the outcomes of a PD-1 therapy in a cancer patient. However, TIM-3 technologies have been around just as long as PD-1, but because of the lack of hyper focus from the media and the market on the latter immune target, research on the former has suffered.

This leads directly to the third theme: the business of healthcare. Decision gating on the business side is dictated by the availability of technology, the demands of the healthcare market and the realities of payment. It may have very little to do with actual science. Business decisions in healthcare, especially among drug developers, are guided by market opportunities. Whether a drug candidate has the ability to actually succeed during trials is a major factor, but it may be secondary to financial requirements and finicky market behaviors. As if to reinforce this message and personalize the consequences, one of the very professors in my last semester encapsulated the issue in a way that identifies the reality. While covered by insurance, she had received medical treatment involving a surgical procedure. The surgery was successful, but then the reality of finance kicked in and a decision had to be made in whether or not a treatment could be afforded in the

continued treatment procedure. Insurance would not cover a physician prescribed and recommended ointment that would assist the healing process and so it was done without. The reality is that hundreds-of-thousands of times daily in the US this is painful reality.

Themes four and five focus on observations on specific disease areas: promising new technologies in regenerative medicine and cancer immunotherapy, and the tougher- to-finance disease areas of anti-infectives and antivirals. Regenerative medicine and immunotherapy both have deep roots in stem cell science. It was through our understanding of stem cells – the way they behaved and operated – that we were able to crack the first codes of the human immune system, generating new compounds that could modulate the body's immune response to different diseases. The excitement in the potential of such technology, which deals with the body's own military, has allowed investment and progress in these two areas to occur rapidly.

Investment in new antibiotics and antivirals, however, is much harder due to the perception of such drugs offering limited economic opportunity. Primarily, they are perceived to be built from older technologies that are taken for a limited amount of time and for which very little can be charged. Yet, antibiotics and antivirals are perhaps the most important drugs to develop for society as pathogens evolve and gain resistance to older treatments. In recent years, the government has stepped in to keep antimicrobial innovation alive and compensate for the lack of free market investment.

All five of these themes combine to form an integral yet grossly flawed part of our healthcare system. Compared to the rest of the developed world, the U.S. spends the most and receives the poorest return on its healthcare expenditures. To better understand this incongruity it is critical to recognize that typical control policies operate with centralized

governance and rational planning that supports not only a thoughtful approach to medicine, but equally ensures accountability.

Other countries focus on cost-benefit analysis when deciding what drugs they will approve, and are often times able to negotiate drug prices, and emphasize preventative practices. Most foreign countries make decisions on what products to approve for state formularies. The state is the recognized ultimate payer in those countries, and they can and do directly negotiate prices with drug makers and hospitals, and can control the distribution.

Meanwhile, the U.S. healthcare system, underwritten but not coherently managed by our government, has more money and is easier to push into payments for a myriad of medical products that drive up costs and often have little impact on patient outcomes. That is why so many overseas drug makers devote the bulk of their resources to commercializing their products in the U.S. markets, while sales in their own countries and the rest of the world are secondary.

However, a reality of non-U.S. models is that they do not lend themselves to fostering innovation. Researchers may be driven by good-will or personal ambition. However, their discoveries do not progress without financial support. And investors are not focused on how their investment treats people, but figuring out how to get U.S. taxpayers to pay the maximum for treatment. Without the possibility of gargantuan returns on their investments, the industry does not have the incentive to develop innovative therapies, for the U.S. or for the rest of the world. And by allowing drug developers to charge exorbitant prices, the U.S. bears the burden for financially incentivizing the bulk of therapies that benefit the whole world.

So how could the U.S. lower costs that are spinning out of control without sacrificing innovation? No satisfactory body of work could end without offering a reasonable solution.

One small step is to reduce wasteful spending by employing precision medicine (i.e. the Obama administration's precision medicine initiative). For example, if a patient is admitted to a hospital with a systemic infection, they should be tested for the type of pathogen, in case an antifungal is required rather than the first-line antibiotic. Insurers and reimbursers will pay less, easing other strains in healthcare expenditures. However, the theory alone will not enact system-wide change.

The overall solution I will proffer is to explore several novel healthcare options in the most challenged medical system in the world: Veterans Affairs hospitals. They may serve as a template for the advancement of healthcare solutions for the rest of the United States—for example, numerous major medical studies show that the VA, even with budget constraints, excels in treating patients with diabetes, using evidence-based protocols and generally producing better outcomes. By testing what works in several sectors of the VA healthcare realm, we can improve the nation's healthcare system, with the best outcomes and the most rational expenditures.

CHAPTER ONE

US GOVERNMENT

Over the last half century the US Government (USG) has operated under a societal pact to provide coverage for our citizenry's healthcare needs on both a macro and micro level. The deal was made incrementally between the USG and stakeholders of the healthcare system, which include corporations, their shareholders, and, the ultimate end user, patients. Over the years the USG enacted various legislative actions and directed budget activity to benefit healthcare stakeholders and build the American pharmaceutical complex which the entire world benefits from.

A prime example on USG policy that began with good intentions only to see them abased was the enactment of an intellectual property scheme aimed to encourage drug development that allowed pharmaceutical companies to maintain monopolies over its approved products. Years of exclusivity would allow companies to recoup investment and maximize profit making. With the average cost of bringing a new drug successfully to market being well over a billion dollars today with many candidates failing, the risk/reward ratio is more attractive to drug developers with such IP considerations in place. The end result became the USG granting successful drug development companies a natural-like monopoly through the use of patents and manufacturing advantages for many years. This system of incentivizing healthcare should have been adequate in its compensation for the investment of time and the significant capital required, but what it belied was a trust in a free-market healthcare system. In theory, as patents near their expiration, drugs should decrease in price given the introduction of competitive markets. However, without the involvement of direct and aware payers (even indirect USG support), the price of these

drugs often go up, not down as seen in other industries as drug makers try to maximize profit potential. When generic drug competition does enter the market, the price and market of the original drug collapses suddenly. For major drugs, only a handful of generic competitors emerge, and only one is granted a limited 180-day exclusivity by the US Food and Drug Administration (FDA) before others are allowed to enter the market. If the original patent holder of a drug is unable to lengthen the term of its patents through modifications, it can co-opt the generic pharmaceutical companies by making deals to share revenue and create what are commonly referred to as branded-generic drugs. In such cases, the generic manufacturer delays release of its drug in exchange for hundreds of millions of dollars from the original patent holder.

The understanding that when even the most fundamental tenet of our US healthcare model has become part of a systemic USG failure means that we must analyze every other aspect of what the US Government's role is in the future of healthcare.

Restructuring the FDA

We are living in uncertain times. The U.S. domestic political environment is undergoing a major shift in the coming months. There will be a new president of the U.S. There is likely to be a significant change in the composition of the U.S. Senate and House of Representatives. Major threats to economic stability will continue with the looming prospect of a major economic downturn. International stability will continue to be threatened with regional disputes like the current one in Russia and Georgia only temporarily overshadowing U.S. military operations in Iraq and Afghanistan. Domestically, the economy is a continuing challenge from the price of oil to the ability to get a loan to send your children to college.

These challenges, breakdowns and failures may or may not be addressable by elected representatives. It is likely that out of frustration and a desire to show some positive impact they will turn to domestic agencies that they can control. One high profile target in such a situation will be the FDA.

The tangle of oversight and regulation in the U.S. food and drug industries is threatening the health and well-being of the nation. There is growing sentiment in Washington, D.C. and in the drug industry that the introduction and oversight of drugs, biologics, medical devices and the subsequent tracking of new drug side-effects has been hampered by the regulatory requirements, structure and funding of the FDA, while the oversight required to monitor the U.S. food supply has failed to keep up with changes in the agricultural industry.

In an October 2006 WBB report, titled *After the Election,* we predicted that in 2007, Congressional leaders in the House and Senate committees charged with FDA oversight would mount a campaign to reform the agency.[1] Starting in 2007, and continuing to today, members of the House of Representatives and Senate from both sides of the aisle have been determined to force changes within the FDA.

On June 26, 2008, while criticizing bonuses to FDA staffers, Rep. John D. Dingell (D-MI), the Chairman of the Committee on Energy and Commerce said, "This is yet another example of the failure of FDA management to understand that its sole purpose for existence is to protect the American people from unsafe food, drugs and medical devices."

In a March 7, 2007 letter to FDA Commissioner Andrew C. von Eschenbach, Senator Chuck Grassley (R. Iowa) made it clear that the Senate would not permit any interference with Congressional investigations of the FDA, saying,

---

[1] *After the Election*, WBB. Securities, 2006.

> Your statements are being interpreted to prohibit FDA employees from talking to Congress and threaten FDA employees who choose not to abide by your decree. I fear that, if not rescinded or clarified, your statements would have a chilling effect on FDA employees' sharing with Congress the information we need to do our jobs… They took your message to mean that their career is in jeopardy if they speak to Congress or outside the agency. To me, it demonstrates poor judgment and intolerance for dissenting opinions and an aversion to transparency… As you should know, interfering with a Congressional inquiry is against the law.[2]

Other long-term critics of the FDA include Representative Henry Waxman (D-California), chairman of the Committee on Oversight and Government Reform who recently called for the FDA to regulate the tobacco industry.

Our research leads us to believe that the need to completely reorganize functioning and structure of the agencies that oversee food and drugs will be seen as the only solution to the currently deteriorating situation and that Congressional investigations and attempts at reformation will begin sometime after this November's elections.

This paper is not an attack on the staffs at the FDA, Department of Agriculture or any of the other agencies charged with oversight of food and drugs. The tangle of regulations and divided responsibilities, which have evolved since 1862, have created an inefficient system. They need to be sorted out and organized to both utilize and regulate modern science and technology. Food and drug regulation has become a Gordian Knot[3] that must be untangled before the U.S. can be confident of its food and drug supply.

---

[2] "Grassley Says FDA Problems Need Sunshine, Calls on Commissioner to Reverse Chill Factor," *United States Senate Committee on Finance,* March 12, 2007, http://www.finance.senate.gov/ranking-members-news/grassley-says-fda-problems-need-sunshine-calls-on-commissioner-to-reverse-chill-factor.

[3] Gordian Knot is often used as a metaphor for difficult, intractable or unsolvable problems. The Gordian knot was an ancient puzzle, and according to legend, the person who unraveled it would become master of all Asia. In 333 BC Alexander tried to untie the knot, but unable to find the ends, he severed it in two with his sword.

In our opinion, and in the opinion of industry insiders with whom we have spoken, when Congress examines the functioning of food and drug regulating agencies, creation of two separate agencies with total responsibility for regulating food and drugs will be the best alternative. All authority, funding and staffing for insuring the healthfulness of the U.S. food supply would be under one agency, while responsibility for approving and monitoring drugs, biologics and medical devices would be under another agency.

Reassigning responsibilities for food and drug regulation to only two agencies would require new legislation, which would hopefully also require a sweeping change in both the responsibilities and methodologies of the agencies that oversee the nation's food, drug and medical device sources and distribution. Hopefully, such clarification of responsibilities would also simplify and expedite new drug approval, improve the ability to track unanticipated problems once a drug is in the supply-chain and insure the purity of drugs from the time their raw materials are manufactured until they go into someone's body. A more simplified structure could also save money, make it easier to track total enforcement expenses and make the agencies more nimble.

The timing of action to clarify the tangled web of oversight for food and drugs may be accelerated if there is a mass tragedy resulting from tainted food or dangerous drugs. Thus far, the U.S. has escaped a severe outbreak of disease resulting from contaminated food, but there have been several close calls, including the most recent scare over close to 1,000 cases of salmonella infection, the cause of which no one was certain after weeks of investigation.

With consolidation in the food industry, fewer producers and importers are feeding more people and a single slip-up could affect thousands. So too in the drug industry, which is rapidly becoming a global enterprise where it is impossible to identify the source of raw

materials or to trace the integrity of finished products as they travel across national borders. Contaminated, adulterated and counterfeit products become more probable as time goes by.

On July 2, the FDA announced "significant progress" on its Food Protection Plan. The FDA press release announced that it is developing a "rapid detection method using flow cytometry to identify *E. coli* and *Salmonella* in food."[4]

The FDA also reported that it is "working with industry to identify best practices for traceability" and is "collaborating with other Federal agencies; State, local, tribal and foreign governments and industry to develop the science and tools necessary to better understand the current risks of the food supply and develop new detection technologies and improved response systems that rapidly react to food safety threats."[5]

A Complex Web of Enforcement

Under the present food inspection system, twelve different agencies have responsibility for enforcing thirty federal laws.[6] Eliminating duplication would reduce or eliminate overlaps and gaps in enforcement, duplicate staffs and wasted resources.

In testimony before a Congressional Subcommittee, Lisa Shames of the Government Accountability Office (GAO) reported that the total cost for overseeing food safety in 2003 was $1.7 billion. She said, "The FDA and USDA spent most of their food safety resources, about $900 million, on inspection and enforcement, a portion of which included overlapping and

[4] FDA, "News and Announcements," *U.S. Food and Drug Administration*, http://www.fda.gov/bbs/topics/news/2008/new01856.html.

[5] Ibid.

[6] GAO Highlights, "Fundamental Restructuring Is Needed to Address Fragmentation and Overlap," http://www.gao.gov/new.items/d04588t.pdf (Accessed March 30, 2004).

duplicative inspections of 1,451 domestic food processing facilities that produce foods regulated by both agencies."[7]

Between 2001 and 2007, food imports grew seventy-five percent but FDA-inspected firms shrunk by seven percent.[8] According to a June 2008 GAO report, the number of domestic food firms within the FDA's jurisdiction increased from 51,000 to approximately 65,500 and the number of firms inspected declined from 14,721 to 14,566 over the same time period. The FDA planned to spend about $90 million over fiscal years 2008 and 2009, but the total cost to inspect every firm would be about $524 million, according to FDA estimates.

FDA in Safety Gridlock

In our opinion, over the past few years, external events have caused the FDA to become overly safety-oriented when considering applications for new medicines. The journal, *Nature Reviews Drug Discovery* reported that the U.S. FDA granted new drug approvals for only seventeen new molecular entities and two biologic license applications in 2007, the lowest number recorded since 1983.

The current obsession with safety on the part of the FDA is often blamed on the problems with Merck & Company's (MRK) non-steroidal anti-inflammatory Vioxx®. However, other drug approvals have been subject to super-vigilance, such as MRK's cervical cancer vaccine, Gardasil, which was denied approval for expanded administration. In our opinion, other decisions by the FDA are based on doctrinaire judgments, such as denial of Geron

[7] GAO Highlights, "Fundamental Restructuring Is Needed to Address Fragmentation and Overlap," http://www.gao.gov/new.items/d04588t.pdf (accessed March 30, 2004).

[8] International Economic Accounts annual tables 2001 and 2007, http://www.bea.gov/international/bp_web/simple.cfm?anon=71&table_id=20&area_id=1.

Corporation's (GERN) request to begin clinical studies for what would have been the first human Embryonic Stem Cell therapy.

The FDA standards differ from other nation's standards from time to time. The FDA gave initial approval for the GlaxoSmithKline type 2 diabetes drug, Avandia®, in 1999. However, on May 21, 2007, the FDA issued a press release stating, "Safety data from controlled clinical trials have shown that there is a potentially significant increase in the risk of heart attack and heart-related deaths in patients taking Avandia."[9] Later that year, in November, Avandia received the FDA's highest safety warning, the black boxed warning, on Avandia. A similar press release the same month by the European Medicines Agency (EMEA) considered the same clinical trials for Avandia to pose a "small increased risk" for heart attacks and heart-related deaths, and patients were advised to continue treatment but speak to doctors at their next regular visit.[10]

Staffing Churn

Another reason for super-vigilance may have to do with circumstances within the FDA. In our opinion, we may be seeing people who are close to retirement being extra careful so as not to endanger their pensions. In an April 12, 2007 speech to the Food and Drug Law Institute, Andrew C. von Eschenbach, the FDA Commissioner, presented some sobering facts about the FDA staff. He reported that FDA workers are, on average, 47.2 years old. Nearly forty-four percent are at least fifty, and fewer than four percent are less than thirty years old. Nearly fifteen percent of FDA's employees are currently eligible for

[9] FDA, "FDA Issues Safety Alert on Avandia," *U.S. Food and Drug Administration*, May 21, 2007, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108917.htm.

[10] "Press Release: EMEA Statement on Recent Publication on Cardiac Safety of Rosiglitazone (Avandia, Avandamet, Avaglim)," *European Medicines Agency*, May 23, 2007, http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500013467.pdf.

retirement, and some fourteen percent are eligible for early retirement. The Commissioner commented that "the future is more worrisome than the present, as nearly thirty percent of FDA's non-supervisors and forty-seven percent of its managers and supervisors will be eligible for retirement in the next five years."[11]

The consequence of such churn will be to place people with limited experience in decision-making positions for which they lack seasoning. These people will be operating at a level of responsibility beyond their current capabilities and the consequence will be to further slow the approval/oversight process and make FDA staffers more susceptible to influence from pharmaceutical company staff members who have more experience, especially in their specialty fields. In the words of Commissioner von Eschenbach, "In our business, experience counts for a lot, but the dearth of young talent presents a serious concern in this age when new discoveries and technologies are transforming science and medicine."[12]

As the FDA's responsibilities grew and became more complex, the staff size was reduced. In fiscal year 1994, total FDA staff size was 9,691.[13] By 2006 it had shrunk to 8,157,[14] nearly a sixteen percent reduction in staff.

---

[11] FDA, "News and Announcements," *U.S. Food and Drug Administration*, April 12, 2007, http://www.fda.gov/NewsEvents/Speeches/ucm051751.htm.

[12] Ibid.

[13] Vernon Dale Jones, *Downsizing the Federal Government* (Armonk: M.E. Sharpe, 1998).

[14] Best Places to Work, "Best Places to Work in the Federal Government," *Best Places to Work*, http://www.bestplacestowork.org/BPTW/rankings/agency.php?code=HE36&q=scores_subcomponent.

Foreign Consumerism and Competition

Regulating food supply is more critical now than at any time since the Food and Drug Act was enacted in 1906. Domestic agriculture, a foundation of the U.S. economy, is under threat from foreign competition. The three countries that are the largest exporters of food to the U.S. are ones with which the U.S. competes on many levels -- Canada, Mexico and China.[15]

Food exports also are under increasing pressure. International consumers are more selective than ever, and without assurance that foods from the U.S. are safe, they will buy elsewhere. Recent demonstrations in South Korea and import restrictions by Japan during the Mad Cow scare are evidence of suspicion of the purity of American meat and other food products by consumers in those countries.

Given the current financial trajectory in the food industries, the U.S. will have a negative balance of trade in the food manufacturing within a few years. In the ten years between 1997 and 2007 U.S. food imports rose 110 percent (from $16.5 billion to $34.7 billion) while exports grew by only fifty percent (from $25.8 billion to $38.7 billion).[16]

According to the U.S. Department of Agriculture Economic Research Service, the U.S. agricultural trade balance will decline from a $15.5 billion surplus in 2008, as bulk exports remain relatively flat while imports continue steady gains. Much of the current surplus is attributable to increased commodity costs and decreased value of the dollar.

---

[15] International Trade Administration, "U.S. Imports for Consumption and Domestic Exports tables," *International Trade Administration*, http://www.trade.gov/td/ocg/imp311.htm , http://www.trade.gov/td/ocg/exp311.htm.

[16] Ibid.

Recent Safety Failures at the FDA and Dept. of Agriculture

Within the last twelve months, the FDA and Department of Agriculture have experienced several major failures in control of food and drug quality.

- The recent heparin tragedy demonstrates the frailty of the FDA's oversight capabilities. The FDA suspects that there have been 246 heparin-related deaths though it can only substantiate 149.[17]
- Two of the three biggest meat recalls in U.S. history have occurred in the past nine months. In October 2007, Topps Meat Co. announced the recall of 21.7 million pounds of ground beef used for frozen hamburgers due to *E. coli* contamination. At the time, the Topps recall was the second largest in U.S. history. The *E. coli*-contaminated meat sickened at least 40 people in eight states.
- On Feb. 17, 2008, Hallmark/Westland Meat Packing Co. announced the recall of more than 143 million pounds of beef, the largest recall in U.S. history.
- More recently a salmonella outbreak, the source of which has not yet been identified, has sickened close to 1,000 people, demonstrating an inability both to identify sources of food contamination and to track the distribution of tainted food.
- The recent pet food poisoning from melamine contamination demonstrated a lack of oversight of foreign supplied pet food, in this case from China, while outbreaks of Mad Cow disease and fears about avian influenza contaminating the poultry and egg supply have increased attention on food safety for humans and pets.

[17] FDA, "Information on Adverse Event Reports and Heparin," *U.S. Food and Drug Administration*, http://www.fda.gov/Cder/drug/infopage/heparin/adverse_events.htm (Accessed June 16, 2008).

Four Years of Problems

Over the past four years, since Vioxx recalls, nine previously approved drugs have been removed from the market or required to print a black box warning on their labels. Vytorin, a drug that is suspected to be ineffective, came under recent scrutiny. As this report was being written, Tysabri, which had been approved in 2004, withdrawn in 2005 and re-approved in 2006, was coming under new scrutiny. The following chart identifies each of these drugs.

Table 1. Drug Approvals That FDA Has Revisited After Approval Since 2004

Drug Approvals That FDA Has Revisited After Approval Since 2004					
Drug	**Company**	**Indication**	**FDA Approval**	**Problem**	**Result**
Vioxx	Merck (MRK)	Arthritis, acute menstrual pain	May 1999	Increased risk of heart attack or stroke	Withdrawn September 2004
Cylert	Abbot Laboratories (ABT)	ADHD, Narcolepsy	1975	Risk of liver failure	Withdrawn May 2005
Paladone	Purdue Pharma, LP (Private)	Pain Management	September 2004	Fatal when taken with alcohol	Withdrawn July 2005
Tysabri	Biogen-Idec (BIIB)/ Elan (ELN)	Multiple Sclerosis	November 2004; Returned to Market July 2006*	Serious viral brain infections	Withdrawn February 2005
Ketek	Sanofi-Aventis (SNY)	Anti-bacterial	2004	Serious liver damage including 4 deaths and 1 transplant	Boxed Warning and 2 indications withdrawn January 2006
Avandia	Glaxosmithkline, plc (GSK)	Type 2 Diabetes	1999	Heart attack and heart-related death	Boxed Warning May 2007
Zelnorm	Novartis (NVS)	Constipation	July 2002	Serious risk of heart problems	Withdrawn March 2007
Trasylol	Bayer (BAY.HA)	Reduce perioperative blood loss	December 1993	50% increase in death	Market Suspension pending review November 2007
Vytorin	Merck (MRK).Schering-Plough (SGP)	cholesterol	July 2004	No more effective than off-patent Zocor and 2x as expensive	Still available

Tysabri came under scrutiny again on August 1, 2008 when two patients were diagnosed with progressive multifocal leukoencephalopathy.

Fragmented Responsibilities

Currently, responsibility for food and drugs is spread over twelve federal agencies under several separate cabinet secretaries. Following are a few examples of diffuse management of food safety.

- Poultry, meat and egg production is overseen by Food Safety and Inspection Service (FSIS) of the Department of Agriculture. According to OMB Watch, a non-profit government watchdog, the FSIS faces resource limitations that make it more difficult for the agency to ensure the safety of the food supply. Although the agency's budget has risen since it was created in 1981, staffing levels have dropped steadily, with staff openings running from ten percent to as high as twenty percent in some locations.
- All other domestic food production, and purity of imports, is overseen by the FDA, an agency of the Department of Health and Human Services.
- The Department of Commerce has responsibility for stimulating import and export business with other countries around the globe. The Department of Commerce, through the National Institute of Standards and Technology, also oversees food and drug-related issues such as food packaging, X-ray standards for mammography, standards and measurement protocols for radiopharmaceutical agents, standards for measuring cholesterol and has collaborated with the American Dental Association to create polymeric and mineral-based materials for tooth restoration and the water-driven precursor of today’s air-driven dental handpiece.

- The 2,200 Agriculture Specialists of the Customs and Border Service, part of the Department of Homeland Security, inspect agricultural products entering the U.S. at 326 land and water ports of entry.
- The National Institutes of Health, another agency of the Department of Health and Human Services, sets the standards for biosafety containment of different pathogens and specifies how they will be handled.
- The Environmental Protection Agency (EPA) is responsible for regulating use of pesticides in food and establishing maximum allowable residue levels in food and animal feed.
- The National Marine Fisheries Service (NMFS) in the Department of Commerce conducts voluntary, fee-for-service inspections of seafood safety and quality.

Brief History of the FDA

The predecessor to the FDA was established by Abraham Lincoln in 1862. He appointed chemist, Charles M. Wetherill, to create the Division of Chemistry within the Department of Agriculture. The purpose of this organization was to inspect the safety of the patent medicines, which were in widespread use throughout the U.S. at the time.

In July 1901, the division was renamed the Bureau of Chemistry. In 1906, following populist writings by Upton Sinclair and others, President Theodore Roosevelt added regulatory functions to the existing science and research-based bureau, when he signed the Food and Drug Act.

In July 1927, the Bureau of Chemistry's name was changed to the Food, Drug, and Insecticide Administration after the non-regulatory research functions were transferred

elsewhere in the department. Three years later the name was shortened to the Food and Drug Administration.

In 1938, Congress passed the Federal Food, Drug, and Cosmetic Act which contained provisions designed to replace the 1906 bill. The new law brought therapeutic devices and cosmetics under control, and it required that drugs be labeled with directions for safe use. Moreover, it mandated pre-market approval of all new drugs, formally authorized factory inspections, and corrected abuses in food packaging and quality.

The FDA transferred from the Department of Agriculture to the Federal Security Agency in 1940, and Walter G. Campbell was appointed as the first Commissioner of Food and Drugs. In 1953 the Federal Security Agency became the Department of Health, Education, and Welfare, and in 1988 the Food and Drug Administration Act officially established the FDA as an agency of the Department of Health and Human Services, its current home.

Top 25 Pharmaceutical Companies by Sales

Following is a list of the top twenty-five pharmaceutical companies by sales. Each of these companies operates in the U.S. under the regulatory control of the FDA and would be influenced by any change in oversight policy. Though individual companies may not be adversely affected by any change in regulatory oversight, as a group, the environment in which they function would change significantly, necessitating operational changes.

Table 2. Top Pharmaceutical Companies by Sales

TOP 25 PHARMACEUTICAL COMPANIES BY SALES		
Rank	Company	Total Revenue (Billions of Dollars*)
1	Johnson & Johnson (JNJ) *	53.67
2	Pfizer Inc. (PFE)	48.84
3	Glaxosmithkline plc (GSK)	45.55
4	Roche Group **	45.20
5	Sanofi-Aventis (SNY)	45.19
6	Novartis AG (NVS)	41.20
7	AstraZeneca plc (AZN)	30.27
8	Abbott Laboratories (ABT)	27.68
9	Merck & Co. Inc. (MRK)	24.19
10	Bayer HealthCare **	23.25
11	Wyeth (WYE)	23.04
12	Bristol-Myers Squibb Co. (BMY)	20.91
13	Eli Lilly & Co. (LLY)	19.73
14	Schering-Plough Corp. (SGP)	16.11
15	Amgen Inc. (AMGN)	14.73
16	Proctor & Gamble (PG) *	13.14
17	Takeda Pharmaceutical Co. **	13.05
18	Genentech Inc. (DNA)	12.18
19	Baxter International Inc. (BAX)	11.83
20	Teva Pharmaceutical Industries Ltd. (TEVA)	10.34
21	Astellas Pharma **	9.10
22	Novo Nordisk A/S (NVO)	8.90
23	Merck KGaA pharmaceutical division * **	7.93
24	Daiichi Sankyo **	7.85
25	Eisai **	6.98

*Revenue in the above chart represents only pharmaceutical/medical device revenue; non-U.S.-based companies reported revenue converted to dollars.

The Probable Outcome of the Current Circumstances

The FDA was created a little more than a century ago. In that time, the pharmaceutical industry has grown into very big business, the role of drugs in treatment of disease has changed radically and the science and technology of pharmaceuticals has become much more

complex. During the same period, every aspect of agriculture has dramatically changed. The use of pesticides and fertilizers, machinery and genetic engineering have altered and complicated the process of growing, harvesting, processing and delivering the food we eat.

The agencies that regulate food and drugs have tried to keep up with the sweeping changes in both industries but have been overwhelmed. There seems to be growing sentiment from many sources to completely review and revise the oversight of food and drugs, including a possible reorganization and redirection of the FDA, Department of Agriculture and other governmental agencies that control these vital substances.

Given the current political climate, increasing breakdowns in food and drug quality and reliability, and the potential for disastrous consequences, 2009 could be the year we see major changes in the way food and drugs are regulated in the U.S.

Trademarks
Avandia is a registered trademark of GlaxoSmithKline, plc
Vioxx is a registered trademark of Merck & Company, Inc
Companies Mentioned in this Report
Abbot Laboratories (ABT)
Amgen Inc. (AMGN)
Astellas Pharmaceuticals (Not Listed)
AstraZeneca plc (AZN)
Biogen-Idec (BIIB)
Baxter Healthcare Corporation (BAX)
Bayer (BAY.HA)
Bristol-Myers Squibb Co. (BMY)
Daiichi Sankyo Co. Ltd. (DSKYF.PK)
Elan (ELN)
Eli Lilly & Co. (LLY)
Eisai Co. Ltd. (ESALF.PK)
Genentech Inc. (DNA)
GlaxoSmithKline, plc (GSK)
Johnson & Johnson (JNJ)
Merck & Company, Inc. (MRK)
Novartis (NVS)
Novo Nordisk A/S (NVO)
Geron Corporation (GERN)
Pfizer Inc. (PFE)

Proctor & Gamble (PG)
Purdue Pharma (Private)
Ranbaxy Labs. Ltd
Roche Holding AG Div. RT (RHHVF.PK)
Sanofi-Aventis (SNY)
Schering-Plough (SGP)
Teva Pharmaceutical Industries Ltd. (TEVA)
Takeda Pharmaceutica (TKPHF.PK)
Topps Meat Co. (Not Listed)
Hallmark/Westland Meat Packing Co. (Not Listed)
Wyeth (WYE)

Why Rejecting the Healthcare Plan is Not an Option

A few years back, two days after Labor Day, when summer traditionally ends in the U.S., President Obama spoke to Congress and the nation about a public health plan. Over the summer, several arguments for and against the public plan were revealed, refuted and rejected individually. Though there are flaws in each justification for a national healthcare plan, we believe, when taken as a whole, the arguments in favor of a national health plan become overwhelming.

As business people and financial analysts engaged in the financial markets, our support of the Obama healthcare initiative is based on financial and business reasoning. Following are eight reasons why we believe it makes sense to significantly revise the way healthcare is delivered in the U.S.

1. In reality, there is no U.S. healthcare system. A system is "a group of independent but interrelated elements comprising a unified whole." What we call the U.S. healthcare system is not really a system. Interrelationships and unity in U.S. healthcare are minimal at best.

The U.S. healthcare system is really a hodgepodge of conflicting interests, each trying to extract a larger share of the huge amounts spent on healthcare in the U.S. Doctors, insurance companies, drug companies, hospitals and even university researchers, all have competing interests. The consequence of all this competition for a finite number of dollars is added cost to consumers and sub-optimized care for most patients.

2. The national cost of healthcare is unsustainable. At $2.5 trillion a year and growing, healthcare represents roughly eighteen percent of the gross domestic product. With a growth-rate faster than the GDP, the growing healthcare cost burden is unsustainable.

   The national healthcare bill is as important as a family's light bill. It must be paid to maintain quality of life, but it must be managed so that other priorities do not go unmet.

   In the final analysis, domestic healthcare expenses contribute very little to national wealth. Healthcare is a cost consumer, not a wealth generator. Unless the U.S. can keep healthcare costs at a reasonable level, they will hobble our economy.

3. The cost of healthcare is a burden on U.S. industries. Employer-sponsored health insurance covers about 158 million nonelderly people in the U.S. – more than any other source. The average family premium for company-provided health insurance is more than $12,000 - twice what it was a decade ago - and it is expected to double again in the coming decade. The Robert Wood Johnson Foundation estimates that total insurance costs for employers could reach $850

billion by 2019 while individual and family spending will jump to $550 billion. That is far more per year than the $1 trillion of national costs to which healthcare opponents are objecting.

Today, most nations with which the U.S. competes offer state-subsidized healthcare. By doing so, they relieve corporations from the cost burden of administering and providing health insurance. As a consequence, healthcare costs are shared among their entire populace and the cost to individual businesses is lower than the cost to U.S. businesses, giving foreign competitors an advantage over the U.S. in the world marketplace.

4. Forty-six million people have no health insurance in the U.S. Instead of getting preventive medical care, they are forced to wait until health issues become an emergency or a critical situation, then they go to Emergency Rooms at hospitals for care. As a consequence, these people are out of work longer, have more financial troubles and end up requiring more support from an already overburdened system.

Even people with insurance are not always able to meet their medical needs. A recent study by Harvard University found that fifty percent of all bankruptcy filings were partly the result of medical expenses. Even those on Medicare are at risk. Fidelity Investments recently estimated that elderly couples will need $250,000 in savings just to pay for the most basic medical coverage during their retirement years and many experts believe that figure is conservative.

5. Innovation in the pharmaceutical industry is being stifled because creating a drug that provides incremental improvement over existing therapeutics is better

business than creating a radically new treatment. It is more difficult to get FDA approval for radically new treatments and as a consequence, more expensive to develop. Radically new treatments often have no better return on investment than incremental improvements over existing drugs.

At a cost of close to $1 billion to bring each new drug to market, pharmaceutical companies would be foolish to roll the dice on high-risk, revolutionary drugs, when they can make acceptable profits on lower-risk improvements to existing ones. Consequently, new, pre-clinical or early-stage drugs, using new technology, often cannot get funded.

6. Doctors aren't making decisions, insurance companies are. It is the insurance companies that determine how much physicians will be reimbursed for specific treatments and it is the insurance companies that determine which treatments will be reimbursed. The consequence of insurance companies making decisions on reimbursement has been to skew coverage from preventive care to interventional care.

It is widely acknowledged that more preventive and less interventional care will cut medical costs, extend lives and improve quality-of-life. Internists and General Practitioners, who are usually the first to examine and identify problems before they become serious, are among the most overworked doctors, often seeing between forty and fifty patients a day. These doctors often have little time to counsel patients with chronic diseases like coronary artery disease, diabetes, overweight, high blood pressure and a myriad of other typical modern medical

problems. Yet it is these doctors on whom we rely for family care and intervention before sicknesses become severe.

7. Insurance companies are rewarded for inefficiency. If a doctor or hospital is not reimbursed for a treatment, it adds to the insurance company's revenue. In effect, reimbursements are a cost to insurance carriers. When benefits become costs, there is an incentive to allow the systems that administer these costs to become inefficient and perhaps prone to errors and omissions. Over the last decade, as doctors have been forced to add more staff to their operations just to recover payments from insurance companies, their costs have gone up further, making low payment specialties such as Internal Medicine or Pediatrics even more unattractive to new doctors.

   In 2007, the top five health insurance companies had total revenues of close to $405 billion with net income of close to $17 billion. If inefficient payment systems caused these insurance companies to save five percent of their revenue, the savings that would go right to the bottom line would be more than twice their total net income for the year.

8. Hospitals are being driven out of business. They are being squeezed by the requirement to treat uninsured patients and competition with non-hospital treatment centers, while reimbursements are continuously reduced. The consequence is greater financial burden on hospitals that are already in financially difficult circumstances.

   According to the American Hospital Association, thirty-two percent of all U.S. hospitals had negative margins in 2001. With the downturn in the U.S.

economy over the last year, hospital finances have gotten even worse. A survey of 736 hospitals in November 2008 showed that total margins for hospitals dropped year-over-year by more than five percent.

In this analysis, we have chosen to avoid any humanitarian justification for creating a national healthcare plan and there are many. We believe our expertise are in business and finance and we have stuck to our area of specialty. We cited eight reasons why it is important to the financial well-being of the U.S. that healthcare become a national responsibility.

Only when the healthcare burden is shared among us all, will it be universally available. Only when the healthcare responsibility is shared among us all will U.S. businesses become free from an anti-competitive burden and U.S. taxpayers free from a financial responsibility that limits their buying power.

A Deadly Loss of Confidence

It is easier to lose the public's confidence than to regain it. That is the situation in which the U.S. food and drug regulatory agencies find themselves these days. The most damming evidence that the government has lost the public confidence when it comes to drug safety is the October 8 Associated Press poll that shows thirty-eight percent of mothers would not give permission for their children to receive the 2009 H1N1 flu vaccine. Mothers were quoted as saying they were concerned about undetected complications from the vaccine that could appear weeks, months or even years later.

April 12, 1955, the day that it was announced that the Salk Vaccine was safe and effective, almost became a national holiday in the U.S. Within two years of the announcement, 100 million doses had been distributed throughout the country.

Granted that polio in 1955 was a bigger threat to the nation's children than H1N1 flu has been thus far, but the gross disparity between parental response to a new government vaccine fifty some years ago and today is dramatic and telling.

Whether it is vaccines, anti-cancer drugs or ground beef, our regulatory agencies must work overtime to regain the confidence of the American people. The risk is too great without it.

Both the CDC and the WHO have repeatedly said that flu viruses are unpredictable. They can turn from benign to deadly without warning. And a fast moving flu like H1N1 could kill scores or even hundreds of people before our systems could track the change. The only way we can achieve some measure of protection is by enough people taking the vaccine for the population to gain what is known as "herd immunity" where there are sufficient numbers of people who are immune to the disease that it cannot gain a foothold.

Today, the challenge to public health is not technology, we have an effective vaccine. It is not distribution: we soon will have 250 million doses, enough for practically every man, woman and child above the minimum vaccination age in the U.S. The critical challenge is the willingness to voluntarily accept the vaccination. We need to fix that before this virus turns or another, more deadly virus, descends on us unexpectedly.

Seeking Innovation: Incentive Funding for Biodefense Biotechs

As investment bankers, analysts, and scientists specializing in healthcare finance for the past two decades, we have witnessed the emerging challenges of funding early stage or first-in-class drug development. Scientists and biopharmaceutical firms are now subject to a growing array of financial obstacles that minimize the likelihood that novel agents will progress through the research and development pipeline and into clinical trials. It is easier to secure funding for late-stage therapeutic agents that proffer incremental improvements to their in-class counterparts, because they present less scientific and regulatory risk and offer greater risk-adjusted economic returns in established markets.[18] [19] [20] This funding paradigm is problematic not only for the advancement of basic science and translational medicine, but also for the development of biothreat countermeasures such as antibiotics, vaccines, and antitoxins. Since, as investment propositions, these agents are predisposed to less quantifiable economic returns, venture funding for their development is significantly less likely.[21] [22] [23] In a world where naturally occurring viruses such as H1N1 can quickly reach pandemic

---

[18] DC. Ackerly, AM. Valverde, LW. Diener, KL. Dossary, and KA. Schulman, "Fueling Innovation in Medical Devices (and Beyond): Venture Capital in Health Care," *Health Affairs* 28, no. 1 (2009): 68-75.

[19] JC. Greenwood, "Biotechnology: Delivering on the Promise," *Science Translational Medicine* 2, no. 13 (2010): 13.

[20] SJ. Projan, "Why is Big Pharma Getting Out of Antibacterial Drug Discovery?," *Current Opinion in Microbiology* 6 no. 5 (2003): 427-430.

[21] Ibid.

[22] PK. Russell, "Project BioShield: What It is, Why It is Needed, and Its Accomplishments So Far," *Clinical Infectious Diseases* Suppl 1 (2007): S68-S72.

[23] J. Stein, "Innovative Antibacterial Drugs: Nothing Ventured, Nothing Gained," *Expert Opinion on Investigational Drugs* 14, no. 2 (2005): 107-109.

proportions and where the materials for chemical, biological, and nuclear acts of terror are increasingly accessible to radical groups determined to destabilize civil society, the systematic absence of a coherent funding infrastructure that actively fosters the development of potential countermeasures presents a significant threat to public health and national security

In recognition of the high cost, high risk, and low profit margins associated with vaccine and antibiotic development, the U.S. government has undertaken several measures to improve its level of preparedness and to encourage the development of medical countermeasures (MCMs) for procurement. An incentive for companies to develop products, the Project BioShield Act of 2004 was passed with a $5.5 billion appropriation primarily to create a market for chemical, biological, radiological, and nuclear (CBRN) responses; it offers a guarantee that the U.S. government would procure successfully developed countermeasures for the Strategic National Stockpile (SNS). While the enactment of this program reduced some market risk, it did very little to help reduce development risk. The biodefense and translational medicine. As we have seen in aerospace, microelectronics, and other high-tech fields, leading-edge advances in science and technology for defense purposes often lead to broader commercial applications. We believe that similar results can be experienced in the domain of biotechnology. With continued research and partnerships between the public and private sectors, advances made for purposes of biodefense can readily be leveraged into broader medical applications, resulting in a tremendous benefit to public health and vice versa.[24]

[24] As an example, one of the strategic goals of BARDA has been the identification of broad-spectrum antibiotics and antivirals that combat bioterrorism. Developments in this area can be leveraged to fight antibiotic resistant strains of bacteria (eg, Methicillin-resistant Staphylococcus aureus, or MRSA), which have emerged as a significant risk to public health.

To date, these legislative efforts have had some success in procuring MCMs for the SNS that are reasonably advanced in the development pipeline. In 2007, for example, the federal government invested $505 million under Project BioShield for the development, manufacture, and purchase of twenty million smallpox vaccines for immune-compromised populations.[25]* However, despite this and similar stockpiling achievements, significant gaps remain in the government's ability to swiftly respond to emergent biothreats. These deficiencies came to light during the 2009 H1N1 influenza pandemic, as HHS procured and tested a successful vaccine candidate for H1N1 but was unable to distribute it before the virus had spread widely in the general population. Another problem specific to Project BioShield has been its inability to expand the nation's pool of anthrax vaccine suppliers beyond a single manufacturer. These and other shortcomings have cast doubt even in the White House about the ability of these government programs to meet the nation's biodefense needs.[26] [27]

Given the deficiencies in the current framework, we believe that the potential exists for an alternative funding structure that can achieve greater synergy between the public and private sectors and foster a more robust development of agents that possess dual-use capabilities in both biodefense and translational medicine. As we have seen in aerospace, microelectronics, and other high-tech fields, leading-edge advances in science and technology for defense purposes often lead to broader commercial applications. We believe that similar

[25] "First Smallpox Vaccine for Special Populations Delivered Under Project BioShield" (news release), *U.S. Department of Health and Human Services,* http://www. hhs.gov/news/press/2010pres/07/20100714c.html (accessed November 5, 2010).

*Delivery of the first million doses into the SNS occurred in May 2010. The remaining doses are expected by 2013.

[26] K. Dilanian, "Cutting Bioterrorism Funds a 'Self-Inflicted Wound,' Obama is Told," *Los Angeles Times,* July 14, 2010.

[27] A. Mundy, "Fight Breaks out Between Vaccine Firms," *Wall Street Journal*, June 28, 2010.

results can be experienced in the domain of biotechnology. With continued research and partnerships between the public and private sectors, advances made for purposes of biodefense can readily be leveraged into broader medical applications, resulting in a tremendous benefit to public health and vice versa.

Current Funding Models for Early-Phase Companies

Drug development is a high-risk, high-cost enterprise. The cost of developing each newly FDA-approved drug (taking into account development costs of failed agents) is approximately $1.3 billion (USD), with elapsed time from identifying a new molecule to approval taking ten to fifteen years. For every five drugs that enter into clinical trials, only one is eventually approved and only two out of ten generate sufficient revenue to recover the cost of their development.[28]

There is a perception that large pharmaceutical companies are powerhouses for advancing first-in-kind therapeutics based on novel technology. That is not the case. These large, publicly held companies are driven by financial metrics such as quarterly earnings-per-share. Risky or overly expensive research and development efforts adversely affect these metrics and are avoided. Thus, instead of focusing on critically needed R&D breakthroughs, large pharmaceutical companies have concentrated their efforts on increasing market size and share of existing drugs and biologics to meet their earnings goals.

In the absence of ''big pharma financing,'' venture capital (VC) investments are widely considered to be one of the most important avenues to new drug and technology

[28] "Pharmaceutical Research and Manufacturers of America," *Pharmaceutical Industry Profile 2008*, March 2008.

development. In 2007, healthcare venture financing accounted for thirty-one percent of the $30 billion in total venture investments.[29] [30] Within the pharmaceutical sector, venture capital–backed biotechnology acquisitions accounted for more than two-thirds of big pharma product pipelines, in essence supplanting in-house research and development efforts.[31] This phenomenon is so pronounced that approximately 26.1 percent of sales from the twenty largest pharmaceutical companies will be derived from in-licensed products in 2010.[32] According to the data, venture capital has become the de facto engine of product development for the majority of biopharmaceutical agents and, as a direct consequence, significantly guides the course of science and discovery, thereby directly determining the pool of new products and technologies that can be evaluated for biodefense and used for public health.

[29] DC. Ackerly, AM. Valverde, LW. Diener, KL. Dossary, and K A. Schulman, "Fueling Innovation in Medical Devices (and Beyond): Venture Capital in Health Care," *Health Affairs* 28, no. 1 (2009): 68-75.

[30] DP. Lee and MD. Dibner, "The Rise of Venture Capital and Biotechnology in the US and Europe," *Nature Biotechnology* 23, no. 6 (2005): 672-676.

[31] R. Klausner, "Translational Science: A View from a Biotechnology Investor," *Science Translational Medicine* 2, no. 34 (2010): 34.

[32] DC. Ackerly, AM. Valverde, LW. Diener, KL. Dossary, and K A. Schulman, "Fueling Innovation in Medical Devices (and Beyond): Venture Capital in Health Care," *Health Affairs* 28, no. 1 (2009): 68-75.

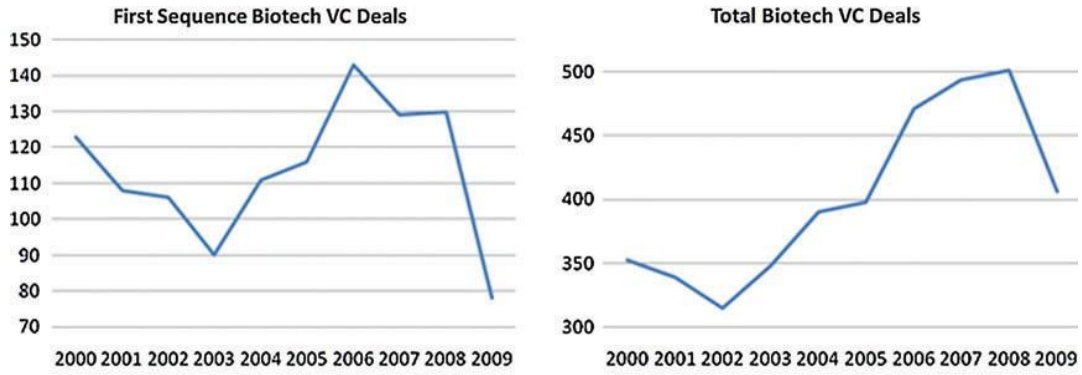


Figure 1. VC Investment in Biotech by Number of Deals 2000-2009. Color images available online at www.liebertonline.com/bsp.

The strict dependence on VC investment to drive biopharmaceutical development is particularly problematic in the current economic climate as VCs struggle to meet their fund-raising objectives. Total U.S. healthcare venture investment dropped by twenty-five to fifty percent in the final quarter of 2008. Similarly, first round VC deals in biotechnology decreased by forty percent from 130 to seventy-eight deals between 2008 and 2009 (Figure 1). Total biotechnology VC deals, including follow-on round offerings, also decreased over the same period, from 501 to 406 deals.[33] Though 2008 and 2009 were unusual recession years, a poll conducted by the National Venture Capital Association revealed that ninety percent of venture capitalists believe the number of VC firms will decline over the next five years, further reducing the availability of private capital to fund product development.[34]

In addition to bringing about an absolute reduction in venture financing within the biopharmaceutical space, the recession also highlighted how the profit maximizing objectives

[33] "VC Investments Q4 '09-Money Tree-National Data," *Price-Waterhouse Coopers/National Venture Capital Association*.

[34] "Venture Capitalists' Predictions for 2010" (press release), *National Venture Capital Association*, December 2009.

of VCs do not necessarily overlap with the government's interest in developing genuinely novel products or diverse, sustainable product pipelines. This notion is apparent as venture investors have recently sought to maximize their returns by shifting investments toward start-ups with immediate clinical assets. In 2004, seventy-seven percent of the twenty-six biotech/biopharmaceutical companies that completed IPOs (initial public offerings) had already developed a late-stage (Phase 2) lead drug, whereas only twelve percent were still at the preclinical stage with their most advanced product.[35] In the last quarter of 2008 and the first two quarters of 2009, only approximately $323 million was invested by healthcare venture capitalists in early-stage biopharmaceutical start-ups.[36]

VC firms have also become increasingly conservative in their risk tolerance.[37] Inherently higher risk practices associated with funding seed or early-stage research, which lack either proven efficacy or proven market viability, are more likely to be rejected in favor of later-stage opportunities with defined markets and predictable annual sales.[38] [39] Next-in-class drugs, in which the regulatory environment is relatively well defined, are also more likely to be supported rather than programs that rethink basic science and explore potentially new biological pathways. As a result, the chance that an investment will be made in a new

[35] A. Klausner, "Biotech Venture Capital—It's Not Too Late to be Early," *Nature Biotechnology* 23, no. 4 (2005): 417-418.

[36] BL. Booth, "Beyond the Biotech IPO: A Brave New World," *Nature Biotechnology* 27, no. 8 (2009): 705-709.

[37] P. Mitchell, "Venture Capital Shifts Strategies, Startups Suffer," *Nature Biotechnology* 27, no. 2 (2009): 103-104.

[38] JC. Greenwood, "Biotechnology: Delivering on the Promise," *Science Translational Medicine* 2, no. 13 (2010): 13.

[39] P. Mitchell, "Venture Capital Shifts Strategies, Startups Suffer," *Nature Biotechnology* 27, no. 2 (2009): 103-104.

therapeutic area has decreased in comparison to the likelihood that it will be made in a ‘‘me-too’’ product space.

From the standpoint of scientific discovery, this approach is detrimental, because it channels resources toward single, incrementally advanced technologies instead of research that has the potential to yield completely new treatment modalities and generations of rich product pipelines. This paradigm also limits the development of products for biodefense, since the expected profits resulting from government consumption may not justify the opportunity cost of forgoing the development of next-in-class drugs with a wider consumer base.[40] [41] Furthermore, this strategy effectively reduces the diversity of technologies that can be procured by the U.S. government, since only those companies that satisfy the risk profile and profit generation potential of private investors are given the opportunity to mature and develop.

A Novel Funding Source for Early-Phase Research

In light of the VC paradigm described above, innovative research and development programs that generate novel biothreat countermeasures, especially those with dual-use potential for broader public health applications, must be identified, funded, and supported financially and structurally early in the development cycle so they have the opportunity to advance to market. Otherwise, vital scientific research and development will continue to diminish. Ideally, such a funding vehicle must also save and create the type of high-tech,

[40] SJ. Projan, “Why is Big Pharma Getting Out of Antibacterial Drug Discovery?,” *Current Opinion in Microbiology* 6, no. 5 (2003): 427-430.

[41] C. Wheeler and S. Berkley, “Initial Lessons from Public-Private Partnerships in Drug and Vaccine Development,” *Bull World Health Organ* 79, no. 8 (2001): 728-734.

innovation economy jobs the U.S. needs to remain globally competitive in the biopharmaceutical space.

After researching several models of current and historical government R&D incentive programs (DeVenCI, On- Point, Red Planet, and In-Q-Tel) and grant-based financing, we believe that a U.S. government–funded Drug Development Incentive Fund (DDIF) should be created to provide risk-capital to privately held or publicly traded early-stage biotechnology and pharmaceutical companies with novel agents or technologies. We believe that the DDIF should follow the venture model as it mirrors the natural pathway for biopharmaceutical development in the U.S. and provides an opportunity for government to synergistically link with private venture firms, albeit through an intermediary. We also favor this approach in contrast to the traditional government grant structure that is commonly used to fund and advance basic science. While it is true that grants encourage scientific innovation, they do not facilitate the translation of that innovation into a commercialized product and are, at best, a passive form of investment. From our experience, a company with good science but led by managers with poor business acumen and little experience in clinical development is unlikely to successfully bring a product to market.

A structure like the DDIF is also preferred to programs such as the Defense Venture Catalyst Initiative (DeVenCI), which provides no funding at all.[42] Rather, the objective of DeVenCI is to increase Department of Defense (DoD) awareness of emerging technologies developed outside traditional DoD procurement. It acts solely as a conduit to improve communication among innovators, private venture capital, and the DoD. Without funding,

[42] DeVenCI website, T*he Defense Venture Catalyst Initiative*, http://devenci.dtic.mil/aboutus.htm (accessed November 8, 2010).

it does little to change the risk calculus associated with private investment and does not motivate venture capital to look beyond the portfolio of companies that are already considered viable investments.

Better incentive models, such as the On Point program developed by the U.S. Army and the CIA's In-Q-Tel, provide funding for technologies that directly benefit the objectives of its target organization and have wide applicability in the commercial sector. Of the two models, In-Q-Tel is of particular interest, since it has enjoyed considerable success[43] and because its investment strategy assures that demand for a technology by its primary government client, the CIA, already exists. Given the clear demand expressed by the DoD and HHS for biopharmaceutical agents that act both as a safeguard against bioterrorism and to protect against infectious agents, we believe that the In-Q-Tel model is one that should serve as the structural framework for the creation of the DDIF. We also note the investments of Silicon Valley venture capital firm Kleiner Perkins Caufield & Bauer's (KPCB) Pandemic and Biodefense Fund, a $200 million source of private capital for the sector. As we have calculated, KPCB's Biodefense Fund has to date made investments in at least five companies with applicable technologies in the space, investing heavily in vaccine technology and microbial detection device companies.[44] While these are important investments, a major differentiating characteristic of the DDIF would be its ability to take positions in companies with riskier technologies in support of novel therapies and potentially breakthrough platforms that may require longer time horizons. Additionally, the DDIF's

[43] J. Lerner, F. Hardymon, A. Laeamon, and K. Book, *In-Q-Tel* (Boston: Harvard Business School, 2005).

[44] Kleiner, Perkins, Caufield, & Byers website, *KPCB*, http://www.kpcb.com/portfolio/portfolio.php?lifescience (accessed November 8, 2010).

sole focus would center on the needs of its government clientele, and one of its primary directives would be to build substantial relationships with partnering VC's in similar endeavors, encouraging other VCs to follow the example of KPCB (see table 3).

In-Q-Tel and Government Precedent for the DDIF

In-Q-Tel is a strategic venture capital and incubation fund brought into existence in 1999 by the CIA to provide the agency with advanced communication and information technologies vital to the U.S. strategic national interest. Backed by funding appropriated by Congress, In-Q-Tel is structured as an independent, not-for-profit corporation that identifies and invests in companies developing these technologies.[45] Through its investment strategies, In-Q-Tel is able to protect and nurture technologies otherwise overlooked and undeveloped by companies pursuing wider consumer markets. By building a network of more than 150 venture capital firms, maintaining affiliations with national laboratories, and fostering university outreach programs, In-Q-Tel is strategically positioned to access new technologies and explore seeding of new start-ups.

Logistically, In-Q-Tel typically takes an interest in emerging companies at the early stage of investment, acquiring equity positions or warrants in investment targets in exchange for capital infusion. With annual appropriations of approximately $30 million, the organization is able to leverage its venture pool by attracting partnering VCs to its deals, thereby inviting more dollars to the table and creating a competitive funding environment. The majority of the companies that In-Q-Tel invests in are small, privately held organizations with advanced technologies with commercial applications. All investments center on a

[45] J. Lerner, F. Hardymon, A. Laeamon, and K. Book, *In-Q-Tel* (Boston: Harvard Business School, 2005).

working plan that links the disbursement of investment capital to mutually agreed upon milestones of product development. Furthermore, In-Q-Tel takes observer seats or full positions on the boards of its portfolio companies. This maneuver facilitates the transfer of knowledge about the product space and the special needs of the consumer.

Table 3. Funding Structures

Funding Structure	Direct Funds	Focus on Funds for Product Development	Conduit for Public/Private Finance	Guidance and Leadership for Development
NIH	Yes	No	No	No
DeVenCI	No	No	Yes	No
In-Q-Tel	Yes	Yes	Yes	Yes
BioShield	Yes	Yes	No	No
BARDA	Yes	Yes	No	No
DDIF	Yes	Yes	Yes	Yes

To ensure that target investments meet the specific needs of its client, In-Q-Tel also makes use of an Interface Center (QIC), which is comprised of CIA employees. The QIC provides a direct link to the agency and supplies a list of specific, unclassified technology needs that serve as a general focus for In-Q-Tel's investments. Perhaps more so than any other component of the In-Q-Tel structure, the direct communication established by the QIC ensures that the fund's investment philosophy remains contemporary to the immediate needs of the client and improves the chances that the right solutions are fully developed and ultimately purchased.

The Drug Development Incentive Fund

Modeled after In-Q-Tel, the DDIF would function as an independent, nonprofit organization that would be a strategic biodefense and drug development venture fund. The DDIF would follow a directive for funding set by the needs of its government clients, which would include HHS BARDA, NIH/NIAID, and potentially the DoD. The work of the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE)—composed of members from various agencies involved in biodefense preparedness, including the Centers for Disease Control and Prevention, the Food and Drug Administration, and the National Institutes of Health—could be used to establish the problem sets the DDIF would seek to address. PHEMCE, as a planning nexus, continuously manages HHS's priorities for countermeasure development. However, the DDIF would have latitude in the strategies it would employ to meet these needs.[46]

Primarily, the DDIF would be charged with generating new development programs that can seek assistance from agencies such as BARDA once they mature. While the NIH can invest in early-stage technologies, and authorities such as BARDA can continue to provide financial support for more developed technologies, we believe the DDIF, a new, potentially sustainable funding source that targets early-stage development, can provide both investment capital and strategic guidance to target companies, which government agencies are restricted in their ability to do. As a result, DDIF investment would bridge the gaps

[46] The DDIF would have wide-ranging discretion in its strategy to meet these objectives. The DDIF may be charged not only with the task of producing a medical countermeasure to a specific threat, but also for a more effective and efficient means of production and manufacture of that response, which may require strategic investments across disciplines.

in federal funding to more aggressively promote first-in-class therapeutics and technologies with potential collateral benefits for biodefense while simultaneously imparting strategic leadership to create a business infrastructure that can sustain product development. This secondary mandate is crucial since, in many instances, the development of novel biopharmaceutical technologies is not hindered by scientific or technical issues alone, but also by a failure of the underlying company to function successfully as a business or navigate the complex regulatory processes involved in drug development.

A second and collateral objective of the DDIF could be to fund early-phase R&D for novel therapeutics for public health. These opportunities (eg, new classes of antimicrobials or orphaned antimicrobials) may or may not have overlapping utility and dual use with biothreat defense, but they should demonstrate some significant benefit to translational medicine. With an emphasis on investing in technologies and biopharmaceutical agents that can successfully transition to BARDA, as well as addressing other unmet public health needs, we believe that investment by the DDIF can reduce the risk profile of its targets and attract leveraged financing from sources of private investment. Because the multiplicative effect of capital from both the federal government and private institutions will support ventures that are currently overlooked by both funding sources, we believe that the government can be more nimble in its ability to produce a robust pipeline of medical countermeasures and revolutionary biopharmaceuticals that advance translational medicine and benefit public health. Culturally, the organization should be agile and free from bureaucracy, but it must remain process oriented and results driven. Additionally, the DDIF would retain transparency and interface with government agencies that have specific,

predefined objectives for biodefense, thereby increasing the likelihood that products are developed with significant procurement potential and with wider translational applicability.

To gain public acceptance and industry legitimacy, the DDIF would be established through legislative action. In conjunction with the DDIF, a QIC-like structure (the DDIF-IC) would also be created as an internal mechanism to interface with PHEMCE and other government clients of the DDIF. This apparatus would provide the DDIF with an internal "problem set" of highly specific strategic needs pertaining to biothreat defense and public health that would guide the investment strategy adopted by the fund. Facilitated communication through an Interface Center would also minimize DDIF funding of potential investments that duplicate the ventures of other government-backed programs.

Given the exorbitant costs associated with product development, the DDIF would seek to leverage its capital investment by attracting traditional VCs and pharma venture arms to co invest in opportunities that were thoroughly evaluated by the DDIF. To maximize the likelihood of follow-on capital, the DDIF would promote transparency in its investments by specifying how a target organization and its technologies meet the needs of the problem set advanced by the DDIF-IC and outline potential transition strategies of these technologies to BARDA or other strategic partners within the federal government should a viable product emerge. Using In-Q-Tel as a guide, the DDIF would attempt to leverage its initial risk capital by at least five to one. As a percentage of the early-stage companies become successful and seek exits, the fund would be repaid like any other investor, recouping its initial investment—

perhaps by as much as ten to one in certain circumstances—and thereby replenish and grow the fund for the future.[47]

Subsequent rounds of financing from the DDIF would not be required if other VCs and government R&D programs are used for continued development. BARDA, for example, provides funding for companies with late-stage technologies and can provide contracts with milestone provisions for purchase and procurement. Cash rich and R&D poor pharmaceutical companies, starved for breakthrough discoveries, would also be logical strategic partners once promising candidates have been brought by DDIF companies to later stages, if not lured earlier by the DDIF, especially if those drugs or the platforms that were developed have applications that are relevant to broader public health needs.

After sufficient initial appropriations, the DDIF would attempt to become a self-sustaining fund. It would receive stock and warrants or hold debt like any other investor through such equity or equity-like instruments. The DDIF would experience a return on investment to be used for future investments when a portfolio company achieved a significant monetizing event such as being acquired by a larger pharmaceutical company, issuing an initial public offering, or exercising open market exit strategies. This is a significant distinguishing characteristic of the DDIF that the NIH/NIAID and BARDA lack: its ability to take an ownership and, consequently, a leadership position in a company.

[47] Despite the current state of diminished VC interest in new therapeutic areas, we believe that leverage ratios at least as high as five to one are possible for several reasons. First, we are informed by the In-Q-Tel model. During the first five years of its existence, In- Q-Tel was able to leverage its government investment by raising $300 million from private sources to co-invest in its projects. Second, initial investment by the DDIF lowers the risk profile of a company and demonstrates a clear customer demand for its biopharmaceutical agents. Third, the imprimatur of DDIF investment would mean that the company's technologies have undergone intense due diligence, thus further increasing the likelihood that private capital would experience significant returns from the commercial potential. High-yield opportunities with ten to one returns currently exist in the market, but their risk profile, sometimes by virtue of novelty, acts as a barrier to entry for private investment.

Like its deal structure, the DDIF's operational structure would follow industry practice, with a board of directors composed of well-respected members from the investment, academic, pharmaceutical regulatory, and drug development fields; a Venture Team, charged with sourcing, structuring, and negotiating deals, financial modeling, conducting due diligence, guiding companies, and protecting DDIF investments by serving on portfolio company boards as observer or voting members; a Scientific Team to evaluate projects, conduct a rigorous technical due diligence process, and ensure projects selected meet the criteria of the DDIF; and a Regulatory Team, assigned to assist portfolio companies in navigating the regulatory pathway (figure 2). Each team would be kept small to promote operational efficiency. These teams would provide valuable insight and leadership to target investment companies and further enhance the likelihood of successful product development, thus making target investments more appealing to private VCs.

The value of the regulatory component of the DDIF should not be underestimated. Private investors meet the regulatory process with open skepticism, discounting investment potential significantly by the hurdles the FDA evaluation process may include. If early in the process and short on resources, the regulatory process around drug candidates is not clearly known by company management. Companies at this stage usually outsource such functions to outside consultants who have varying degrees of expertise. DDIF's experienced regulatory guidance would provide early-stage companies with a capability that otherwise would be very costly and, depending on who is selected by companies to provide regulatory guidance, risky. A DDIF Regulatory Team would reduce the risk associated with regulatory processes that the investment community uses to discount the investment potential of

biotechnology and pharmaceutical targets, adding an additional layer of comfort for sources of private capital.

With these mandates and an appropriate structure, we believe that the DDIF is capable of altering the current funding paradigm associated with the development of novel biopharmaceuticals. Transparency in the funding process, DDIF guidance for business development, and the potential to produce technologies with broader commercial applicability would lower the risk calculus for private VCs and facilitate follow-on investment. Investment by the DDIF would also be attractive to development/early-stage companies themselves. DDIF endorsement would carry significant weight in the investor and scientific communities, validating the scientific merit and commercial potential of portfolio assets and attracting VCs and pharmaceutical venture arms to take part in the funding process. While there can never be a guarantee of product procurement, the likelihood that BARDA or some other agency will use the product for the SNS or that that the product itself has viability within broader commercial markets would be enhanced. Furthermore, DDIF endorsement would provide easier funding for early-stage companies with innovative therapeutics that otherwise would have difficulty raising capital.

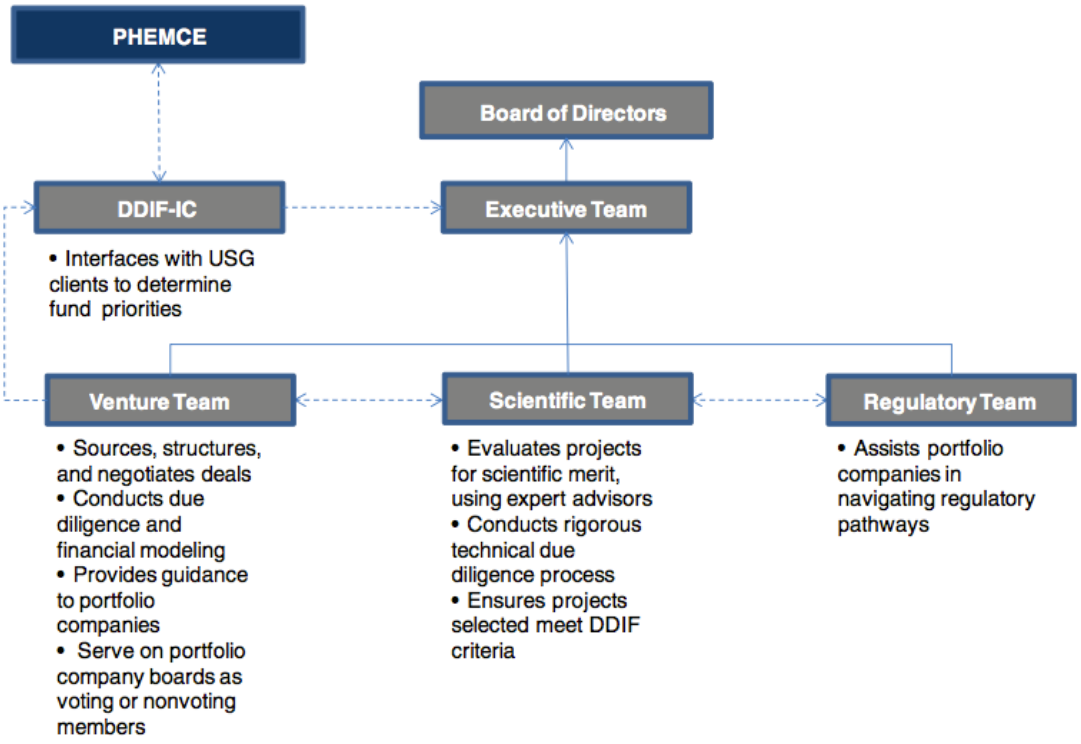


Figure 2. DDIF Organizational Structure. Color images available online at www.liebertonline.com/bsp.

Conclusion

Ultimately, by establishing a relatively modest-sized fund to stimulate early development of treatments, the U.S. government can both meet the national defense objective of creating biothreat countermeasures and stimulate development of first-in-class therapeutics that will benefit public health. With sufficient appropriations, the DDIF could invest $100 million a year for three years with partial exit strategies starting as early as year four, followed by reinvestment of newly available funds. Individual investments by the DDIF would be made in the range of $2 million to $10 million in co-investment opportunities potentially as high as $50 million to $100 million, with participating VCs providing the additional funding.

Creation of the DDIF would result in significant dividends. In a single act, this organization would secure science of national importance from disappearing, invest in projects that yield significant public health returns, advance the promises of preclinical and early phase research, revitalize biopharmaceutical investment, and create valuable innovation-economy jobs. The externality of job creation would not be trivial: venture-financed life science companies supported 493,800 jobs in 2006 and generated more than $132 billion in revenue.[48] [49] Some projections indicate that for every job in biopharmaceuticals, an additional 6.7 jobs are created in other sectors of the economy, yielding a total employment of 3.3 million jobs in the sector (2.1 percent of total U.S. employment).[50] Most important, more than 250 biotechnology products have been approved by the FDA with more than 600 new drugs in clinical trials today.[51] [52]

We note in closing that the idea of a government-backed venture fund is beginning to gain traction among policymakers in Washington, DC. In the recent HHS Public Health Medical Countermeasures Review, published in August 2010, HHS reviewed and identified several barriers to the development of a robust arsenal of medical countermeasures, including regulatory limitations, manufacturing capacity, financial

---

[48] R. DeVol, P. Wong, A. Bedroussian, et al., *Bipharmaceutical Industry Contributions to State and U.S. Economies* (Santa Monica: Milken Institute; 2004).

[49] M. Platzer, "Patient Capital: How Venture Capital Investment Drives Revolutionary Medical Innovation," *National Venture Capital Association*, http://www.nvca.org/index.php?option¼com_content&view¼article&id¼268:patient-capital- how-venture-capital-investment-drives-revolutionary-medical- innovation&catid¼40:research (accessed November 5, 2010).

[50] R. DeVol, P. Wong, A. Bedroussian, et al., *Bipharmaceutical Industry Contributions to State and U.S. Economies* (Santa Monica: Milken Institute; 2004).

[51] JC. Greenwood, "Biotechnology: Delivering on the Promise, *Science Translational Medicine* 2, no. 13 (2010): 13.

[52] *Guide to Biotechnology 2007* (Washington, DC: BIO, 2007).

incentives, and the like. In postulating a multiplicity of solutions to this problem, the review recommended that HHS consider establishing and sponsoring an independent strategic investment firm and seek any required statutory authority to implement this initiative.[53] This idea is the very essence of the DDIF that we have espoused in this article.

In summary, the DDIF provides an opportunity for advancing early medical breakthroughs where a dangerous healthcare and national security fault now exists. Using a strategy of public/private leverage, a relatively modest government investment could address this dangerous shortcoming. The original tactic of leveraging was a useful tool to increase profit and reduce risk in investments. Unfortunately, recent Wall Street abuses have made leveraging a pejorative term. With successful execution of the DDIF program, the strategy of leveraging could begin its needed rehabilitation. If the fund's investments were to result in a single drug that significantly improved the quality of health care, the total investment program could be justified even without the consideration of pharmaco-economics.

State can Boost Drugmakers' Health

These young biopharma companies are critical in their efforts to combat every kind of disease and disability.

New Jersey is still recovering from Hurricane Sandy, one of the state's worst natural disasters. It may have felt like eternity for those spending days without power or heat, yet the storm passed in just thirty-six hours. For Shore communities, recovery will take years. But there is still another disaster looming.

---

[53] "Public Health Emergency Medical Countermeasures Enterprise Review," *U.S. Department of Health and Human Services*, http://www.phe.gov/Preparedness/ mcm/enterprisereview/Pages/default.aspx (accessed November 5, 2010).

It is a man-made disaster, resulting in the loss of jobs in the pharmaceutical, biotechnology and medical device industry, often called "biopharma." New Jersey has long been the nation's so-called medicine chest, but it's being depleted as the state loses jobs and revenue.

The economic contributions of biopharma and the Jersey Shore are similar. The Shore generated $19 billion in revenue and 168,750 jobs in 2012, while New Jersey's biopharma payroll netted more than $14 billion in 2009, and supported 121,655 jobs in 2011. New Jersey is losing ground: A nationwide survey shows New Jersey dropped from second to seventh in U.S. biopharma jobs—a loss of 9,500 jobs between 2007 and 2010.

New Jersey may still be home to some of the world's biggest pharmaceutical and medical device companies, but the most dramatic biopharma advances are taking place in smaller biotechnology companies that are focused on developing a few new drugs or medical devices. These smaller, so-called "development-stage" biotech companies can grow tenfold or even a hundredfold in a few years. Celgene, headquartered in Summit, is one such company that in 1998 had a $100 million market capitalization. Today, it's valued at more than $41 billion.

These development-stage companies are critical in their efforts to combat every kind of disease and disability. They lead in treating everything from heart attacks to rejuvenating scar tissue with stem cells. They develop vaccines for cancer and novel arthritis treatments. They discover new antibiotics to combat drug-resistant bacteria.

In spite of enormous potential, these promising companies continue to be in need of early, continuous, but often modest funding.

Big pharmaceutical companies are not leaving New Jersey to go elsewhere. They're shrinking or merging because their income from blockbuster drugs is decreasing and they are choosing to save money. At the same time, early-stage biopharmaceutical companies aren't moving into New Jersey.

These young biopharma companies are critical in their efforts to combat every kind of disease and disability.

There is recognition among New Jersey's top leaders that action is needed. At the State Trade Industry BioNJ awards in early February, Lt. Gov. Kim Guadagno emphasized New Jersey's need "to improve its economic vitality, encourage job growth, streamline government and make business feel welcome again." Her speech was simple; it's critical to restore New Jersey's leadership in biopharma.

New Jersey has made efforts to stem the loss of big pharmaceutical companies through tax credits, such as the $36.6 million offered to Siemens to keep the manufacturer from moving to Indiana. Though such tax breaks continue to be necessary to retain industry, they can no longer grow industry. In this "triage" setting, a drastic step is needed. The state should provide incentives for companies that are at the forefront of biopharma to locate in New Jersey.

A bold initiative is needed to convince development-stage companies to come, at the same time, filling the state's coffers. The ideal solution would be a corporate/state cooperative investment model, rather than continued corporate relief.

Just as the state will recover much of its investment in restoring the Jersey Shore through tourism and resort spending, the state would recover more if it invests in biopharma growth. Think of what would happen if one-hundred percent of state corporate taxes paid by

large pharmaceutical companies were credited back to those companies when they partnered or invested in New Jersey-based development-stage biotech companies. Any economist will tell you that everyone wins.

Large pharmaceutical companies would get a tax inducement and would have an incentive to invest in, or partner with, smaller companies at the forefront of biopharma. Promising young companies would get funding to advance treatment of often-deadly diseases. This new source of capital would attract development-stage companies to New Jersey.

The state would get additional revenue from income and sales taxes paid by employees of New Jersey-based biopharma companies. If any of the companies became successful, large pharmaceutical companies that invested would profit, as well, and New Jersey would receive capital gains revenue at their disposition. Meanwhile, there would be increased revenue from property taxes and more traffic for local businesses.

The tax benefit is one of many potential initiatives, and several could be combined to increase rewards. One thing is certain: Action is necessary to preserve this segment of the economy and to create a new generation of businesses that will safeguard New Jersey's position as the nation's medicine chest.

A 21st Century Nosocomial Issue with Endoscopes[54]

Endoscopic procedures provide lifesaving diagnostic information, but do they put patients at unnecessary risk of deadly infection from cross contamination?

On 3 January 2014 the results of a year-long investigation by the US Centers for Disease Control (CDC) into an outbreak of New Delhi metallo-β-lactamase (NDM)-producing carbapenem resistant Enterobacteriaceae (CRE) were released. Of sixty-nine patients with confirmed CRE infections, twenty-nine went to Advocate Lutheran General Hospital (ALGH) for the same procedure—an endoscopy.[55] The endoscopy itself is not dangerous, but the current cleaning process used between procedures leaves patients susceptible to infection and troubles many healthcare practitioners.

With more than 18.6 million gastrointestinal endoscopies and at least a half million bronchoscopies every year in the US alone,[56] medical practitioners must take the utmost care during the cleaning process between patients, especially with the emergence of superbugs such as CRE. But the safety profiles of the cleaning protocols are less than acceptable in preventing life threatening outbreaks. The endoscopes are frequently the means for facilitating pathogenic cross contamination between patients—making the case at ALGH far from unique.

The threat of cross contamination may not be visible to a clinician from personal experience alone, but broader and more comprehensive studies show that the cleanliness of endoscopes varies greatly. A mid 2013 study

---

[54] Anne Marie Noronha and Steve Brozak, "A 21st Century Nosocomial Issue with Endoscopes," *British Medical Journal* (2014): 348: g2047.

[55] "Notes from the Field: New Delhi metallo-ß-lactamase–producing Escherichia coli Associated with Endoscopic Retrograde Cholangiopancreatography," *Centers for Disease Control and Prevention (CDC)*, 3 www.cdc.gov/mmwr/preview/mmwrhtml/ mm6251a4.htm (accessed January 3, 2014).

[56] AF. Peery, ES. Dellon, J. Lund, SD. Crockett, CE. McGowan, WJ. Bulsiewicz, et al., "Burden of Gastrointestinal Disease in the United States," *Gastroenterology* (2012).

reported that about fifteen percent of endoscopes in US hospitals failed to achieve an accepted standard of cleanliness after liquid reprocessing (the prevailing disinfection process used between patient procedures).[57] In this study, duodenoscopes were the dirtiest at a thirty percent contamination rate, and colonoscopes were the cleanest at a three percent contamination rate.[58]

All in all, reprocessing is time consuming, labor intensive, expensive and, most importantly, susceptible to failure. Among the most problematic features of an endoscope are the luminal channels, which often become contaminated by endoscope accessories.[59] The lumen are difficult to access and can easily harbor pathogens through multiple reprocessing procedures, even when the protocol is followed correctly.[60] Not only must the cleaning protocol be followed strictly, but the equipment and reprocessing environment also must be well maintained.[61] Disinfectants and cleaning materials for endoscopes are often contaminated themselves in these incidents.[62] Ironically, the commonly used liquid reprocessing procedure is sometimes called "liquid sterilization" even though it does not sterilize the instrument. According to guidelines from the Society of Gastroenterology Nurses and Associates, Inc. (SGNA) the protocol requires up to forty-three steps and,

---

[57] M. Bommarito, "A Multi-Site Field Study Evaluating the Effectiveness of Manual Cleaning of Flexible Endoscopes with an ATP Detection System," *APIC 2013 Annual Conference*, June 9, 2013.

[58] Ibid.

[59] R. Hervé and CW. Keevil, "Current Limitations about the Cleaning of Luminal Endoscopes," *Journal of Hospital Infection* 83 (2013): 22-9.

[60] Ibid.

[61] "Standards of Infection Control in Reprocessing of Flexible Gastrointestinal Endoscopes," *Society of Gastroenterology Nurses and Associates, Inc.*, sgna_stand_of_infection_control_0712_FINAL.pdf (accessed 2012).

[62] E. Seoane-Vazquez, R. Rodriguez-Monguio, J. Visaria, and A. Carlson., "Exogenous Endoscopy-Related Infections, Pseudo-Infections, and Toxic Reactions: Clinical and Economic Burden," *Current Medical Research and Opinion* 22 (2006): 21.

according to another study, over half an hour of labor.[63] [64] To begin, debris is removed during pre-cleaning. Next, leak testing makes sure that all internal channels are intact and that no holes contribute to instrument contamination. The scope then must be taken apart to allow access for manual cleaning, which removes any foreign material that may interfere with disinfection. The endoscope is then immersed in a high level disinfectant.[65] The disinfectant must be potent enough to remove contaminants, yet gentle enough to preserve the integrity of the instrument, since a disinfectant that is too concentrated may decrease the life span of the instrument.[66] The scope is then rinsed, dried, and stored.[67] The SGNA also offers several guidelines for maintaining the cleaning reprocessing environment to help make reprocessing as effective as possible.[68]

Regrettably, endoscope contamination is not a new phenomenon. In 2006 Seoane-Vazquez and colleagues reported meta-data analysis on all available contamination incidents in the US during the thirty-year period between 1974 and 2004.[69] Research showed that 10,989 patients were exposed to a contaminated instrument and 740 patients were contaminated (although not all reports stated how many were exposed).[70] The

---

[63] "Standards of Infection Control in Reprocessing of Flexible Gastrointestinal Endoscopes," *Society of Gastroenterology Nurses and Associates, Inc.*, sgna_stand_of_infection_control_0712_FINAL.pdf (accessed 2012).

[64] A. Krebs, JF. Borin, IY. Kim, DJ. Jackson, EM. McDougall, and RV. Clayman, "Evaluation of Practice Efficiency with a Novel Sheathed Flexible Cystoscope: A Randomized Controlled Trial," *Urology* 70 (2007): 883-887.

[65] "Standards of Infection Control in Reprocessing of Flexible Gastrointestinal Endoscopes," *Society of Gastroenterology Nurses and Associates, Inc.*, sgna_stand_of_infection_control_0712_FINAL.pdf (accessed 2012).

[66] RB. Sabnis, A. Bhattu, and M. Vijaykumar, "Sterilization of Endoscopic Instruments," *Current Opinion in Urology* 24 (2014): 195-202.

[67] "Standards of Infection Control in Reprocessing of Flexible Gastrointestinal Endoscopes," *Society of Gastroenterology Nurses and Associates, Inc.*, sgna_stand_of_infection_control_0712_FINAL.pdf (accessed 2012).

[68] Ibid.

[69] E. Seoane-Vazquez, R. Rodriguez-Monguio, J. Visaria, and A. Carlson., "Exogenous Endoscopy-Related Infections, Pseudo-Infections, and Toxic Reactions: Clinical and Economic Burden," *Current Medical Research and Opinion* 22 (2006): 21.

[70] Ibid.

implicated types of endoscopy varied. Bronchoscopy and gastrointestinal endoscopy contributed the highest numbers of incidents (see table 4); and upper GI endoscopy infected the most patients per patients exposed (see table 5).[71] The infectious agents identified the most were *Mycobacterium tuberculosis* and *Pseudomonas aeruginosa*, both of which are life threatening and have associated antibiotic resistant strains.

Owing to limited surveillance, limited reporting, and lack of immediate clinical symptoms of patients, experts agree that the endoscopic cross contamination is significantly under-reported and its incidence cannot be accurately determined.[72] Outbreaks that are recognized usually involve severe or unusual pathogens, which then prompt thorough investigations.[73] If an older patient contracts tuberculosis, a doctor is not likely to suspect that the patient's latest endoscopy is implicated, even though *M tuberculosis* transmission represents a significant

---

[71] E. Seoane-Vazquez, R. Rodriguez-Monguio, J. Visaria, and A. Carlson., "Exogenous Endoscopy-Related Infections, Pseudo-Infections, and Toxic Reactions: Clinical and Economic Burden," *Current Medical Research and Opinion* 22 (2006): 21.

[72] Ibid.

[73] Ibid.

proportion of recent outbreaks.[74] Even so, since 2000, several outbreaks of life threatening pathogens have been traced to contaminated endoscopes in facilities throughout the US and Europe.[75] [76] [77] [78] [79] [80] [81] [82] [83]

In 2009, 11,000 patients were notified of possible infection after the US Department of Veterans Affairs (VA) learned through an internal investigation that only 42.5 percent of its endoscope reprocessing units were adequately cleaning endoscopes.[84]

---

[74] E. Seoane-Vazquez, R. Rodriguez-Monguio, J. Visaria, and A. Carlson., "Exogenous Endoscopy-Related Infections, Pseudo-Infections, and Toxic Reactions: Clinical and Economic Burden," *Current Medical Research and Opinion* 22 (2006): 21.

[75] "Healthcare Inspection: Follow-up Colonoscope Reprocessing at VA Medical Facilities," *Department of Veterans Affairs Office of Inspector General*, www.va.gov/ oig/54/reports/VAOIG-09-02848-218.pdf (accessed September 17, 2009).

[76] A. Srinivasan, LL. Wolfenden, X. Song, K. Mackie, TL. Hartsell, HD. Jones, et al., "An outbreak of Pseudomonas aeruginosa Infections Associated with Flexible Bronchoscopes," *New England Journal of Medicine* 348 (2003): 221-227.

[77] PK. Tosh, M. Disbot, JM. Duffy, ML. Boom, G. Heseltine, A. Srinivasan, et al., "Outbreak of Pseudomonas aeruginosa Surgical Site Infections after Arthroscopic Procedures," *Infectious Control and Hospital Epidemiology* 32 (2011): 1179-86.

[78] JC. Cêtre, MC. Nicolle, H. Salord, M. Pérol, S. Tigaud, G. David, et al., "Outbreaks of Contaminated Broncho-alveolar Lavage Related to Intrinsically Defective Bronchoscopes," *Journal of Hospital Infection* 61 (2005): 39-45.

[79] P. Corne, S. Godreuil, H. Jean-Pierre, O. Jonquet, J. Campos, and E. Jumas-Bilak, "Unusual Implication of Biopsy Forceps in Outbreaks of Pseudomonas aeruginosa Infections and Pseudo-Infections Related to Bronchoscopy," *Journal of Hospital Infection* 61 (2005): 20-26.

[80] F. Gonzalez-Candelas, S. Guiral, R. Carbo, A. Valero, H. Vanaclocha, F. González, et al., "Patient-to-Patient Transmission of Hepatitis C Virus (HCV) during Colonoscopy Diagnosis," *Virology Journal* 7 (2010): 217.

[81] JL. Larson, L. Lambert, RL. Stricof, J. Driscoll, MA. McGarry, R. Ridzon, et al., "Potential Nosocomial Exposure to Mycobacterium Tuberculosis from a Bronchoscope," *Infectious Control and Hospital Epidemiology* 24 (2003): 825-30.

[82] C. Aumeran, L. Poincloux, B. Souweine, F. Robin, H. Laurichesse, O. Baud, et al., "Multidrug-Resistant Klebsiella pneumoniae Outbreak after Endoscopic Retrograde Cholangiopancreatography, *Endoscopy* 42 (2010): 895-899.

[83] K. Ryan, "Patients at Chanute Hospital Possibly Exposed to Hepatitis, HIV," *Wichita Eagle*, July 16, 2013, www.kansas.com/2013/07/16/2890467/patients-at-chanute-hospital-possibly. html.

[84] "VA Continues Notification process for Veterans Affected by Reprocessing Issues," *U.S. Department of Veterans Affairs*, April 3, 2009, www1.va.gov/opa/pressrel/ pressrelease.cfm?id=1661.

Because US government agencies are generally required to publicly divulge their findings, the VA's information may provide better representation of all endoscope facilities, including those that are not subject to the same mandated reporting.

Infections resulting from scope contamination break the trust between patients and doctors and place a financial burden on healthcare institutions. Two VA patients (one with hepatitis C and the other with HIV) successfully sued the federal government.[85] [86] The statute of limitations meant an unfortunate veteran who was infected with hepatitis B could not seek compensation because the time limit had expired before he learned that he had been infected.[87]

Following an outbreak last year at the Neosho Memorial Regional Medical Center, substandard scope cleaning was detected and 244 patients were notified of possible exposure to HIV, hepatitis B, and hepatitis C.[88] In 2002, an outbreak of *P aeruginosa* infected at least thirty-two of 414 exposed patients at Johns Hopkins Hospital and may have played a role in three deaths.[89] At an unnamed Texas hospital in 2009, an arthroscope transmitted the same bacteria to seven patients.[90]

---

[85] D. Smiley, "Vet Who Contracted Hep C Wins Malpractice Suit Against VA Hospital," *Miami Herald*, November 21, 2012, www.miamiherald.com/2012/11/21/3108483/vet-who- contracted hep-c-wins.html.

[86] KM. Hall, "Court Rules Against Tenn. Vet in Colonoscopy Case," *Associated Press*, June 1, 2012, http://bigstory.ap.org/article/court-rules-against-tenn-vet-colonoscopy-case.

[87] Ibid.

[88] K. Ryan, "Patients at Chanute Hospital Possibly Exposed to Hepatitis, HIV," *Wichita Eagle*, July 16, 2013, www.kansas.com/2013/07/16/2890467/patients-at-chanute-hospital-possibly. html.

[89] A. Srinivasan, LL. Wolfenden, X. Song, K. Mackie, TL. Hartsell, HD. Jones, et al., "An outbreak of Pseudomonas aeruginosa Infections Associated with Flexible Bronchoscopes," *New England Journal of Medicine* 348 (2003): 221-227.

[90] PK. Tosh, M. Disbot, JM. Duffy, ML. Boom, G. Heseltine, A. Srinivasan, et al., "Outbreak of Pseudomonas aeruginosa Surgical Site Infections after Arthroscopic Procedures," *Infectious Control and Hospital Epidemiology* 32 (2011): 1179-86.

Among those healthcare organizations that were able to determine the exact cause of their disease outbreaks, the lumen of the endoscope was most often found to be the chief culprit.[91] The lumen, through which auxiliary equipment such as biopsy forceps can be threaded, is difficult to clean and inspect, making it an easy place for bacteria to hide.[92] In 2001, three consecutive outbreaks in one French hospital were caused by a loose port at the entrance of one luminal channel.[93] The resulting infection rates were 117 out of 418 scoped patients.[94] In 2003, two implicated bronchoscopes in a different French hospital had damaged lumens, which were promptly replaced. In this incident, four of sixteen scoped patients were infected.[95]

Despite the high rate of endoscope contamination and published outbreaks resulting from such contamination, the medical community tends to attribute mishaps to negligent cleaning and human error. The Emergency Care Research Institute, which lists inadequate reprocessing of endoscopes as one of its "2014 Top 10 Technology Health Hazards," asserted that guidelines should be continuously reviewed and technicians should be better trained.[96] However, this advice is over two decades old and the problem still persists. The CDC has also been warning about cross contamination since 1991[97] and other medical organizations have concurrently

---

[91] R. Hervé and CW. Keevil, "Current Limitations about the Cleaning of Luminal Endoscopes," *Journal of Hospital Infection* 83 (2013): 22-29.

[92] Ibid.

[93] JC. Cêtre, MC. Nicolle, H. Salord, M. Pérol, S. Tigaud, G. David, et al., "Outbreaks of Contaminated Broncho-alveolar Lavage Related to Intrinsically Defective Bronchoscopes," *Journal of Hospital Infection* 61 (2005): 39-45.

[94] Ibid.

[95] P. Corne, S. Godreuil, H. Jean-Pierre, O. Jonquet, J. Campos, and E. Jumas-Bilak, "Unusual Implication of Biopsy Forceps in Outbreaks of Pseudomonas aeruginosa Infections and Pseudo-Infections Related to Bronchoscopy," *Journal of Hospital Infection* 61 (2005): 20-26.

[96] "2014 Top 10 Health Technology Hazards," *Health Devices*, Emergency Care Research Institute (ECRI) (2013). www.ecri.org.

[97] "From the Centers for Disease Control (CDC). Nosocomial Infection and Pseudoinfection from Contaminated Endoscopes and Bronchoscopes—Wisconsin and Missouri," *JAMA* 266 (1991): 2197-2198.

tightened procedural guidelines.[98] [99] Meanwhile, the proportion of incidents caused by equipment defects and cleaning equipment contamination (not human error) has since risen, according to the thirty year US based study.[100] Additionally, not all incidents covered in the study were reported to have had an in-depth investigation into the causality of events; thus, human error could be an assumption in many of the cases.[101]

As past experience demonstrates, even the most stringent liquid reprocessing guidelines do not prevent outbreaks. The complexity of reprocessing protocols and the intricacy of endoscope design are inherent flaws, because they foster statistically predictable failures that allow pathogens to persist on the endoscope, particularly in the luminal channels[102] [103] [104] and in the cleaning equipment and detergent.[105]

---

[98] S. Banerjee, B. Shen, DB. Nelson, DR. Lichtenstein, TH. Baron, et al., "Infection Control During GI Endoscopy," *ASGE Standards of Practice Committee, Gastrointestinal Endoscopy* 67 (2008): 781-790.

[99] "Choice Framework for Local Policy and Procedures 01-06—Decontamination of Flexible Endoscopes: Operational Management," *U.K. Department of Health* (2013), www. gov.uk/government/uploads/system/uploads/attachment_data/file/192522/ Decontamination_of_flexible_endoscopes.pdf.

[100] E. Seoane-Vazquez, R. Rodriguez-Monguio, J. Visaria, and A. Carlson., "Exogenous Endoscopy-Related Infections, Pseudo-Infections, and Toxic Reactions: Clinical and Economic Burden," *Current Medical Research and Opinion* 22 (2006): 21.

[101] Ibid.

[102] Hervé and CW. Keevil, "Current Limitations about the Cleaning of Luminal Endoscopes," *Journal of Hospital Infection* 83 (2013): 22-29.

[103] JC. Cêtre, MC. Nicolle, H. Salord, M. Pérol, S. Tigaud, G. David, et al., "Outbreaks of Contaminated Broncho-alveolar Lavage Related to Intrinsically Defective Bronchoscopes," *Journal of Hospital Infection* 61 (2005): 39-45.

[104] P. Corne, S. Godreuil, H. Jean-Pierre, O. Jonquet, J. Campos, and E. Jumas-Bilak, "Unusual Implication of Biopsy Forceps in Outbreaks of Pseudomonas aeruginosa Infections and Pseudo-Infections Related to Bronchoscopy," *Journal of Hospital Infection* 61 (2005): 20-26.

[105] E. Seoane-Vazquez, R. Rodriguez-Monguio, J. Visaria, and A. Carlson., "Exogenous Endoscopy-Related Infections, Pseudo-Infections, and Toxic Reactions: Clinical and Economic Burden," *Current Medical Research and Opinion* 22 (2006): 21.

One of the very few positive outcomes of a contamination incident is the change of disinfection practices that follows. After its superbug outbreak, the ALGH switched to ethylene oxide gas sterilization.[106] Alternatively, several other facilities in the US and the UK have begun using sterile disposable sheaths on scopes and have reported improvements in safety.[107] [108] [109] [110]

The sheath provides a single use sterile barrier between the scope and the patient without hindering functions such as visualization and biopsies. The device incorporates a sterile "working channel" that allows equipment such as biopsy forceps to pass through unhindered.[111] Studies show that using the sheath, along with a simple alcohol wipe down between uses, guarantees sterility, offering a vast improvement over current decontamination procedures.[112] [113] Even if there is a defect in the integrity of a single sheath, research confirms that the second sheath prevents contaminants from infecting the next patient.[114] The central idea behind the sheath is that a pathogen cannot overcome it. Because each sheath is used only once, pathogens cannot hide on the

---

[106] "Notes from the Field: New Delhi metallo-ß-lactamase–producing Escherichia coli Associated with Endoscopic Retrograde Cholangiopancreatography," *Centers for Disease Control and Prevention (CDC),* 3 www.cdc.gov/mmwr/preview/mmwrhtml/ mm6251a4.htm (accessed January 3, 2014).

[107] A. Krebs, "Evaluation of Practice Efficiency with a Novel Sheathed Flexible Cystoscope: A Randomized Controlled Trial," *Urology* 70 (2007): 883-887.

[108] KH. Baker, MP. Chaput, CR. Clavet, GW. Varney, TM. To, and CD. Lytle, "Evaluation of Endoscope Sheaths as Viral Barriers," *Laryngoscope* 109 (1999): 636-639.

[109] N. Lawrentschuk and M. Chamberlain, "Sterile Disposable Sheath System for Flexible Cystoscopes," *Urology* 66 (2005): 1310-1313.

[110] D. Gupta, A. Srirajakalidindi, and H. Wang, "Reduced Turnover Times Make Flexible Optical Reusable Scope with EndoSheath® Technology Significantly Cost-Effective," *Journal of Biomedical Research* 26 (2012): 241-247.

[111] Ibid.

[112] N. Lawrentschuk and M. Chamberlain, "Sterile Disposable Sheath System for Flexible Cystoscopes," *Urology* 66 (2005): 1310-1313.

[113] SC. Winter, A. Thirwell, and P. Jervis, "Flexible Nasendoscope with a Disposable-Sheath System Versus Standard Nasendoscopy: A Prospective, Randomized Trial," *Clinical Otolaryngology and Allied Sciences* 27 (2002): 81-83.

[114] KH. Baker, MP. Chaput, CR. Clavet, GW. Varney, TM. To, and CD. Lytle, "Evaluation of Endoscope Sheaths as Viral Barriers," *Laryngoscope* 109 (1999): 636-639.

outside of sheaths or become resistant to disinfecting liquids. One added benefit to using sheaths, which no other decontamination protocol offers, is protection against prions, such as that which causes Creutzfeldt-Jakob disease.[115]

By using sheathed endoscopes, healthcare facilities will spend less on labor and equipment[116] [117] and avoid exposure to noxious chemicals.[118] [119] Although acquiring new endoscopes that accommodate sheaths may require an initial investment, the scopes are less expensive than unsheathed models and better in terms of long term benefits in patient care, efficiency, and lower operating costs.[120] The sheath eliminates unreliable and cumbersome reprocessing, condensing the protocol into just a few steps, and reduces reprocessing time by up to

---

[115] SC. Winter, A. Thirwell, and P. Jervis, "Flexible Nasendoscope with a Disposable-Sheath System Versus Standard Nasendoscopy: A Prospective, Randomized Trial," *Clinical Otolaryngology and Allied Sciences* 27 (2002): 81-83.

[116] A. Krebs, "Evaluation of Practice Efficiency with a Novel Sheathed Flexible Cystoscope: A Randomized Controlled Trial," *Urology* 70 (2007): 883-887.

[117] D. Gupta, A. Srirajakalidindi, and H. Wang, "Reduced Turnover Times Make Flexible Optical Reusable Scope with EndoSheath® Technology Significantly Cost-Effective," *Journal of Biomedical Research* 26 (2012): 241-247.

[118] A. Krebs, "Evaluation of Practice Efficiency with a Novel Sheathed Flexible Cystoscope: A Randomized Controlled Trial," *Urology* 70 (2007): 883-887.

[119] N. Lawrentschuk and M. Chamberlain, "Sterile Disposable Sheath System for Flexible Cystoscopes," *Urology* 66 (2005): 1310-1313.

[120] D. Gupta, A. Srirajakalidindi, and H. Wang, "Reduced Turnover Times Make Flexible Optical Reusable Scope with EndoSheath® Technology Significantly Cost-Effective," *Journal of Biomedical Research* 26 (2012): 241-247.

thirty-one minutes. [121] It also is more cost effective, reduces repair costs, and decreases investment in multiple scopes that are out of operation while being cleaned.[122] [123] [124]

Other sterilization methods exist for endoscopes, but each has its drawbacks in terms of safety, efficiency, and cost. Ethylene oxide gas sterilization is a toxic and carcinogenic process, requiring additional time for a post-sterilization aeration period.[125] Hydrogen peroxide gas plasma sterilization also has a long processing time, is expensive, and can be corrosive to certain materials. Neither of these methods protects against prions.[126]

The advent of antibiotic resistant bacteria such as CRE and deadly viruses requires that cleaning standards be continuously improved. Just about every invasive instrument we use is sterilized better than the endoscope. Syringes and needles are almost universally disposable and many surgical instruments are subjected to intense heat and pressure between uses. Endoscopy demands the same standards, because the instruments come into contact with or break the delicate mucosal membranes.

In 2013, the UK Department of Health (DH) recommended a "tracking, traceability and audit trail" designed to systematically expose instances of cross contamination before becoming widespread.[127] US

---

[121] A. Krebs, "Evaluation of Practice Efficiency with a Novel Sheathed Flexible Cystoscope: A Randomized Controlled Trial," *Urology* 70 (2007): 883-887.

[122] Ibid.

[123] N. Lawrentschuk and M. Chamberlain, "Sterile Disposable Sheath System for Flexible Cystoscopes," *Urology* 66 (2005): 1310-1313.

[124] D. Gupta, A. Srirajakalidindi, and H. Wang, "Reduced Turnover Times Make Flexible Optical Reusable Scope with EndoSheath® Technology Significantly Cost-Effective," *Journal of Biomedical Research* 26 (2012): 241-247.

[125] RB. Sabnis, A. Bhattu, and M. Vijaykumar, "Sterilization of Endoscopic Instruments," *Current Opinion in Urology* 24 (2014): 195-202.

[126] Ibid.

[127] "2014 Top 10 Health Technology Hazards," *Health Devices*, Emergency Care Research Institute (ECRI) (2013), www.ecri.org.

outbreaks between 2000 and 2004 lasted an average of eighty-four days,[128] and the recent CRE outbreak at ALGH lasted the full year,[129] highlighting the importance of a vigilant surveillance system. The system proposed by the DH will provide the medical community with a more accurate and active survey of epidemiology, and hopefully push its constituents to replace liquid decontamination with a more effective alternative.

The *BMJ* is an appropriate venue for this discussion because of its undeterred criticism of conformist practices with the intent of improving healthcare. In 2012, the *BMJ* addressed nosocomial infection in an article titled "Dirty, deluded and dangerous" by Gary L French,[130] which exposed the recent trend of doctors who wash their hands much less frequently than expected.[131]

The issue of scope cross contamination and the growing incidence of negligence in hand washing have a common historical background. In the 1800s, most European physicians rejected the theories of Ignaz Semmelweis,[132] who proposed that hand washing would lower the postpartum mortality rate.[133] Since the advent of antibiotics, doctors have paid less attention to the value of meticulous sterilization.[134] However, with the recent appearance of superbugs, we need to be more mindful of careful sterilization.

---

[128] E. Seoane-Vazquez, R. Rodriguez-Monguio, J. Visaria, and A. Carlson., "Exogenous Endoscopy-Related Infections, Pseudo-Infections, and Toxic Reactions: Clinical and Economic Burden," *Current Medical Research and Opinion* 22 (2006): 21.

[129] "Notes from the Field: New Delhi metallo-ß-lactamase–producing Escherichia coli Associated with Endoscopic Retrograde Cholangiopancreatography," Centers for Disease Control and Prevention (CDC), 3 www.cdc.gov/mmwr/preview/mmwrhtml/ mm6251a4.htm (accessed January 3, 2014).

[130] GL. French, "Dirty, Deluded, and Dangerous," *BMJ* 345 (2012): e8330.

[131] JM. Boyce and D. Pittet, "Guideline for Hand Hygiene in Health Care Settings. Recommendations of the Healthcare Infection Control Practice Advisory and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force," *Infection Control and Hospital Epidemiology* 23 (2002): S3-40.

[132] KC. Carter and BR. Carter, *Childbed Fever: A Scientific Biography of Ignaz Semmelweis* (Transaction Publishers, 2005).

[133] CH. Routh and MD. Loud, "On the Causes of the Endemic Puerperal Fever of Vienna," *Lancet* 1848;2:642-3.

[134] GL. French, "Dirty, Deluded, and Dangerous," *BMJ* 345 (2012): e8330.

We must not make the same mistake as Semmelweis's contemporaries, who remained passive as their patients suffered the consequences of doctors with dirty hands while a simple, lifesaving alternative was sensible, affordable, and available. Like hand washing in Semelweis's day, better procedures for cleansing and even sterilizing scopes between uses are mandatory to prevent cross contamination, prevent infection, and potentially save lives.

Table 4. Patients exposed to endoscope related contamination by type of intervention (1974-2004

Intervention	Outbreaks reporting patients
Arthroscopy	1
Bronchoscopy	35
Cystoscopy	3
Endoscopic retrograde	7
Lower gastrointestinal endoscopy	12
Upper gastrointestinal endoscopy	10
Gastrointestinal endoscopy*	1
Total	69

*Outbreaks not included in lower or upper GI endoscopy.
Data only include outbreaks that also report patients exposed.
Adapted from: E. Seoane-Vazquez, R. Rodriguez-Monguio, J. Visaria, and A. Carlson., "Exogenous Endoscopy-Related Infections, Pseudo-Infections, and Toxic Reactions: Clinical and Economic Burden," *Current Medical Research and Opinion* 22 (2006): 21.

Table 5. Ratio of patients exposed to patients contaminated by type of intervention

Intervention	Number of	Number of	Number	%
Arthroscopy	1	352	7	2.0
Bronchoscopy	15	4001	270	6.7
Cystoscopy	2	773	25	3.2
Endoscopic	4	554	38	6.9
Lower	4	4179	42	1.0
Upper	3	1130	107	9.5
Total	29	10<thin>989	489	4.4

*Note: Data only include outbreaks that report patients exposed and patients contaminated.
Adapted from: E. Seoane-Vazquez, R. Rodriguez-Monguio, J. Visaria, and A. Carlson., "Exogenous Endoscopy-Related Infections, Pseudo-Infections, and Toxic Reactions: Clinical and Economic Burden," *Current Medical Research and Opinion* 22 (2006): 21.

Harvard Professors Balk as Obamacare Comes to Cambridge[135]

Challenging Obamacare is sure to be one of the top priorities of the newly convened 2015 Congress. With Republican majorities in both the House of Representatives and the Senate, bills that attempt to chip away at what is formally known as the Patient Protection and Affordable Care Act are likely to be regularly launched at the White House. Ironically, the ammunition for overturning Obamacare could come from one of the institutions whose economists heartily endorsed it.

Harvard faculty members were among those consulted about the Affordable Care Act while it was being written and the Act's impact has caused dissension among the ranks of the faculty. Changes are being made to Harvard's health plan to bring it into line with one of the controversial elements of the law, the so-called Cadillac tax on health plans, which goes into effect in 2018. The Cadillac tax is a forty percent surcharge on health-insurance spending above $27,500 for a family or $10,200 for an individual, and most institutions, including Harvard, are not willing to pay it. Most for-profit and non-profit companies are adjusting their employee health insurance benefits to avoid the increased cost of the Cadillac tax.

Healthcare insurance is big business. The top ten healthcare insurers posted 2012 revenue of $267 billion. The two publicly traded healthcare insurers with the most revenue – Humana, Inc. (NYSE:HUM) and Aetna, Inc. (NYSE:AET)—each reported more than $21.7 billion in revenue, with each representing 3.8 percent of the total healthcare insurance market,

---

[135] Steve Brozak, "Harvard Professors Balk as Obamacare Comes to Cambridge," *Forbes.com*, July 9, 2015, https://www.google.com/url?q=http://www.forbes.com/sites/stephenbrozak/2015/01/09/harvard-professors-balk-as-obamacare-comes-to-cambridge/%23579f1dda61c2&sa=D&ust=1461915775557000&usg=AFQjCNF7rR88VDYRSPus1QhuweSJGi-krA.

ranking fourth and fifth in total healthcare insurance revenue. Harvard's healthcare provider, Harvard Pilgrim Healthcare, is a small, private company, insuring 1.2 million people with $2.6 billion in 2013 revenue.

The Harvard arts and science faculty unanimously condemned the change in their insurance plan, reflecting the pain that people in business experienced a few decades ago when corporations put a cap on how much they would pay for employee healthcare and began shifting healthcare costs to employees through higher premiums, higher deductibles and higher co-payments. Elite institutions and privileged people in business were exempt from the added costs to employees until now. In this case, the Affordable Care Act may be forcing Harvard dons to experience the healthcare system in the same way as others do.

Harvard full professors, who make close to $200,000 a year, and assistant professors, who make around $100,000 thousand per year, will continue to have a generous healthcare package. Premiums will be reduced in 2015 and coverage will include a maximum of $250 in deductibles per year for medical appointments, and ninety percent coverage of treatment costs after the deductible is met. Total out-of-pocket costs are capped at $1,500 a year for individuals and $4,500 a year for families of three or more. This is in keeping with what employees must now pay out of pocket due to changes caused by Obamacare at large corporations like Bristol-Myers Squibb Company (NYSE:BMY) and PNC Financial Services Group, Inc. (NYSE:PNC) where premiums and out of pocket expenses have increased. Premiums are also increasing for the most popular healthcare plan offered by the largest U.S. employer, Wal-Mart Stores, Inc. (NYSE:WMT). Wal-Mart provides healthcare insurance to 1.2 million of its more than 1.3 million employees with significantly higher

deductibles, co-payments and out-of-pocket maximums than the Harvard faculty members pay.

What the Harvard faculty is now learning is that the U.S. healthcare system is complex. There are many players with different agendas – doctors, hospitals, insurance companies, pharmaceutical manufacturers and corporations that buy insurance all have a stake in the $2.9 trillion healthcare economy. Unintended consequences are inevitable; make one change here and it is likely to affect something else over there. Trying to figure it out is like the proverbial group of blind men trying to describe an elephant.

In the case of the Harvard faculty one must ask if they are making a bold stand for egalitarian healthcare coverage or whining because they are being required to share the cost of healthcare. Most employees have had to wrestle with the confusing and often gut-wrenching impact of increasing healthcare costs for many years now. It is time that those in the ivory tower experience some of the challenges most of us face daily.

Obama's New Healthcare Proposal: A Precise Vision or A Political Football[136]

When President Obama unveiled his Precision Medicine Initiative, he declared a two-fold challenge. The first was a challenge to advance healthcare technology. The second was directed at his critics to support or work with him on addressing one of the most significant budgets in recent memory. Unfortunately, the latter challenge of cooperation on the overall

[136] Steve Brozak, "Obama's New Healthcare Proposal: A Precise Vision or a Political Football," Forbes.com, February 3, 2015, https://www.google.com/url?q=http://www.forbes.com/sites/stephenbrozak/2015/02/03/obamas-new-healthcare-proposal-a-precise-vision-or-a-political-football/%23336958385b5b&sa=D&ust=1461915775555000&usg=AFQjCNFx_KtTF9DNP3Gcauf4PSJ8-EzDig.

budget puts the former challenge of a scientific initiative into the realm of simply becoming an unfunded mandate.

With more than three quarters of the Obama presidency completed, both his opponents and supporters entirely agree that he has attempted to make change in healthcare a cornerstone of his legacy. If they are candid, they also will agree that any positive change in healthcare demands a level of innovation that we seldom see.

This is the crux of the disagreement between the two political parties. All sides agree that change needs to be made to our healthcare system to improve the quality of care people receive, to expand the boundaries of modern medicine into new realms, and to hold down, if not bring down, costs. The points of disagreement are what the changes should be and how they should be implemented. The outcome will determine not only what the last two years of the Obama tenure looks like, but also how U.S. healthcare will function and evolve for generations to come.

As modern research and development initiatives go, $215 million for the President's Precision Medicine Initiative is a small amount and it is divided in descending order of funding among the National Institutes of Health (NIH), the National Cancer Institute, which is a part of the NIH, the FDA and the Office of the National Coordinator for Health and Information Technology, which are units within the Department of Health and Human Services. Without definitive additional financial support to these organizations, the funding is almost certain to become another series of unfunded mandates versus an innovative blueprint that U.S. healthcare desperately needs.

What becomes apparent when examining this initiative and is even more problematic than its size and fragmentation, is the decline of dollars available for research for over a

decade. The budget for the National Institutes of Health has been cut eight of the nine years between 2004 and 2013 by a total of twenty-eight percent in constant 2003 dollars. At the same time, the cost of research has risen, resulting in a severe reduction in the breadth of our national healthcare research.

The Precision Medicine initiative has at its heart an innovative spirit but innovation is much different than people think. While innovation and vision are commonly found buzzwords in most consultants' reports evaluating a corporation, the truth is that vision and innovation are both rare and initially unwelcome. When Henry Ford was asked what led him to build the automotive giant that still bears his name, he said the public was hungering for faster horses. What they needed, and what he gave them, was reliable, personal, motorized transportation through assembly line manufacturing. Today Ford Motor Company (NYSE: F) continues to be a world leader in automobiles.

At Apple, Inc. (NASDAQ: AAPL) Steve Jobs faced a Board of Directors that demanded short-term earnings-per-share growth. Rather than focusing on quarterly results, he took a long-term view and gave the world devices for personal access to information that fostered unparalleled growth in communications and entertainment, thereby disrupting those industries.

Identifying nascent disruptive technology is always problematic, and there are no easy comparators to disrupters in healthcare. However, innovative companies do exist. Examples that mirror the innovative intent of the Precision Medicine initiative are found in companies such as Ilumina, Inc. (NASDAQ: ILMN), Celldex Therapeutics , Inc. (NASDAQ: CLDX) and Foundation Medicine, Inc. (NASDAQ: FMI).

Ilumina is working to increase the availability and power of genetic analysis for physicians, while also developing companion diagnostics for new therapies. A companion diagnostic indicates whether a patient's illness expresses a weakness or characteristic that a therapy can exploit.

Celldex Therapeutics is developing a cancer vaccine for brain cancer patients whose tumor exhibits a certain growth factor. A companion diagnostic would be used to ascertain whether or not a patient would receive benefit from Celldex's cancer vaccine.

Foundation Medicine is empowering physicians to make better clinical choices by providing comprehensive analysis and information that is specific to individual patients. Oncologists can use the genetic information Foundation Medicine provides to make treatment choices tailored to the analysis.

What these three companies are doing is the very essence of precision medicine – pinpointing patients with genetics that would benefit from targeted therapies and developing targeted therapies that are effective against specific disease variants. The Precision Medicine announcement maybe trying to accelerate efforts like these, but it may fall short of the intended results.

The Role of the NIAID Partnerships Program in the Life Sciences Industry

A recent budget proposal, combined with a prior declaration of the Precision Medicine Initiative tries to give us what some experts are asking for, but in the spirit of Henry Ford and Steve Jobs, does it give us what we need? President Obama's initiative seems more like an infrastructure project than it does a major commitment to ushering in a new scientific age. There's no question that many of the most important medical breakthroughs were fostered

through initial investments made by the U.S. Government, but to be a true investment, at all costs, it cannot be perceived as an unfunded mandate.

NIH's National Institute for Allergy and Infectious Diseases (NIAID) division has managed successful grant and partnership programs—including its Biodefense partnership—to develop critical therapeutics, vaccines, diagnostics and resources for serious infectious diseases for several decades.

Almost no major drugs that are sold and approved in the United States could have been developed or commercialized without initial support—both "seed" money and guidance through HHS processes—from the federal government. There are many blockbuster drugs in Big Pharma that call NIH their home.

Measuring corporate success is vital to what we on Wall Street critically analyze and financially quantify in private industry. However, the outcomes must reflect different metrics and goals if an accurate quantification or audit of performance is done on government involvement.

Infectious disease is the perfect example of a healthcare business that does not lend itself well to quantification by typical Wall Street metrics and certainly does not compare well to other business lines in standard return on investment decisions.

Failures are not always failures in drug development. The critical key to success is transparency and an understanding how to learn from the data.

Diagnostics are the striking example of how important Government involvement is in healthcare research.

The Ebola crisis underlines the premise of how Government involvement can be the backstop (and sometimes the only one) to a global healthcare crisis.

NIAID's Partnership Program may provide valuable information about quantifying the cost of development for a new drug. Though private industry puts the price well over $1 billion today, NIAID's stewardship of small and mid-sized grants to determined scientists and research labs shows that such cost may be overestimated.

The NOVA study has basic flaws in its design – some of the questions in the survey could not be expected to provide reliable data, it included no comparators outside of the responder pool, and it did not measure certain endpoints that are critical to assessing the industry value information about the program.

When a report like this misses the mark in obtaining the basic data needed, trying to understand and promote Government success in a visible manner cannot even be contemplated.

Suggestions for future *NIH/NIAID/Division of Microbiology and Infectious Diseases (DMID) Partnerships Program Evaluation Survey*:

- A more comprehensive set of questions should be used in the survey.
- Use comparator infectious disease products from outside the Program.
- Track development of products rigorously, using the SBIR performance outcomes database system (PODS), a system which was used to assess the success of SBIR-funded products over time and acknowledge that over the course of development, ownership of products changes.
- Most importantly, collecting and keeping objective data on the grants and limiting dependence on subjective data in way that can be amassed and analyzed for performance value.

Background

Without federal funding for research in the United States (US), medicine would not be where it is today. Each advanced healthcare product, no matter how critical to human health, cannot be developed without initial investment. But except inside the federal government's medical branches and the medical research industry, few people realize that the US government has been responsible for starting, funding, guiding and nurturing almost every important advancement in life-saving medicine for nearly a century and seeing those medicines ultimately commercialized. The US Government has contributed to the development of some of the last two decades' blockbuster drugs promoted by private industry in American TV ads today, as well as orphan medicines that treat rare but complex conditions around the globe.

Tuft University's Center for the Study of Drug Development (TCSDD) reported in 2014 that the average out-of-pocket cost of a traditional Phase I/II/III drug including the amortized cost of unsuccessful drugs is about $1.395 billion.[137] Additionally, the failure rate of drugs that enter the traditional Phase I/II/III path is reported to be up to ninety-five percent.[138] With those odds, the life sciences industry is highly selective and risk-averse when choosing technology to develop that is in translational or early preclinical stages.

Not only do industry partners want products and resources that work, but they also need to instill confidence in investors or other funders to be able to continue developing technologies. Early-stage, innovative technologies are so often perceived as risky that they do

---

[137] "Cost to Develop and Win Marketing Approval for a New Drug Is $2.6 Billion," *Tufts Center for the Study of Drug Development*, November 18, 2014, http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study.

[138] J. Arrowsmith, "A Decade of Change," *National Reviews Drug Discovery* 11 (2012): 17-18.

not get partnered and could come to a dead-stop in development for lack of funding, regardless of their importance to human health.

The issue is especially dire in the infectious disease realm, where innovative defenses are continuously and increasingly required. For example, no new classes of antibiotics were launched between the early 1970s and 1999, and since then the situation has only slightly improved.[139] As a result, emerging multidrug-resistant (MDR) pathogens have built up resistance against old antibiotics, raising a major public health concern, and any new antibiotics derived from old antibiotics have limited efficacy.

Unfortunately, the model of the life science industry is biased against private investment in infectious disease products, particularly innovative ones, which typically have low market share, high competition and short duration of use in each patient (compared to chronic indications such as high cholesterol). The overall global market value of infectious disease diagnostics, vaccines and pharmaceuticals is only expected to be $89.8 billion in 2016,[140] which is little more than one percent of the total projected market value of healthcare in 2016 of $8.4 trillion.[141] Few industry partners have a financial incentive to pursue and assume the risk of developing infectious disease products.

Federal funding operations like the Partnerships Program bridge the gap between basic research and industry by sustaining continued development of the product so that they become ripe for future industry partnerships, acquisitions, and licensing, while also raising the return on investment and lowering risk of failure in trials.

---

[139] M. Butler, M. Blaskovich, and M. Cooper, "Antibiotics in the Clinical Pipeline in 2013," *The Journal of Antibiotics*, 66, no. 10 (.2013): 571-591.

[140] *Global Markets for Infectious Disease Treatments* (BCC Research, May 2013).

[141] *World Industry Outlook: Healthcare and Pharmaceuticals* (The Economist Intelligence Unit, May 2014).

Markets Targeted by the PartnershipsP Program

A review of just some of the successful grant recipients from product development funding programs of the National Institutes of Health, including National Institute of Allergy and Infectious Diseases (NIAID) and its Partnerships Program, reveals a number of critical achievements. They demonstrate that not every innovation that protects human health has to be a therapeutic with direct use in humans—diagnostics and environmental products can also have a significant impact.

They also demonstrate that even limited "seed" money or early-stage funding in the hands of innovative and determined researchers can have widespread impact by saving lives and ultimately generating revenue for those that partner:

- Prevnar®: a pneumococcal conjugate vaccine for children and older adults. It is currently owned by Pfizer, Inc. and generated $846 million in sales between mid-2014 and mid-2015.
- Equivac®: a vaccine to inoculate horses against the Nipah virus, which can be transmitted to humans. In humans the virus has a sixty percent fatality rate. The vaccine is owned by Zoetis, Inc. and was made available in 2012 in Australia, where the virus has typically been associated with horse-to-human transmission.[142]
- Brincidofovir: an antiviral small molecule and the lead product of Chimerix, Inc. The smallpox program for brincidofovir was of special interest to the NIAID. Chimerix has since received funding from Biomedical Advanced Research and Development Authority (BARDA), which recently awarded a contract for the use

[142] "Hendra Virus," *Australian Veterinary Association*, http://www.ava.com.au/hendra-virus (accessed 2015).

of brincidofovir in smallpox that is worth between $100 and $435 million. Currently the company Chimerix, which has only one other clinical stage product, has a total market value of $2.4 billion.

- FilmArray® biosurveillance system: an automated diagnostic system capable of sample preparation, reverse transcription for RNA viruses, and PCR to detect other pathogens. It is capable of detecting *Zaire ebolavirus* and has been used in a Sierra Leone hospital.[143]
- Px563L: a mutant recombinant protective antigen anthrax vaccine being developed by Pfenex, Inc. Pfenex was recently awarded a BARDA contract up to $143.5 million for the development of Px563L.

The funding process of NIAID has also nurtured a neglected category: diagnostics. Unfortunately, the life sciences industry widely does not recognize infectious disease diagnostics as meaningful investments. The diagnostics sector is predicted to generate only $12.4 billion in 2016 in global revenue,[144] which is miniscule compared to the $8.4 trillion value prediction of the global healthcare market in 2016.[145] Diagnostics take less time and money to develop and have less stringent requirements than therapeutics for humans, and are therefore perceived as commodities with low profitability.

However, diagnostics are said to be responsible for an estimated sixty to seventy percent of healthcare decisions.[146] This is one reason the government funding of infectious

---

[143] T. Leski, R. Ansumana, C. Taitt, J. Lamin, U. Bangura, J. Lahai, et al., "Use of the FilmArray System for Detection of Zaire ebolavirus in a Small Hospital in Bo, Sierra Leone," *Journal of Clinical Microbiology* 53, no. 7 (2015): 2368-2370.

[144] *Molecular Diagnostics: Major World Markets* (Kalorama Information, 2007).

[145] *World Industry Outlook: Healthcare and Pharmaceuticals* (The Economist Intelligence Unit, May 2014).

disease diagnostics is so critical. The fact that diagnostics may prevent much greater costs to those receiving medical care increases their desirability to clinicians and patients, which makes them attractive to industry partners. Diagnostics also have the potential to increase the use of other, more profitable therapeutics as a result of accurate and precise diagnosis. Despite these factors, diagnostics still suffer from a problem of perception. With government "seed" money, diagnostics can become more attractive to and net a greater profit for industry partners.

A simple review of some of the therapies and diagnostics clearly shows that these government partnership programs in health science research have achieved some success. But it has proven difficult to quantify the success of government funding programs innovation for research for a variety of reasons. One is that over time, a drug's rights may be transferred from the original funded grantee to a different institution, or partnered into industry.

Perspective on the *NIH/NIAID/Division of Microbiology and Infectious Diseases (DMID) Partnerships Program Evaluation Survey*

The NIAID is limited in ways to track the path of a product over the course of its development. Provided at the end of this report are some suggestions for improvement in future assessments of the NIAID Partnerships Program funding projects with principal investigators, in terms of study design and long-term tracking.

The study of the Partnerships Program performed by NOVA relied on a survey completed by grantees of the Program. It had several important findings but was limited due to the lack of tracking objective data for products and inconsistent response to survey requests.

---

[146] R. Forsman, "Why is the Laboratory an Afterthought for Managed Care Organization?," *Clinical Chemistry* 42, no. 5 (1996): 813-816.

The requests were submitted to grantees that were awarded during award periods 2003-05, 2006-08 and 2009-10. The most recent period contributed forty-one percent of responses, while the oldest period contributed twenty percent.

What is particularly problematic, however, is the overall response rate of only fifty-nine percent of grant recipients. We believe that biases could have been introduced: those who have canceled their development projects due to technical failure of the product or are no longer interested in the Partnerships Program due to success may be disinclined to respond. The highly varied responses among the periods lend themselves to this belief.

Out of the 184 grantees of PP that responded to the survey, thirty-two percent were developing a vaccine, thirty-seven percent were developing a therapeutic, an additional eight percent were developing immunotherapeutics, and twenty-one percent developed diagnostics. Over seventy percent of the respondents were developing a totally new product, process or service.

The written responses from the study indicate that some of the products are not for direct use in humans or in vitro but for the environment, yet the survey did not attempt to quantify this item, even though it has an effect on the regulatory pathways the products follow and developmental costs that must be incurred in the future. Products used in the environment will have less regulatory and experimental barriers; their developers seek Generally Recognized As Safe (GRAS) certification in the United States, which is generally much simpler, as intensive clinical trials are not required and only safety must be demonstrated. Diagnostics are typically approved in the United States through Clinical Laboratory Improvement Amendments (CLIA), a program run by the Centers for Medicare and Medicaid Services.

As mentioned earlier, diagnostics are as important as they are undervalued, and federal grant money will only increase their viability in industry. In contrast, vaccines used in humans have a higher market value and have an expected global market value of $57.8 billion by 2019, growing at 11.8 percent per year.[147]

Products were also broken down by pathogen type into Categories A-C, Emerging Pathogens, Multiple Pathogens and Other. Products focusing on Category A pathogens were in the greatest proportion among respondents at thirty-two percent. They are easily transmitted, result in high mortality and may require special action for public health preparedness, but they are not normally prevalent, particularly in the United States. Because they are additionally acute diseases with short treatment duration, they inherently represent a limited market for therapeutics and vaccines in humans. Category A pathogens include anthrax, smallpox, *Francisella tularensis*, (tularemia) and Ebola, among others.

To illustrate the role of government and industry in Category A pathogens, consider the recent Ebola epidemic in 2014. Before it posed a worldwide concern, very few companies had products in active development to treat the indication. At the time, the most advanced product specifically for Ebola with encouraging data was being developed by Mapp Pharmaceuticals in collaboration with the NIH. Most other life sciences partners are not positioned to develop Category A pathogens, unless the partner receives government grants and contracts for development and manufacturing to replace sales revenue. However, diagnostics and environmental products have high value among these pathogens because of lower regulatory barriers, lower costs and potentially high frequency of use.

---

[147] "Vaccines Market by Technology (Live Attenuated, Toxoid, Conjugate, Subunit, Synthetic, Dendritic Cell, Inactivated), Type (Preventive, Therapeutic), End User (Pediatrics, Adults), Disease Indication (Infectious Disease, Cancer, Allergy) - Forecasts to 2019," *MarketsandMarkets*, January 2015.

Category B and C pathogens each represented twenty-one percent of the respondents' targets. Category B includes pathogens that are moderately easily transmitted, and cause moderate morbidity and low mortality. They have an inherently higher value to the industry due to higher frequency. Examples of Category B targets include Salmonella, *Toxoplasma gondii*, and Hepatitis A among others. Category C includes emerging pathogens that can be engineered for mass dissemination and have the potential for a major health impact. The incidence of these infectious diseases has recently risen and therefore potential future impact is unknown. However, they do not pose an immediate danger to public health. Category C includes Hendra virus, tuberculosis and antimicrobial-resistant pathogens among others. Out of A B and C, C may have the greatest value to industry because of their growing prevalence and the expectation that their impact may become much larger. Several industry players are developing products to address life-threatening emerging infectious diseases and drug-resistant pathogens.

NIAID's Partnerships Program contributes value to industry in two ways: (1) it seeks to lower the risk of continuing development of the product for future industry partners by allowing investigators to accrete proof of concept for their innovative products or resources and (2) the selective process of awarding grants to investigators is a vote of confidence that may attract private industry partnership. As the perception of risk is lowered, innovation is more likely to be partnered. The *NIH/NIAID/DMID Partnerships Program Evaluation Survey* demonstrates the resulting value with the partnering rate, the subjective responses, and the rate of discontinuation of the candidates.

Acquisition of intellectual property rights of products is often critical for acquisition by or licensing to industry partners. Potential industry partners are more interested in

ownership that can be protected from competitors through intellectual property rights. Products that are able to acquire them have more market value and lower risk. This helps to explain that products that were acquired by/licensed to industry were 2.48 times more likely to have acquired rights and 3.13 times more likely to have a pending application for rights than those products that were not acquired or licensed out. The fact that sixty percent report that Partnerships support contributed to a pending rights application and thirty percent report that it contributed to the acquisition of rights suggests that the Partnerships Program played a role, but the data cannot definitively establish that rights were acquired because of data from the Partnerships support.

Twenty-four responders out of 158 claimed they discontinued their product (See NOVA study Exhibit 20 for a breakdown by product focus). Discontinuation is not always an indication of failure, especially not of the Partnerships Program's efforts.

Discontinuation means that added funding has helped weed out development products that could not be validated and has moved forward development of products with more potential. This is of value to industry, because the pool of products that can be partnered has been narrowed down to higher-quality, more effective candidates. Also, discontinued products are an opportunity to learn from past mistakes and move on to a new project.

Twenty-two of those who reported discontinuation gave a reason. Half said their reasons included not enough funding, while twenty-seven percent said that the idea of the product failed due to insufficient efficacy. All the participants in the study received a Partnerships grant, so perhaps other investors or health research funding organizations did not agree with NIAID's rationale for awarding the research or the evidence accumulated after the NIAID grant was insufficient to compel others to provide follow-up funding. Discontinued

products reported the lowest rate of twenty-five percent of follow-up funding between the time of the Partnerships award and completion of the survey, less than one-third of the highest rate of eighty-three percent for products that are in use by the target population and less than one-half of the overall average of fifty-four percent.

Suggestions for the *NIH/NIAID/DMID Partnerships Program Evaluation Survey*

Because of the various statistical concerns resulting from the low response rate of fifty-nine percent and possible responder biases, it is important to increase survey compliance with future grantees and to use rigorous documentation of funded projects to supplement the understanding of the Partnerships Program's contribution. The effect of responder biases is especially apparent in the disparity of responses between time points. For example, nineteen percent of respondents in 2003-05, twenty-one percent of respondents in 2006-08, and forty-four percent in 2009-10 said that support contributed to acquisition of IP. This outcome seems counter-intuitive because over time, the proportion of products with acquired IP should rise. The biases should be brought to light and avoided in future surveys. Also, response to the survey should be more incentivized and ensured. The 2008 SBIR survey garnered a response that was nineteen percent higher,[148] but the NIAID study was at a disadvantage because it surveyed those that were awarded their funding further into the past.

Additionally, some of the survey questions were problematic because the answers may not be reliable due to limitations of the recipient's knowledge and the answers may be misleading. For example, question twenty asks, "Did Partnerships support contribute to acquisition of intellectual property rights?" An investigator might have submitted the data that

[148] "National Survey to Evaluate the NIH SBIR Program," *National Institutes of Health Office of Extramural Research*, January 2009, http://grants.nih.gov/grants/funding/sbir_2008surveyreport.pdf.

resulted from Partnerships support, but there may not be a way of knowing whether intellectual property rights were granted because of the data.

In another example, when question twenty-six and twenty-seven ask about the industrial partner (Which of the following best describes this company's (or industrial partner's) major field of business? What is the current status of the company (or industrial partner)?), the grant recipient's knowledge may not be credible or may not be up to date. To find out more about industry partners, perhaps they should be surveyed or otherwise researched.

To measure and assess NIAID's success in the future, it is important both to increase survey compliance with future grantees, and to use rigorous documentation of funded projects to supplement the understanding of the contribution of NEPP.

It is also time to adapt or add to the survey model – it is based off of SBIR survey (by Humanitas, Inc.), which works for late-stage development but does not completely capture the value, both technologically and financially, when applied to earlier stage products. It also does not capture the value of a program that focuses on an early stage. The most useful component which SBIR did but NEPP did not do was build a performance outcomes database system (PODS) for all products which were not discontinued at the time of the survey to track their projects into the future.[12]

We know that funding benefits the development of a product and biomedical research overall, but a comparator would be the most useful way to assess the success of the Partnerships Program with regard to driving industry. The following questions must be answered: 1) Does funding objectively affect the rate of acquisition or licensing? 2) How do

total follow-up funding and the amount of follow-up grants change after Partnerships grants are awarded or not awarded? 3) How do other infectious disease products compare to those that are funded through the Partnerships Program perform over the course of development? How often are they put on hold or discontinued for lack of funding? Do they complete development more or less frequently? These questions are critical to understanding the value of the program to industry partners.

The NIAID has the potential to incentivize investment and development in the infectious disease space, which is incredibly important given the emergence and biothreat of many pathogens today. The Partnerships Program has made a significant impact on the way industry develops innovative infectious disease products—no doubt it has reduced the risk of industrial with the products it selects—but its full impact has yet to be quantified. The evaluation survey is in theory a good approach for looking at past shortcomings for future improvements. We conclude that we can elucidate the positive value of the program to industry by first improving how we assess it.

How Mental Health Is Shortchanged by Lack of Reimbursement for Vagus Nerve Stimulation[149]

With a continuing weekly newsfeed on the destructive consequences of inadequate mental healthcare and with growing data on how depression negatively impacts the ability to perform daily tasks and engage in social interactions, why does a proven therapeutic intervention for chronic depression still remain far out of reach for so many patients?

---

[149] Jared Meyer, Anne Marie Noronha, and Steve Brozak, "How Mental Health Is Shortchanged by Lack of Reimbursement for Vagus Nerve Stimulation," *Brain Stimulation* 9, no. 2 (December 30, 2015), http://www.wbbsec.com/wp-content/uploads/2016/03/12.30.15-Brain-Stimulation-Journal-VNS-Reimbursement.pdf DOI: http://dx.doi.org/doi: 10.1016/j.brs.2015.12.002.

More than one-third of the patients who can tolerate first-line antidepressant pharmacotherapies do not achieve remission or response to treatment; they may be defined as having treatment- resistant depression (TRD).[150] While the variety of available drugs and treatment courses demonstrate efficacy in some patients, the current treatment paradigm continues to fail millions of people worldwide each year, which emphasizes the need for new, accessible classes of therapies with greater promise.

As healthcare industry analysts from Wall Street, we have the unique perspective of focusing on the developing landscape of therapies available to patients. We make a living analyzing concrete scientific results, healthcare policy, and the cost–benefit of therapies to patients and health economics as a whole. Here we discuss the obstructed availability of a novel antidepressant, which has objectively demonstrated efficacy in the TRD population, and its cost-effectiveness.

In 2005, a vagus nerve stimulation (VNS) device called VNS Therapy® was approved for TRD by the United States' Food and Drug Administration (FDA).[151] The device, while novel in the treatment of mood disorders, had already been approved in 1997 for the treatment of epilepsy. A decade of newer research shows that VNS offers a unique and indispensable antidepressant mechanism of action to patients who have not previously responded to traditional pharmaceuticals or electroconvulsive therapy (ECT). Developed by Cyberonics, Inc., VNS Therapy uses an electrical pulse generator implanted in the chest that periodically

---

[150] M. Fava and KG. Davidson, "Definition and Epidemiology of Treatment-Resistant Depression," *Psychiatric Clinics of North America* 19 (1996): 179–200.

[151] "VNS Therapy System," *United States Food and Drug Administration*, http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm078532 .htm> (accessed July 30, 2014).

stimulates the left vagus nerve in the mid cervical region,[152] which sends signals through the nucleus tractus solitarius and to various regions of the brain.[153]

However, as TRD patients and their doctors know, FDA approval is not always the final hurdle in facilitating patient access to emerging medical technologies. In 2007, the United States' Centers for Medicare and Medicaid Services (CMS) essentially nullified FDA approval by denying reimbursement for the device to TRD patients, effectively blocking access for those under either Medicare or Medicaid, regardless of history of failed treatment. This decision hits those with TRD especially hard, as they are highly likely to rely on affordable or state-subsidized healthcare. For example, persistently depressed men in the United States were 3.64 times more likely to be unemployed if they are in the labor force, and 3.28 times more likely not to participate in the labor force than men who are depression-free.[154]

The CMS overstepped its own jurisdiction, which is to determine whether reimbursement is necessary and reasonable following the FDA's approval of safety and efficacy. The CMS decision instead relied on its own assessment of the available studies of efficacy, thus performing a *de facto* override of the function of the FDA. In its National Coverage Decision (NCD) on VNS Therapy for TRD, it argued that the data in the available short-term studies were insufficient to show that the device benefitted patients.[155]

---

[152] "Welcome to VNS Therapy.com for Health Care Professionals," *Cyberonics*, <http://dynamic.cyberonics.com/depression/hcp/ForSurgeons/implanted.aspx> (accessed May 30, 2014).

[153] SC. Schachter and D., *Vagus Nerve Stimulation* (London: Martin Dunitz, 2001).

[154] Z. Luo, AJ. Cowell, YJ. Musuda, SP. Novak, and EO. Johnson EO, "Course of Major Depressive Disorder and Labor Market Outcome Disruption," *Journal of Mental Health Policy and Economics* 13 (2010): 135–149.

[155] S. Phurrough, M. Salive, B. Lofton, J. Schafer, "Decision Memo for Vagus Nerve Stimulation for Treatment of Resistant Depression (TRD)," (CAG-00313R) 2007.

Ironically, the NCD has restricted the growth of additional long-term efficacy data; additionally, it failed to consider the ethical ramifications of long-term sham controls. We are acutely aware that the CMS decision may hinder global receptivity to the therapeutic device, and perpetuate the dearth of promising treatments for TRD.

The data with which CMS made its decision in 2007 may have been premature. Evidence of VNS efficacy has since continued to accumulate, along with the results of a five-year study that included surprisingly unequivocal data. A TRD population treated with VNS Therapy and treatment as usual (VNS + TAU) was compared to a TRD population that only received treatment as usual (TAU). TAU entails pharmacological treatment and the possible addition of electroconvulsive therapy (ECT). The data show twenty to thirty percentage-point separations from placebo in response and remission rates on the Montgomery–Åsberg Depression Rating Scale (MADRS), with compelling statistical significance. The median duration of response was also significant, at forty months with VNS Therapy versus nineteen without the device.[156]

Preliminary results were presented in 2014 at the annual meeting of the American Society for Clinical Psychopharmacology (ASCP). Its lead author Dr. Scott Aaronson said at the meeting.[157] "It's very rare in psychiatry to see five-year data about anything, so this is very unusual, and the results are very positive." The findings echoed those of a 2013 meta-analysis of six VNS Therapy trials[158] that measured participants at up to two years. Remission and

---

[156] S. Aaronson, P. Sears, F. Ruvuna, M. Bunker, "A Five Year Observational Study of Patients with Treatment Resistant Depression Treated with VNS Therapy® or Treatment as Usual: Comparative Response/Remission Rates, Duration of Response, and Quality of Life," *American Society of Clinical Psychopharmacology* (2014).

[157] F. Lowry, "Long-Term VNS Safe, Effective for Resistant Depression," *Medscape Med News* (2014).

[158] SM. Berry, B. Broglio, M. Bunker, A. Jayewardene, B. Olin, AJ. Rush, "A Patient-Level Meta-Analysis of Studies Evaluating Vagus Nerve Stimulation Therapy for Treatment-Resistant Depression," *Journal of Medical Devices: Evidence and Research* 6 (2013): 17–35.

response rates grew over the period among the VNS-treated population, and those who had achieved either at twenty-four weeks were more likely maintain it over time.

The five-year study's positive news has yet to bring access to VNS to more TRD patients. In 2014, the Appeals Board of the US Department of Health and Human Services rejected an appeal sought by two Medicare beneficiaries.[159] stating that the NCD in question was valid given the information available on the device at the time. They additionally ruled that new evidence (including results from the Berry et al. two-year study but not the Aaronson et al. five-year study) did not contradict the NCD, despite favorable statistical and clinical significance. There is no record of the CMS or the Appeals Board reviewing the five-year data. But as doctors search for better ways to treat TRD patients, data supporting the use of VNS such as the five-year study will become increasingly difficult to dismiss.

The CMS explicitly states that its coverage decisions are not based on cost, unlike many government health agencies that use a cost-effectiveness threshold. However, it must nonetheless operate within a budget that is allocated by Congress.[160]We, as healthcare industry analysts, wonder whether the upfront cost of the device played a part in the NCD outcome.

The NCD sets a precedent for private insurance companies and governmental reimbursement agencies abroad, which can include cost in their evaluations.[161] If cost did play

---

[159] "Departmental Appeals Board. Decision that the NCD Record is Complete and Adequate to Support the Validity of NCD 160.18(C)," *Vagus Nerve Stimulation* (2014).

[160] M. Drummond, B. O'Brien, GL. Stoddart, and GW. Torrance, *Methods for the Economic Evaluation of Health Care Programmes*, 2nd ed. (Oxford University Press, 1997).

[161] J. Clemens and JD. Gottlieb, *In the Shadow of a Giant: Medicare's Influence on Private Physician Payments* (Cambridge, MA, 2013).

a role in the NCD, then we would argue that the high cost of the implant (excluding the cost of programming it and including the cost of surgical incision), which is US$26,152,[162] is misleading. Consider that the generic version of the atypical antipsychotic aripiprazole, approved to augment antidepressants in major depressive disorder (MDD), may cost up to over US$900 for a month's supply in the United States.[163] This drastically accumulates to dwarf the cost of VNS Therapy over the course of its minimum battery life of three years.[164] Unfortunately, the CMS decision has already been reflected by several major private insurers' rejections of VNS for TRD. In addition, foreign national health agencies may follow the US example and similarly suppress availability of VNS treatment.

After detailed review, we found that the cost–benefit analysis of the proven VNS therapy overwhelmingly favors such treatment. A retroactive study of Medicare patients found that TRD beneficiaries with VNS implants (who were treated before the NCD) had an average of US$8749 per year in medical expenses post-implantation, which is far better than the cost of US$13,618 per year for TRD beneficiaries who do not use VNS.[165] Added to the cost of the implant amortized over the maximum life of the replaceable battery, the total comes to US$12,018, which remains lower than the cost of not treating patients with VNS. In one case report[166] a patient treated with VNS was able to halve the frequency of maintenance ECT

---

[162] "Hospital Codes," *Cyberonics Inc.*, http://us.livanova.cyberonics.com/static/ pdfs/Hospital-Coding-Sheet.pdf (accessed June 15, 2015).

[163] "Abilify Prices and Abilify Coupons," *Goodrx*, <http://www.goodrx.com/ abilify> (accessed June 25, 2015).

[164] "Welcome to VNS Therapy.com for Health Care Professionals," *Cyberonics*, <http://dynamic.cyberonics.com/depression/hcp/ForSurgeons/implanted.aspx> (accessed May 30, 2014).

[165] RL. Feldman, "Medicare Patient Experience with Vagus Nerve Stimulation for Treatment-Resistant Depression," *Journal of Medical Economics* 16 (2013): 62–74.

[166] RL. Warnell and N. Elahi, "Introduction of Vagus Nerve Stimulation into a Maintenance Electroconvulsive Therapy Regimen," *Journal of ECT* 23 (2007): 114–119.

sessions, further demonstrating the possibility of cost savings. The patient reported "feeling as well as he had felt at any time he could remember."

Not only does VNS have the potential to lower the long-term cost of treatment for patients, thus the fiscal burden on the CMS and private insurers, but also it provides much-needed relief and increases functionality in patients. This allows them to achieve more gainful employment, which is an important and highly valuable return on investment in VNS therapy, even if indirect.

The CMS's mistake in refusing coverage of VNS highlights an unmet need for new therapies to reduce the severity of depression. While antidepressants demonstrate some efficacy, antipsychotics often prescribed as a stronger treatment to address chronic and treatment-resistant depression present a serious risk of deleterious side effects. Those adverse effects include an expected drop of 17.7 IQ points not attributable to the symptoms treated.[167]

By contrast, cognitive deficits have not been reported with the use of VNS Therapy. The reduction in IQ with antipsychotics is dramatic enough that it is comparable the cognitive impairment from neurodegenerative disease or brain injury, which may even qualify the patient for Social Security disability benefits in the United States.[168]

---

[167] S. Donaldson, LH. Goldstein, S. Landau, V. Raymont, and S. Frangou, "Bipolar Disorder Project: The Effect of Medication, Family History, and Duration of Illness on IQ and Memory in Bipolar I Disorder," *Journal of Clinical Psychiatry* 64 (2003): 86– 93.

[168] "12.00-Mental Disorders-Adult," *Social Security Administration [US]*, https://www.ssa.gov/disability/professionals/bluebook/12.00-MentalDisorders -Adult.htm (n.d).

The side effects of currently available pharmaceutical antidepressants are less severe than those of antipsychotics, but pharmaceuticals overall are prone to failure or tachyphylaxis. SSRIs demonstrated in one study a 14.1 percent rate of tachyphylaxis.[169] Another study found twenty-five percent of patients experienced tachyphylaxis during maintenance treatment of their MDD over the course of three years.[170] In a surprising meta-analysis of all FDA-filed clinical studies for four new-generation antidepressants, each drug-placebo difference was found to be relatively small.[171] The CMS should have considered the partial efficacy and numerous side effects in the standard of care.

The agency should have also considered the ethical issues of using a sham control in studies of implantable devices before criticizing the lack of such studies. The use of implanted sham devices in studies is already controversial because they pose risks in surgery and add no potential benefit, and using shams in VNS trials for long durations would be even more egregious.[172] [173] The CMS rested its criticisms on the only available sham-control study, which observed masked active or sham over a ten-week period and showed benefit, albeit

---

[169] MA. Posternak and M. Zimmerman, "Dual Reuptake Inhibitors Incur Lower Rates of Tachyphylaxis than Selective Serotonin Reuptake Inhibitors: A Retrospective Study," *Journal of Clinical Psychiatry* 66 (2005): 705–707.

[170] DA. Solomon, AC. Leon, TI. Mueller, W. Coryell, J. Teres, and MA. Posternak, "Tachyphylaxis in Unipolar Major Depressive Disorder," *Journal of Clinical Psychiatry* 66 (2005): 283–290.

[171] I. Kirsch, BJ. Deacon, TB. Huedo-Medina, A. Scoboria, TJ. Moore, and BT. Johnson, "Initial Severity and Antidepressant Benefits: A Meta-Analysis of Data Submitted to the Food and Drug Administration," *PLoS Med* 5 (2008): e45.

[172] AJ. London and JB. Kadane, "Placebos that Harm: Sham Surgery Controls in Clinical Trials," *Statistical Methods in Medical Research* 11 (2002): 413–427.

[173] R. Macklin, "The Ethical Problems with Sham Surgery in Clinical Research," *New England Journal of Medicine* 341 (1999): 992–996.

limited, to patients with active VNS Therapy.[174] Unfortunately, the agency regarded the activation of the device in sham- control patients after ten weeks as a study design flaw rather than as a standard ethical consideration. This is not the first time we as healthcare industry analysts have seen a promising surgical implant blocked due to the lack of long-term sham controls.

It was also important to consider that the patients included in the VNS trials had not improved or had relapsed after using pharmacotherapies or ECT. If prior pharmacotherapies did not improve the long-term outlook for these patients through placebo effect, as is the case, then it seems unlikely that the long-term improvement observed with VNS is attributable to a strong placebo effect.

Meanwhile, suicide remains the second leading cause of death for American youth between the ages of fifteen and twenty-four, and it ranks among the top ten leading causes of death in the United States overall.[175] Of people alive today, 1.5 million Americans and more than twenty million worldwide (extrapolated) with major depression or bipolar disorder are likely to commit suicide;[176] [177] [178] [179] lack of long-term medication for sufferers of depression

---

[174] AJ. Rush, LB. Marangell, HA. Sackeim, MS. George, SK. Brannan, SM. Davis, et al., "Vagus Nerve Stimulation for Treatment-Resistant Depression: A Randomized, Controlled Acute Phase Trial," *Biological Psychiatry* 58 (2005): 347–354.

[175] "Ten Leading Causes of Death and Injury," *Centers for Disease Control and Prevention*, http://www.cdc.gov/injury/wisqars/ leadingcauses.html (accessed June 15, 2015).

[176] "The World Factbook," *Central Intelligence Agency*, https://www.cia.gov/library/ publications/the-world-factbook/ (accessed June 15, 2015).

[177] *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. (Arlington, VA: American Psychiatric Publishing, 2013).

[178] GW. Blair-West, CH. Cantor, GW. Mellsop, and M. Eyeson-Annan, "Lifetime Suicide Risk in Major Depression: Sex and Age Determinants," *Journal of Affective Disorders* 55 (1999): 171–178.

[179] P. Waraich, EM. Goldner, JM. Somers, and L. Hsu, "Prevalence and Incidence Studies of Mood Disorders: A Systematic Review of the Literature," *Canadian Journal of Psychiatry* 49 (2004): 124–38.

correlates with a higher likelihood to do so.[180] It is imperative that all treatment avenues for TRD be afforded the opportunity to demonstrate merit and, for cases such as VNS where merit is demonstrated, that these avenues be appropriately available to patients. To deny affordability of treatment to this population is to deny access to that treatment.

For all these reasons, the CMS decision simply falls short – it shortchanges patients, doctors, and scientific progress. The compelling data published after the 2007 NCD, including Aaronson et al.'s comparative five-year results, shows VNS Therapy can help fill in the gap left by existing pharmacological treatments. From our perspective, VNS is clinically – and financially – a viable treatment that is worth paying for.

---

[180] J. Angst, F. Angst, R. Gerber-Werder, and A. Gamma, "Suicide in 406 Mood-Disorder Patients with and without Long-Term Medication: A 40 to 44 Years' Follow-Up," *Archives of Suicide Research* 9 (2005): 279–399.

CHAPTER TWO

INTERNATIONAL MACRO ISSUES

Our world has become more interconnected in ways unimaginable only ten years ago. What would have been local medical challenges a generation ago now poses the threat of worldwide medical catastrophes. Threats such as the Fukushima disaster, the Ebola epidemic and now the Zika virus now have worldwide implications.

These threats were all ameliorated or addressed by the U.S. healthcare system, either through surveillance, technology introduction or through U.S. investment and intervention. The U.S. is the only country with the resources to reduce the threat and impact of pandemic-threatening diseases, and often, the only country with the desire to do so.

The importance of U.S. intervention is best illustrated by a failure of the U.S. to react and act. HIV has become embedded in the world population. Short of development of a vaccine and/or miracle drug to cure people of the virus, it will be a human medical threat for an unforeseeable future. HIV could have been contained and eradicated had the U.S. healthcare system detected it as a unique virus and taken early steps to contain it. Unfortunately, the medical community was looking elsewhere and the virus became embedded in the human herd.

This chapter highlights the responsibilities and consequences of societies where the health and well-being of citizens were not a top priority.

Winners and Losers of the Greek Financial Crisis[181]

From French Winemakers to U.S. Pharmaceutical Companies, Who Stands to Gain and Lose From the Greek Financial Crisis and the European Bailout

A Greek financial tragedy was barely averted … when the European Union and the International Monetary Fund promised the equivalent of up to $1 trillion to guarantee the Greek national debt and the debts of other financially shaky countries like Spain and Portugal.

The end of this act was much like the predetermined outcome of an ancient Greek drama. After months of back-and-forth negotiations, an agreement to save Greece and the European Union was inked hours before nervous Asian markets could open on Monday morning. But this move may only stem the tide of default in Europe. Other countries are likely to seek bailouts and, in a worst-case scenario, it could lead to Greece being evicted from Club Euro.

Whatever happens, there will be winners and there will be losers, both in the near-term and over time. What we are likely to see in the near-term is a devaluation of the euro as a currency. This will happen either through European Union action, or through bankers saying the euro just isn't worth what it used to be.

U.S. Pharmaceutical Companies Could See Lower Profits

As a research firm, dedicated to the analysis of businesses in the health care sector, we believe U.S. drug and medical device companies could be among the big losers as the euro is devalued. The euro's strength against the dollar has given U.S. pharmaceutical companies an

[181] Steve Brozak, "Winners and Losers of the Greek Financial Crisis," *ABCNews.com*, May 12, 2010, http://abcnews.go.com/Business/winners-losers-greek-financial-crisis/story?id=10619137.

edge in selling goods on the continent. In the first quarter 2010, companies like Merck & Co., Johnson & Johnson and Pfizer, Inc. reported favorable financial benefit from growing sales of U.S. products in Europe and they showed significant profits from managing fluctuations in a relatively strong euro.

Johnson & Johnson reported that domestic sales decreased by 9.6 percent while international sales increased by 11.1 percent, of which there was a positive currency impact of 9.7 percent. Merck announced that international sales of drugs and vaccines grew by ten percent, including favorable impact of foreign exchange. Pfizer said that international revenues were $9.4 billion, an increase of sixty percent compared with the prior-year quarter, which reflected forty-eight percent operational growth and a twelve percent favorable impact of foreign exchange.

But what foreign exchange giveth, foreign exchange taketh away. The decline of the value of the euro would, over time, make U.S. pharmaceutical and medical device products more expensive for European consumers. Existing contracts with government insurance plans, written in euros will stay the same. However, since the euro will be worth less on international currency markets, U.S. companies will experience lower profits. Over time, as new contracts are written, U.S. companies will try to increase their prices, but will be at a disadvantage when competing against Europe-based firms.

European Manufacturers Win, European Politicians Lose

European manufacturers stand to benefit from a weaker euro both at home and abroad in other ways. As the euro's value decreases, European goods will become more affordable to foreign purchasers, making computers, cars, MRI machines and fine French wine more

attractive to purchasers worldwide. Tourists to Europe this summer are also likely to benefit from a better exchange rate compared to the euro.

Democratically elected European leaders are likely to be among the losers. Discontent is in evidence throughout Europe. Gordon Brown already had to step down as prime minister of Great Britain, riots in Greece and falling popularity of George Papandreou could be the beginning of a change of government and Angela Merkel in Germany is facing significant resistance from her electorate for helping Greece during its crisis.

The governments that spotted Greece the trillion dollars are also likely to be losers. A trillion dollars sounds like a lot of money to most of us, but a trillion dollars just isn't what it used to be. What has already been offered may not be enough to pay the debts of the weaker Eurozone partners.

Managing a multinational currency, like the euro, requires thoughtful and deliberate action. It is a case of not doing too much and not doing too little, but doing it just right. National governments have been notoriously inept at managing complex economic situations. In this case, seventeen governments, with competing national interests and capabilities are almost guaranteed to be unable to achieve the delicate balance needed to restore Europe's economic growth, without imposing harm on other nations.

What Happens After the Greek Bailout

The final act of this play could have one of three endings.

In the first scenario, the euro is devalued too much, pushing the euro under one-hundred cents to the dollar, as it was in 2002. U.S. and perhaps even Chinese sales in Europe and elsewhere would suffer greatly. U.S. manufacturers would be locked out of sales of high-

ticket goods such as medical devices, locomotives, power plants, computers and telecommunications networks. Nations could begin erecting tariff barriers to protect their economies as they did before World War II, which would further depress world commerce. Carried to its extreme end, the final curtain comes down and everyone loses.

In the second scenario, the European Union would be unable to reduce the value of the euro to other currencies. If this were to happen, not only would countries like Greece, Portugal, Spain and Italy continue their downward spiral, but economies in strong countries like Germany and France could be damaged. More support of European economies would be necessary with continuing uncertainty in capital markets. The results could be an eventual economic gridlock.

The successful ending to this drama will be difficult to achieve. In a perfect world, done just right, balancing the euro against other world currencies would allow European manufacturers to better compete with U.S. and Chinese manufacturers, restore the European manufacturing base and have no negative impact on the U.S. recovery or growth of China's economy. Sad to say, we do not live in a perfect world.

Success depends on multiple countries managing through complex issues, acting wisely, with split-second timing, in their mutual interest. Given that it has taken more than two months to avert the current Greek crisis, it seems highly unlikely that Eurozone governments will be able to act quickly in the future as other problems arise.

The likelihood that all will turn out well without harm to anyone is therefore small. It is more than likely that some individual investors and some national economies will be disadvantaged by the current situation while others profit from it. We can only hope that, in the end, the players in the current situation depart from a zero-sum game strategy to one of

mutual equilibrium so that what is now a Greek drama does not become a full-blown Greek tragedy.

Greece Is On the Verge of a Health Catastrophe[182]

Over 2,500 years ago, Thucydides, known as the father of scientific history because he relied on facts and his observations rather than divine intervention to explain events, once described a plague that struck Athens. As disease spread unchecked and healthcare standards disappeared almost one-third of the city's population perished. The sick were left to fend for themselves and social order disappeared. The Plague of Athens took a prominent position not just in Greek, but in world history. Now a new type of plague is emerging in Greece involving healthcare and we can't wait for future historians to really understand what is happening to Greece.

Though the Greek economic crisis may have been pushed back to page two in the news by Janet Yellen's Federal Reserve testimony and the Iranian nuclear deal, Greece faces a medical crisis as deadly as the Plague of Athens, one that could throw the country deeper into economic crisis. Today, in the face of severe pharmaceutical drug shortages, 12,000 pharmacists throughout Greece will begin an open-ended strike to protest changes to draft legislation that they say will limit the role of pharmacies and threaten their livelihood. Such a prolonged strike could prove catastrophic to diabetics, heart patients, cancer patients and others. With this in mind there are three indications that the Greek medical system, once one of the best in Europe, is on the verge of collapse.

---

[182] Steve Brozak, "Greece is on the Verge of a Health Catastrophe," *Forbes.com*, July 15, 2015, http://www.forbes.com/sites/stephenbrozak/2015/07/15/greece-medical-collapse/#6ec1dd8d12b1.

The first and most immediate disaster to the Greek medical system, a drug shortage, has already begun. The impact on most Greeks is difficult to quantify immediately, but expensive biological drugs have been unavailable for the ordinary citizen for quite some time. It's now a question of when inexpensive generic medicines and other commonly used but necessary therapeutics become hard to get. For example, Denmark's Novo Nordisk is the world's biggest maker of insulin and suspended shipments of modern insulin to Greece in May 2010. The company only resumed shipping to Greece after prices for the drugs were raised. There is no substitute for insulin to treat diabetes. Expensive, first-line anti-cancer drugs often cannot be substituted or duplicated either and are also in short supply. What makes a drug shortage even more problematic is that even if Greece imports these drugs, the government must work to ensure that they are not hoarded, placed into the black market, or exported by wholesalers into other markets for more reliable profit.

Turmoil in the Greek drug market already exists. Greece owes pharmaceutical manufacturers $1.2 billion for drugs previously delivered, patients are having to make hard decisions in the face of drug shortages, and the head of the Hellenic Association of Medicine Wholesalers has accused pharmaceutical companies of placing quotas on drugs shipped to Greece to limit losses. The protests specifically identified Novartis , AstraZeneca , and the Janssen unit of Johnson & Johnson. The complaints have yet to be verified, but the Greek government put exportation limitations on twenty-five drugs from these three companies.

The second indication of a Greek crisis is behavioral changes within the country leading to increased death and disability. People are already going to the doctor less frequently, even though there is no co-pay for primary care physician visits. Greece's 132 hospitals had a budget of $735 million for the first four months of 2014. This year the budget

for the same time period was $50 million total. Historically, reports have shown generally low suicide rates in Greece compared to other countries, but the economic woes of the country have had a dramatic effect on this phenomenon. A study published in the British Medical Journal reported that the mean suicide rate rose by thirty-five percent between 2010 and 2012 in response to austerity measures. The study concluded "increased suicide risk in Greece is a health hazard associated with austerity measures." Though the reported increase in suicide is dramatic, the available data masks the true extent of the problem since suicides tend to be under-reported in Greece to spare families and the departed the stigma of suicide.

Over the long-term other, more intractable problems will be exacerbated. Heart attacks and heart failure will continue to rise, especially as people stop taking anti-cholesterol medications. Complications from type 2 diabetes will proliferate as an accumulated impact of failure to keep blood glucose under control becomes obvious. Common medical devices like eyeglasses and hearing aids, which enable normal living standards for people as they age, may no longer be available and more expensive devices like defibrillators, pacemakers and artificial joints will become luxury goods.

The third and most dangerous health impact of a Greek financial meltdown is a healthcare "Brain Drain" as migration of doctors, especially young doctors, to other European nations occurs. Although the practicalities of employment vary from country to country, doctors from The European Economic Area (EEA), which is comprised of the European Union and European Free Trade Association, are entitled to full registration in any country in the EEA providing they are citizens of a member state, they have completed primary training in a member state and hold a recognized qualification. This gives Greek doctors up to thirty-three different countries to move to and practice medicine in. According to one report,

approximately 3,500 doctors have left Greece to practice medicine in Germany alone. Once physicians relocate for better economies, they rarely return to the country of their origin.

The practice of modern medicine is complex and interconnected. If any one element of the medical care system is disrupted, the entire structure will collapse. Once it has fallen it would take years, perhaps generations, to revive. With these three flashpoints, it is highly likely that there will be a breakdown in healthcare in Greece that will further exacerbate its financial and social woes.

Thucydides took great pains to preserve the events around the Plague of Athens in painstaking detail in case symptoms showed themselves again in the future. Remarkably, what he captured were the ramifications of disease left unchecked. He understood then that a failure of a healthcare system to respond to systemic threat could ruin a society. The significance of a healthcare meltdown in Greece would not be confined. In an interconnected world, if deadly infectious diseases like TB and hepatitis become entrenched in Greece, they could easily spread throughout Europe. Most European capitals are a plane ride away from Athens, and Greece is a popular tourist destination in the region. Without a humanitarian effort to provide essential drugs and healthcare services for Greece in the coming years, the country could descend into a healthcare crisis that would further depress the economic conditions of the country. As classical history should remind us, it's not just in Greece's interest to prevent a healthcare meltdown; intervention would benefit all of society.

Fukushima Joins Titanic, Katrina as Iconic Word for Disaster[183]

Large-Scale Events Often Unavoidable; Planning Necessary to Blunt Impact

There is a strong possibility that the name Fukushima could become remembered as an iconic phrase for disaster, like Titanic or Katrina. Most disasters of similar severity can't be averted but with proper preparation, loss of life can be minimized. With enough life boats, the Titanic would be just another sunken ship. With a proper levee, Katrina would have been just another big storm.

Since the disaster, news coverage has been consumed by an earthquake of unprecedented magnitude and an ensuing tsunami, followed by multiple breakdowns in nuclear electrical generation plants.

The earthquake and tsunami are estimated to have taken close to 10,000 lives, but it is the breakdown of the nuclear plants that has captured most of the attention. Though most natural disasters have the half-life of one news cycle, the Fukushima disaster could be with us for as long as the half-life of an encapsulated reactor.

As people who have spent time in Japan, studied Asian society and been trained in defense against radiation events, we believe that it is reasonable that the Japanese government is carefully managing the release of information about this event. In a society that is used to conformity and cooperation, a breakdown in social predictability could cause widespread panic.

By the same token, the Japanese government and Japanese engineering are not to blame for what is happening. The sequence of events was unforeseeable and engineering for an earthquake of unprecedented size was unimaginable. But as a consequence of the disaster, a

[183] Stephen Brozak and Henry Bassman, "Fukushima Joins Titanic, Katrina as Iconic Word for Disaster," *ABCNews.com*, March 16, 2011, http://abcnews.go.com/Health/japans-fukushima-prepare-disaster/story?id=13143270.

peacetime radiation tragedy is a strong possibility and there is no approved medicine to meet the threat of widespread radiation sickness.

The United States is not immune from a similar nuclear power plant accident. We have slightly more than one hundred nuclear reactors generating electricity in the U.S., some of which are near known geological faults.

Several radioactive countermeasures are now in development, but none has been approved for use in a nuclear disaster. Once approved, a radiation countermeasure could be stockpiled for use in the event of a Fukushima-like emergency or a terrorist attack to treat military personnel and civilians exposed to high doses of radiation.

And even though these medicines have a secondary use, to increase the amount of radiation that can be given to cancer patients, they don't have the billion-dollar revenue potential that attracts investors and research agreements with large pharmaceutical companies.

In 2004, the Biomedical Advanced Research and Development Authority (BARDA) was created by Congress with a $5.5 billion budget to purchase medical countermeasures to meet natural disasters like pandemic flu and man-made disasters like radiological contamination.

Though BARDA has the funds to purchase biothreat countermeasures, the number of companies that can actually supply them is limited and even then, those available products are in early clinical development.

This is where government can and must be involved, to foster development of countermeasures to natural and man-made disasters, to prevent disabling disease and potentially to avert the threat of death. Developing new medicines can take decades and

cost hundreds of millions of dollars. But there is no coherent funding system for medicines to meet the kinds of disaster that BARDA is compelled to prepare for.

One remedy to the challenges BARDA faces in meeting its Congressional mandate is to enable what we call the Drug Development Incentive Fund (DDIF).

In last quarter's journal of *Biosecurity and Bioterrorism: Biodefense Strategy, Practice and Science*, we formally proposed the formation of the DDIF as a not-for-profit corporation, funded by the government, to foster development of new medical technology in the national interest. The DDIF would provide seed money to get promising technologies off the ground and prove their potential.

There is precedent for an entity similar to the DDIF. In-Q-Tel, a government-funded corporation, was created by Congress in 1999 to advance communication and information technologies beneficial to national security that government agencies needed, but that were not being developed at the time by private corporations. Among many other technologies, we owe advanced encryption technologies used every day in e-commerce to early investments made by In-Q-Tel.

The ability to take ownership and leadership positions in a company would be a significant distinguishing characteristic of the DDIF that government agencies lack.

While the National Institutes of Health can invest in early-stage technologies through grants, and government authorities such as BARDA can provide financial support for more developed technologies through contracts, there is no government entity that can provide early-stage development companies with both a funding source and strategic guidance as an investor.

The DDIF would make modest investments in promising technologies with the prospect that government investment would reduce risk of success and encourage private investors to invest much more in the company.

Like other investors, the DDIF would receive stock and warrants or hold debt in the companies in which it invested. If those companies are successful, the DDIF would share in their success. In this way, with even modest success, the DDIF could become a self-sustaining, not-for-profit corporation.

Creation of the DDIF would result in significant dividends. In a single act, such an organization would provide for the advancement of strategic science of national importance, invest in projects that yield significant public health returns, advance the promises of preclinical and early phase research, revitalize biopharmaceutical investment, and create valuable innovation-economy jobs.

Though a fund like the DDIF could not prevent natural or man-made disasters from ever occurring, it could provide the U.S. with the necessary countermeasures to minimize human tragedy resulting from such disasters.

Fukushima -- A Nuclear Threat to Japan, the U.S. and the World[184]

… Radioactive leaks from the Fukushima nuclear power plants have been incapacitating a large part of Japan. Information from the Japanese government and TEPCO, the power company that operates the site, has been sparse, often incomplete and sometimes contradictory. A confidential assessment by the Nuclear Regulatory Commission obtained by

[184] Stephen Brozak and Henry Bassman, "Fukushima -- A Nuclear Threat to Japan, the U.S. and the World," *ABCNews.com*, April 6, 2011, http://abcnews.go.com/Health/fukushima-leak-threat-japan-us-world/story?id=13303513.

The New York Times suggests that the damaged Fukushima Daiichi plant is far from stable. The report concludes that the Fukushima plant is facing a wide array of fresh threats that could persist indefinitely.

The Fukushima disaster has become more than a local, regional or national Japanese event. The worldwide implications of the event are becoming apparent: though a major leak in a maintenance pit of the plant has been plugged, there is still a great likelihood that significant amounts of radioactive water will continue to be released into the Pacific Ocean; the worldwide Just-In-Time manufacturing cycle has been interrupted; and increased levels of radiation have been detected on the U.S. East Coast. Though the amount of radiation to reach the U.S. is small and poses no present danger, its presence demonstrates that the Fukushima event has global impact.

Circumstances are still evolving too fast and too out-of-control for the consequences to be fully appreciated in real time. Every day brings new revelations of failure and growing frustration in Japan and elsewhere. It has become obvious that all the facts about the Fukushima tragedy won't be known until the danger is long past.

In Japan, there continues to be uncertainty about the extent of the danger from radiation exposure and lack of information about how many people have already been exposed to health-impairing radiation. We don’t know how much contamination has leaked into surrounding land and water or when and how those leaks can be repaired.

The Japanese government announced an evacuation zone extending nineteen miles from the crippled Fukushima plants, the same distance as the exclusion zone around Chernobyl in Ukraine. But Japan is neither as large nor as sparsely populated as Ukraine. Close to seventy-three percent of Japan is unsuitable for agricultural, industrial, or

residential use. Millions of people could be dislocated in addition to those already homeless from the quake. These people will need to be relocated and new homes will have to be created for them.

With the international challenge of wars in Iraq, Afghanistan and Libya, and national concerns about Congress being unable to agree on Federal Government funding, the U.S. news spotlight that was on Fukushima has been pointed elsewhere. However, smart investors and social observers continue to monitor the responses to the Fukushima tragedy and gauge its potential impact on world markets.

It will take the equivalent of billions of dollars for the Japanese to recover from these disasters and the U.S. economy is closely linked to theirs. The Japanese government and Japanese investors comprise the second largest holders of U.S. Treasuries, at $885 billion. The Bank of Japan also is reported to hold $493 billion in its reserve balance to avert credit problems. Some financial observers have speculated that the earthquake and tsunami may force Japan's government and investors to liquidate much of the U.S. debt they hold. This possibility doesn't even consider that there is no transparency as to what plans exist for using these funds.

The wholesomeness of much of Japan's food supply has come under question. Farmers have been forced to destroy crops and dispose of dairy products. As a consequence of continuing contamination of seawater, the healthfulness of seafood from the Pacific Ocean is in question. Japan is already a net food importer. In response to a continuing shortage of Japanese home-grown food, the Japanese government may encourage importation of even more foreign food, which is likely to increase the price of food in a nation where food

is already an extremely expensive commodity. Worldwide, increased competition for food is likely to affect prices, causing some people in marginal economies to go hungry.

Japanese manufacturers are increasingly in competition with other Asian countries. With the domestic Japanese industrial base severely damaged by the earthquake, delivery of Japanese-manufactured products to the U.S. has been disrupted. Some U.S. plants using Japanese parts have been forced to slow down or halt production. They will probably recover when Japan begins exporting a full supply again, but in an already shaky economy, that could take months. If severe enough, the postponements could cause demand to disappear.

Some industries where Japan now has a predominant position are already threatened. Pre-Fukushima Japan produced a significant percentage of the world's supply of silicon wafers, the base on which integrated circuits and memory chips are made. Because of the earthquake, it has been estimated that wafer supply has diminished by twenty-five percent.

A shortage of wafers is likely to cause the price to rise, thus increasing the price of chips worldwide, which would have impact on the price of all sorts of goods from jumbo jet airplanes to programmable coffee makers. Korean manufacturers said they would fill the void. If customers establish supply agreements with new manufacturers in Korea, return to their former suppliers in Japan will become even more difficult.

Japan is a culturally unified nation with more than ninety-eight percent of its population sharing the same ethnicity. It also is a nation where the social norm is to achieve consensus and conform to standards. Japanese people are careful about expressing dissent or participating in controversy. Yet, we are seeing increased, almost unprecedented criticism of

TEPCO and the government beginning to be expressed. If this is possible in such a polite and restrained society, imagine the response to a similar disaster elsewhere.

Increasingly, reports of heroic workers, dubbed Fukushima Fifty by the press, are making their way into Western news sources. There may be as many as 1,000 workers who are sacrificing themselves to prevent additional damage and repair existing damage to the nuclear reactors. It is possible some of these workers have been exposed to so much radiation that their normal lives will be changed in unforeseen ways. It is likely many of these workers will suffer the long-term effects of radiation exposure, including increased likelihood of leukemia within a few years and other cancers as much as a decade or more from now. DNA damage to workers could become apparent only when these workers have children.

Though the aftermath of Fukushima will be with us for decades, and perhaps generations, immediate attention to this matter is imperative to save lives, provide knowledge that will avert a similar disaster elsewhere, and minimize domestic and worldwide economic impact.

After almost a month, there continue to be more questions than answers. There has been marginal success in cooling the at-risk reactors and little success stemming the flow of radioactive waste water. We have no credible estimate of the impact this disaster will have on the Japanese economy in particular or the world economy in general. There have been no credible steps in the U.S. or by the International Atomic Energy Agency to begin learning from this event and its aftermath and to apply those lessons to avert or minimize future tragedies.

The Japanese authorities, with the help of other experts, will have to muddle through this disaster, making up solutions as they go along. Hopefully, the damaged reactors will be

brought under control before serious permanent harm is inflicted on national and international resources.

Looking to the future, as fossil fuels are depleted and become more costly, the world inevitably will become more dependent on nuclear power. It is likely that another nuclear disaster will occur sooner or later. Depending on ad-hoc solutions to disasters of this magnitude is shortsighted at best. In the U.S., we have seen no concentrated response by U.S. regulators and nuclear power operators to re-examine safety standards in the 104 nuclear plants in this country, most of which are decades old, some of which are based on the same design as Fukushima and some of which sit on or near fault lines as unstable as those in Japan.

What is needed, in our opinion, is a permanently staffed, international nuclear rescue team. The team could have a core staff of full-time team members with stand-by team members, drawn from government and industry experts, who would be activated in the event of a disaster. The team would be furnished with the scientific, technical and equipment resources necessary to address an equivalent or a worse level of nuclear disaster than Fukushima. It would create scenarios, plans and tactics for remediating disasters when they occur. It would train to prepare to respond to a nuclear accident as a cohesive unit.

Such a resource would not provide a full-proof solution to inevitable nuclear disasters. However, it is a necessary first-step in controlling the potentially cataclysmic effects of a Fukushima-scale, or worse, nuclear reactor tragedy. After Chernobyl, Three-Mile Island and now Fukushima, failure to prepare in advance for another such tragedy would be foolishly self-destructive.

Fukushima and Nuclear Power: Playing with Fire[185]

As we commemorate the anniversary of the BP Oil Spill in the Gulf of Mexico, the insatiable human hunger for energy has caused the world to confront an even more devastating event -- the Fukushima nuclear power plant failures. Both of these disasters have many elements in common, but the one clear commonality is human miscalculation of the overwhelming power of nature.

Both events demonstrate that there is no such thing as a zero-defect human endeavor. No matter how well we plan and prepare, the failure rate will never reach zero. Eventually, an unexpected event or a failure will occur, and in the case of a nuclear power plant, the ensuing breakdown can be catastrophic.

Nuclear power, like other human technologies, owes much of its advancement to trial and error. Engineers may try to predict the outcome of new applications of technology based on previous experience. Yet, even with today's sophisticated computers and predictive modeling, engineering calculations frequently fail to anticipate catastrophic events of record-breaking proportions. Viewed as a current news event, Fukushima is a tragedy. Viewed through the lens of time, it will be seen as a tragedy that provided information to advance nuclear power technology.

Later this year, we will celebrate the 108th anniversary of powered flight. The space shuttle fleet represents the current high-point of manned flight even though it will be retired this month. The first orbital shuttle mission took place in 1981, almost eighty years after the Wright

[185] Stephen Brozak and Henry Bassman, "Fukushima and Nuclear Power: Playing with Fire," *ABCNews.com*, April 25, 2011, http://abcnews.go.com/Health/fukushima-nuclear power-energy-lessons-japans-tragedy/story?id=13439654&page=3.

Brothers first flight. Five years later an explosion destroyed the Challenger, and in 2003, the Columbia disintegrated on re-entry into the earth's atmosphere. Decades of aviation and space engineering could not prevent the loss of forty percent of the space-capable shuttle fleet in catastrophic accidents that killed their entire crews.

Nuclear power has had a much better safety record than the space shuttles. Nuclear power plants can be found throughout the world and the total amount of radiation they can produce is huge. According to the International Atomic Energy Agency, operation of the 443 currently active nuclear power reactors in thirty countries requires more than 68,000 tons of uranium. That amount of fissionable material represents both a current and long-term threat to humanity.

Since 1952 there have been only thirty-three reported accidents or incidents in 568 reactors that are now in operation or previously built and shut down. Only two of the thirty-three incidents were considered "major accidents". Percentage-wise, six percent of these nuclear reactors have had a serious incident or accident. If the number of safe days of operation were calculated against the total number of accidents, the margin of error for nuclear power plants would be infinitesimal.

In any other industry, nuclear power's safety record would be enviable. But nuclear power is not any other industry. Nuclear power represents a major new challenge to the inevitability of human failure. When a space shuttle fails, a handful of people die tragically, and the likelihood of bystander injury is very small. When a nuclear reactor fails, hundreds of people can suffer or die soon after the event, and thousands, or conceivably millions of bystanders can become sick or bear children with severe birth defects.

Nuclear Plants Safe, But Not Disaster-Proof

Our firm has engaged in financial analysis and commentary of biotechnology, pharmaceutical and medical device technologies for decades. Thus far, no universally accepted treatment option for radiation sickness and its ensuing healthcare complications has emerged. The effects of radiation exposure are so calamitous that we are compelled to turn our attention from medical treatment to prevention of this deadly disease.

Of the world's reactors, 104 are in the United States, representing twenty-four percent of the total. Less than a month after the Fukushima failures, Charles Pardee, chief operating officer of Exelon Generation, owner and operator of the largest fleet of U.S. nuclear reactors, and the third-largest nuclear power operator worldwide, testified to a Senate committee investigating the safety of U.S. nuclear plants. In describing the safety of Exelon's nuclear plants, he said: "These plants were designed and licensed to withstand a variety of natural disasters, including earthquakes, floods, tornados, and, where appropriate, tsunamis. Plants are designed to withstand potential disasters based on the most extreme event known in their geographic location, with significant margin added on to that extreme event."

Such confidence flies in the face of facts.

Japan is widely respected for its engineering expertise, social responsibility and dedicated workforce. Yet Japanese know-how failed to foresee or plan for the eventuality of a 9.0 earthquake and the ensuing tidal wave. In Fukushima, just as in Chernobyl, the severity of the event was mitigated by small groups of workers who volunteered to stay behind while others were evacuated.

In Japan, the workers who stayed behind to battle the breakdown became known as the Fukushima Fifty. They were the last line of defense at that site. We need to ask what would have happened if this selfless group of people had not been willing to put themselves in grave danger to protect others. And, we need to wonder if a similar group will emerge when another disaster occurs.

As gasoline in the U.S. approaches $4 a gallon, on its way to $5 or more, the power from nuclear reactors becomes more significant to the nation's energy resources. Nineteen percent of the electricity generated in the U.S. comes from nuclear power. As energy needs increase and old plants are decommissioned, new ones will be needed just to maintain the current level of production.

Downsizing or eliminating nuclear power generation from the U.S. energy mix at this time would be extremely costly and have a significant negative impact on the U.S. economy. Yet more than half of the U.S. power reactors have been in operation for twenty-five years or more, and there have been no new construction sites for nuclear power plants since 1977. With each year, the likelihood of a breakdown in these old reactors increases.

Totally safe nuclear power is unattainable. There will only be safer nuclear power. As Chernobyl and Fukushima have shown, severe nuclear power plant failures are international events and prevention of them must be addressed by an international body.

International Cooperation Needed

Before anything can happen to bring more order and improved standards to the international threat of nuclear reactor failure, involved nations must agree to agree. Like the European Union, which now includes twenty-three countries using a common currency,

and others that wish to join, if nations perceive that cooperation is in their best interests they will cooperate.

Of the twenty-nine countries with operating nuclear reactors today, twelve countries operate ten or more reactors, constituting seventy-two percent of the total number of reactors. The top twelve reactor operators include the U.S., France, Japan, Russian Federation, Republic of Korea, India, United Kingdom, Canada, Germany, Ukraine, China and Sweden. Of the thirty-three documented accidents and incidents since 1952, twenty-two took place in eight of these countries.

These are nations with histories of international cooperation and accords. They could build on or evolve from existing agencies like the International Atomic Energy Agency, which operates under the United Nations, the Nuclear Energy Agency, which has twenty-nine member countries, or the U.S. Nuclear Regulatory Commission. Rather than observing, assisting and advising, an international agency needs to be created that can establish safety standards, inspect nuclear sites, and if necessary enforce compliance.

Once established, this alliance of nuclear operating countries would be in a position to reach out to less well-developed nations and countries with fewer reactors. The alliance could bring other nuclear power players into its sphere to assure that their reactors are operating to world standards. It would not be out of the question to enforce compliance by withholding foreign aid or to imposing economic sanctions on nations with non-compliant nuclear reactors.

There are several historical examples of nations, even those hostile to one another, working together in their mutual interest. Usually those alliances occur during wars. In other instances the alliances address narrow specific interests, like the need to have a

unified, international airline flight management system with a single, universal language that all pilots can understand and speak. Today, hundreds of planes are in the air at the same time around the globe. Without such an international system, chaos would reign and tragic airline collisions would be common occurrences.

It has already been demonstrated that an international nuclear regulatory system is crucial. There have already been three nuclear power near-misses—Three Mile Island, Chernobyl and now Fukushima, where it is estimated that close to 80,000 people will be dislocated from their homes and farms. If we do not learn from these events that nuclear disasters know no boundaries, it is inevitable that an even greater disaster will occur.

Partial measures will not increase the safety level of nuclear power facilities. Only a coordinated, global effort will provide individual nations, and the world as a whole, with an improved ability to prevent and withstand nuclear emergencies. Without such resources, nuclear power is playing with fire. Eventually, someone will get burned very badly.

Fukushima
If Not Now, When? The Immediate Need for Radiation Sickness Countermeasures

As we approach the … anniversary of the Fukushima nuclear plant disaster, the reactors may be coming under control, but all of Japan continues to suffer. A new, lethal radiation hot spot near Reactors No. 1 and No. 2 was discovered and acknowledged by TEPCO, the plant operator. New makeshift cooling systems will not be in place until early next year. A new wall that reaches sixty feet underground is being built to keep radioactive groundwater from seeping into the Pacific Ocean. Throughout Japan, beef from radiation-contaminated cattle has reached markets and radioactive hot spots are being discovered by villagers in locations that were previously declared safe.

Even in uncontaminated areas, people's day-to-day lives have become more difficult. August in Japan brings unrelenting and enveloping heat. With average daily temperatures in the nineties, the government has called for an electricity cutback of twenty percent. Out of patriotic duty, air-conditioning thermostats in homes and high-rise office buildings are turned to eighty-two degrees or higher, electric lights are turned off and even the strict Japanese business dress code has become more relaxed.

The potential consequences of a nuclear power plant breakdown were ignored for forty years but the Daiichi power plant disaster caused governments to take notice. Recently, the Japanese Prime Minister proposed his nation learn how to exist without nuclear power. The German government declared that all its nuclear plants will be closed within ten years. France's newest nuclear reactor was delayed for two years because of safety concerns. New York's governor called for closing Indian Point, a nuclear generating station that has been operating for thirty years just thirty-five miles from Manhattan and the U.S. Nuclear Regulatory Commission is reviewing safety standards for all U.S. nuclear plants.

The potential for a nuclear disaster will be with us as long as we need nuclear power and it is likely that nuclear power will be increasingly needed throughout the U.S. and elsewhere. The increasing cost of fossil fuels and the growing threat of climate change from hydrocarbon emissions are too great to overcome without nuclear power.

As new nuclear plants come online and existing plants grow older, it becomes predictable that sooner or later, a major breakdown will occur. On-site, trained staff members are the last line of defense. Their split-second decisions can either increase or decrease the impact of an event. At Fukushima, in the hours following the tsunami, Masao Yoshida, the

plant manager, continued flooding the reactors with seawater, refusing to obey the orders of his superiors and preventing an even greater disaster.

In the after-effects of a nuclear accident, hundreds or even thousands people could be exposed to high doses of radiation. In the past, many of these people would have been doomed to near-term death by radiation sickness, but we know today they could potentially be saved.

Like seatbelts and airbags in automobiles, radiation sickness countermeasures are necessary safeguards in the nuclear age. Several biotechnology companies are now developing radiation therapeutics and preventives to treat people after a nuclear accident. Several are in the proof-of-concept or early developmental stages and they are moving forward slowly.

Even when operated one-hundred percent safely, nuclear plants create tons of radioactive waste from spent fuel, which poses significant risk. 71,900 tons of spent fuel are now in storage, most in pools of water like the ones used to store spent fuel in Fukushima according to a recent Associated Press report and 2,000 tons of spent fuel are created every year by U.S. nuclear power plants. According to current estimate, the U.S. will have exhausted all its spent nuclear fuel storage space within four years.

It is now within our power to protect large numbers of people from the consequences of a nuclear accident. Whether they are the first-responders who prevent a disaster from becoming more severe, people who live within the vicinity of a nuclear plant or those who are hundreds of miles downwind of a plant, they are entitled to protection from a potential nuclear plant failure.

Drugs to protect people from radiation overexposure could also provide an immediate benefit. It is highly probable they would increase the amount of radiation exposure cancer patients could endure while undergoing radiotherapy.

Funding is an issue. But there is a precedent in the government's encouragement of the regrowth of the vaccine industry within the U.S. A decade ago it was deemed crucial that the U.S. government provide direct funding to businesses and non-profit research centers to encourage and financially support the rehabilitation of domestic vaccine production to protect public health in case of a communicable disease outbreak. Millions of dollars were dedicated to the creation of vaccines, vaccine laboratories and an advanced vaccine manufacturing plant within the U.S.

In a time of growing awareness of government debt and the potential impact it could have on our economy, it is difficult to call for yet another government program, but the continuing threat of a nuclear accident with widespread and deadly consequences makes it equally compelling that we provide coordinated and dedicated resources for development of effective radiation countermeasures. The tragedy at Fukushima demonstrated that nuclear tragedy can happen without warning. Protective measures must be in place before the event. If we don't engage in protecting ourselves from this threat now, when will we?

Fukushima - Two Years Later

Radiation from the Fukushima Daichi Nuclear complex is a greater threat today than it was … when the tidal wave engulfed the reactor complex. Since then, workers have cobbled together stop-gap measures to contain deadly radioactive materials and contaminated water used to cool the reactors and keep them from causing an even greater disaster. Every day that passes without a long-term solution to the mounting threat brings the world closer to a large-scale nuclear disaster.

Workers are still battling to cool the melted and fused nuclear fuel rods in three reactors within the complex. More than 100 thousand tons of contaminated water are stored in huge tanks on the complex. At least 300 tons of contaminated water has leaked from one of those tanks and it is suspected other tanks have also leaked radioactive-tainted water.

The radioactive water in those tanks is so potent a person standing within twenty inches for an hour would receive five-times the average annual global limit of radioactive exposure for nuclear workers. After ten hours, the person would develop radiation sickness with symptoms including nausea and a drop in white blood cells.

In addition to the huge tanks of water on the site, water that seeped underground during the frantic attempts to cool the reactors immediately following the tidal wave, is slowly migrating toward the Pacific Ocean. The threat continues to grow as 400 tons of water, from nearby mountains, seeps into the reactors and must be pumped out daily.

It is estimated that 300 tons of contaminated water leaks into the Pacific Ocean daily. Workers are now constructing a steel sea wall to contain the underground water, but there is no certainty that it will work. One proposal calls for freezing the ground water surrounding the facility to create a barrier against water intrusion. This is a solution that is technically possible but given the long time such a system will need to be in operation, it may not be practical

The radioactive material from Fukushima is likely to be a threat forever. The Fukushima nuclear fuel was a mixture of uranium and plutonium. Contaminated water from the plant contains Cesium 137, which has a half-life of thirty years. Plutonium 239, is produced by the reactor. It has a half-life 24,000 years, and decays to U-235 which has a half life of 703.8 million years. U-238, which is the basic fuel used in most reactors has a half life of 4.5 billion years.

As time passes, the situation at Fukushima will continue to become even more dangerous. Piping used to bring cooling water to the reactor cores will become corroded. Steel barrels will begin to rust and the pressure from underground water will grow. Eventually, as the amount of radioactive material increases, the threat of a spill would be catastrophic.

… From the moment the Fukushima event first began, TEPCO, the plant operator, has been less than forthcoming with information about what was happening inside the reactors, how dangerous the situation had become or how the company plans to restore the location to some form of stability. The people and political leaders in Japan were embarrassed and at times outraged by the lack of competency and credibility of TEPCO. Recently, the Japanese government reported that it is assuming overall control of Fukushima from TEPCO.

… There is still no clear explanation of the current or continuing threat Fukushima poses. There also is no clear explanation of plans to remediate that threat. Some might say, Fukushima is a domestic problem exempt from the meddling of other nations. Given the potential for worldwide impact, it is imperative that fixing the Fukushima problem requires the cooperation, skill and knowledge of people from all nations of the world. Until the Japanese people and government acknowledge that Fukushima is on the verge of being out of control and assistance from wherever it can be recruited is necessary to fix the problem, we will go from bad news to worse news and the threat will grow ever greater to us all.

CHAPTER THREE

HEALTH AND HEALTHCARE BUSINESS

Former President Calvin Coolidge was once famously quoted:

"After all, the chief business of the American people is business. They are profoundly concerned with producing, buying, selling, investing and prospering in the world. I am strongly of the opinion that the great majority of people will always find these the moving impulses of our life."[186]

Today's assessment would be the chief business of much of corporate America is to handle the American people's healthcare concerns and make sure the US Government pays for it with the least amount of accountability possible. The irony of this may be that the earlier statement was descriptive of a disorganized but efficient system of commerce, whereas the latter reflects a highly organized yet highly inefficient system that represents a central pillar of the current US economy.

The Search for A New Sweet Spot

The new Coke and Pepsi Challenge: How to profit from new high-caloric sweetener

Taxes and sweetener science

The United States is addicted to two commodities – oil and high-caloric sweeteners in the form of high fructose corn syrup and other sugar-based sweeteners. If the oil stops flowing our economy will come to a halt; if the high-caloric sweetener stops flowing, our economy and the health of the nation could benefit greatly. The cost of the U.S. high-caloric sweetener

[186] Robert Sobel, "Essays, Papers & Addresses: Coolidge and American Business," *Calvin Coolidge Presidential Foundation, Inc.*, 1988, https://coolidgefoundation.org/resources/essays-papers-addresses-35/.

addiction is huge. Nationally, two-thirds of adults and nearly one-third of children and teens are currently obese or overweight and sweetened beverages are increasingly seen as a prime cause of the national weight gain.

Increases in deadly diseases over the past few decades have been linked to increased caloric intake from high-caloric sweetened beverages. The American Heart Association reported that increased consumption of high-caloric-sweetened beverages between 1990 and 2000 contributed to 130,000 new cases of diabetes, 14,000 new cases of coronary heart disease, and 50,000 additional life-years living with coronary heart disease.

Several states and a few municipalities are responding to the high-caloric health threat by proposing new taxes on high-caloric sweetened beverages. They see sweetened beverages as an acceptable tax target du-jour to reduce the collective waistline and increase the public coffers.

The Coca Cola® Company (KO) and Pepsico®, Inc. (PEP) are facing a challenge. They can either pay the high-caloric sweetened tax, which will increase the cost of a can of soda and decrease consumption, or they can offer consumers a calorie-free alternative. But that is where the challenge begins. Beverage companies can't just take out the high-caloric sweeteners and add an artificial sweetener.

In the beverage world, taste is king. When it comes to taste, Diet Coke® and Diet Pepsi® are not the same drinks as real Coke® and Pepsi®. That is because taste is a highly complex experience. In addition to the amount of sweetness your tongue detects, the full taste experience includes the viscosity of the liquid, any added flavor and any after taste. Current no calorie sweeteners cannot provide the same overall taste experience as high-caloric beverages.

The new taxes also offer opportunities to increase profits. High-caloric sweetener substitutes and sweetener enhancers cost less than high-caloric sweeteners. Since high-caloric sweetener is a primary ingredient in soda, a can of non-caloric cola is cheaper to produce than a can of high-calorie cola, meaning higher profits per can for the low-calorie drink.

Though branding and marketing strategies in the two dominant soda companies are closely guarded trade secrets, early responses to the high-caloric sweetener challenge seem to indicate each is going in a somewhat different direction. Both companies have had problems when they tampered with their iconic brands. Some Pepsi Cola variants were discontinued when they failed to catch hold and Coca Cola faced a consumer rebellion after attempting to replace its iconic brand with New Coke in 1995.

Instead of changing the Coke formula, Coca Cola appears to have embarked on a diversification strategy, introducing new products to capture control of additional segments in the beverage market. Coca Cola now lists 3,300 products in 200 countries on its Web site. Among them are familiar brands like Dasani® water, Fanta® orange soda, Fruitopia® juice drinks, Minute Maid®, and less familiar brands such as Haru No mint green tea, which is sold in Korea.

Pepsico may be preparing to meet the high-caloric sweetener tax challenge differently. Though Pepsi was first to diversify, and now lists hundreds of products under the Pepsi-Cola, Frito Lay®, Tropicana and Quaker® brands, Indra Nooyi, Chairman and CEO of PepsiCo, has written, "Companies like PepsiCo can and must continue to provide more information, healthier products, and encourage people everywhere to embrace more active lifestyles." By 2020, she is committed to reducing the average added high-caloric sweetener to Pepsico

products by twenty-five percent and saturated fat by fifteen percent, and by 2015, she wants to reduce the average sodium per serving by twenty-five percent.

A high-caloric sweetener tax could be a win-win-win for beverage manufacturers, governments and people's health. In the short-term, states, and possibly the Federal government, would collect much-needed revenue. Over the longer term, beverage companies are likely to see a reduction of the cost of goods for sweetened beverages.

Sometime, further into the future, as people switch from high-caloric sweetened sodas to non-caloric ones, high-caloric sweetener consumption would decline and so would the frequency of overweight and obese people, thus reducing the incidence of weight-related disease.

A consumption tax would apply equally to every can or bottle sold. That means a flat beverage tax would be a greater burden on those with lower incomes, which would be doubly beneficial since the incidence of overweight, obesity and accompanying weight-related medical problems go up as income goes down.

A Study by the Trust for America's Health and the Robert Wood Johnson Foundation, concludes that 35.3 percent of adults earning less than $15,000 per year were obese, compared to a 24.5 percent obesity rate among adults earning $50,000 or more per year. Their studies show that obesity is more prevalent among poorer people, Southerners, Blacks and Latinos.

Beverage companies can't step up to the high-caloric sweetener tax challenge alone. Two small companies are ready to help. They are developers of unique high-caloric sweetener substitutes and sweetener-enhancers that hold the promise of reducing both soft drink calories and soft drink cost of goods.

Senomyx, Inc. (SNMX) recently received a $7.5 million non-refundable payment from PepsiCo just to negotiate an exclusive agreement for a unique high-caloric sweetener substitute that would be used in all non-alcoholic beverages. If Senomyx and Pepsico can develop new non-caloric beverages that are indistinguishable from high-caloric sweetened beverages, both companies will benefit greatly.

Senomyx currently collaborates with seven of the world's leading food, beverage, and ingredient supply companies: Ajinomoto Co. (AJINY.PK), Inc., Campbell Soup Company (CPB), Firmenich SA, Nestlé SA (NSRGY.PK) and Solae. These collaborations provide Senomyx with research and development funding, milestone payments and sales royalties

Redpoint Bio Corporation (RPBC.OB) is another small company developing an artificial sweetener. Redpoint signed an agreement with International Flavors & Fragrances Inc. (IFF) at the end of June to develop a sweetener enhancer in virtually all food and beverage categories. Redpoint's enhancer is based on Reb C, a byproduct of extracting Reb A, the all-natural sweetener ingredient, from the Stevia plant. When used alone, Reb C allows a twenty-five percent reduction in high-caloric sweetener when combined with Reb A, it allows a fifty percent reduction in high-caloric sweetener while still maintaining the taste quality of the fully sweetened product.

We may start seeing new high-caloric sweetener taxes in the near future. In the 2009-2010 Legislative Season, sixteen states and two cities tried to impose new high-caloric sweetened beverage taxes and the Congressional Budget Office recommended a national excise tax that would generate an estimated $50 billion between 2009 and 2018. The revenue from these taxes would be directed to healthcare costs and anti-obesity programs.

These taxes are controversial. Some people see them as an infringement of individual freedom, but increasingly, Americans see them as beneficial steps to improve health, much like the cigarette taxes imposed several decades ago. Support for such taxes increases when people are told the revenue will be used to combat obesity.

The potential benefit for the health of the nation is great. Reducing diseases caused by overweight and obesity can make a significant impact on the national healthcare bill of $2.5 trillion a year. A high-caloric sweetener tax will not, in itself, solve the healthcare issues we face. We need to reform overall diet, increase exercise and improve our quality of life to have a major impact on the health of the nation, but such a tax would be a step in the right direction.

Trademarks

Coca Cola, Coke, Diet Coke, Fruitopia, Minute Maid are registered trademarks of the Coca Cola Company.
Pepsi Cola, Pepsico, Pepsi are registered trademarks of Pepsico, Inc.
Frito-Lay is a registered trademark of Frito-Lay North America, Inc.
Quaker is a registered trademark of the Quaker Oats Company
Listed Companies Mentioned in this article: Coca Cola Company (KO), Pepsico, Inc. (PEP), Senomyx, Inc. (SNMX), Redpoint Bio Corporation (RPBC.OB), Ajinomoto Co. (AJINY.PK), Inc., Campbell Soup Company (CPB), Nestlé SA (NSRGY.PK)

Big Pharma Learned the Wrong Marketing Lesson[187]

As the art and science of marketing focuses on statistically smaller but economically more powerful targeted customer groups, large pharmaceutical companies need to take a lesson from small companies that are creating new markets and new opportunities for already cleared drugs. Two such companies - Alexza Pharmaceuticals and NuPathe are leading the

[187] Steve Brozak, "Big Pharma Learned the Wrong Marketing Lesson," *Forbes.com*, May 25, 2013, http://www.forbes.com/sites/stephenbrozak/2013/05/25/big-pharma-learned-the-wrong-marketing-lesson/#7cf1c346c452.

way, by developing new distribution devices to more effectively deliver already approved drugs using innovative new technology.

Large pharmaceutical companies like Pfizer, Merck and Lilly are often celebrated for their marketing acumen. But, when compared with really successful marketing companies like, for example, the Internet giant Google, their performance is less than stellar. True marketing leaders, like Google, must innovate continuously to stay ahead of the market, by creating needs, rather than only responding to them. To them, marketing begins with choosing which products to develop and ends with the sales process. That is what Google has accomplished with Google Glass.

With the advent of the Information Age, marketing has been transformed from mass distribution to targeted, individualized communications aimed at smaller and smaller demographic groups. Recipients of marketing messages are chosen based on criteria such as age, income level and the last item for which they searched on the Internet. Eventually, marketing efforts could become unique to the individual for whom it is intended.

Large pharmaceutical companies have yet to catch up to the trend. For decades they have thrived on a one-pill-for-all model and an old-fashioned, door-to-door approach to marketing, where so-called "detail people" hand out starter-dose samples of new drugs they want doctors to prescribe. In the past several years, big pharma companies have also begun advertising directly to consumers on television and in print, telling potential patients, "ask your doctor" to prescribe a variety of powerful medicines that can often have multiple and potentially dangerous side-effects.

Big pharma needs to learn to stay ahead of the marketing curve—to innovate targeted products for specific populations and to focus its marketing on those populations. Yet big

pharma seems locked into the quest for billion dollar blockbuster drugs that can support large bureaucratic organizations.

One way big pharma can learn from companies like Google is to give old products new life by improving the products themselves or the delivery systems of existing products. New delivery systems provide an opportunity for drug companies to repackage tried-and-true drugs and regain market exclusivity based on the innovative delivery process. That is what Google is doing with Google Glass. Glass delivers existing products, like mobile telephony, the Internet, global positioning systems and more, through a new, wearable system. In this case, Google is applying new technology to enhance the effectiveness of existing technology, something big pharma rarely does.

What big pharma shuns, little pharma sees as an opportunity. We have followed two companies with new delivery systems for previously approved drugs. These delivery systems make administration of the drug easier, increase the speed the drugs become effective, reduce side-effects and promise to deliver healthy revenues to their developers.

One of these companies is Alexza Pharmaceuticals (ALXA) It has developed an aerosol delivery system for already-approved drugs, called the Staccato system. The company's first product, ADASUVE was approved in January 2013. It combines a 1974-vintage anti-psychotic drug, loxapine, with the company's new delivery device. (An animation of the Staccato system can be seen at http://www.alexza.com/about/the-staccato-system/staccato-animation).

The $33 billion Israeli pharmaceutical company Teva Pharmaceutical Industries Limited (TEVA) must have seen significant potential for the Staccato system when it signed a deal with Alexza in early May worth up to $235 million including $40 million

up front. Under the deal, Teva will be responsible for all U.S. development and commercialization of ADASUVE, including the U.S. post-approval clinical studies and any additional clinical trials for new indications. Alexza will manufacture ADASUVE and supply it to Teva for clinical trials and commercial sales.

The broad implications of this technology reflects a logical paradigm shift in critical emergency room and acute-care medical settings. Teva's foresight is that it is not acquiring just an individual drug, but a platform for many new drug combinations.

Thomas King, President and CEO of Alexza says, "The Staccato system is potentially a disruptive new technology because it increases speed of availability and action of known drugs. Staccato exemplifies the benefits of changing the method of drug delivery to address critical unmet medical needs, where speed of action and ease of administration are key to the meeting the patient's need."

NuPathe (PATH) is another company with a unique and new delivery system for already approved drugs. NuPathe created a system called SmartRelief. It delivers medication through the skin, using iontophoresis, which transports molecules through the skin using mild electrical stimulation. It is sometimes called an injection without a needle. The company's lead product, ZECUITY, delivers sumatriptan, which became a generic drug in 2009,[188] to treat acute cases of migraine with or without aura in adults. ZECUITY was approved by the FDA in January 2013.

Armando Anido, CEO of Nupathe said "Zecuity is the first and only FDA-approved migraine patch and is a game-changing treatment option for millions of patients who suffer from migraine headache pain and migraine-related nausea. We look forward

[188] "Imitrex Generic: An Introduction," *Migraine.com*, http://migraine.com/migraine-treatment/imitrex/generic/.

to securing commercial partners and preparing for the launch of Zecuity, which is expected in the fourth quarter of this year." The fact that NuPathe continues to negotiate for partners reflects a major lack of understanding in the greater pharmaceutical industry.

The point is that corporations, like animal species, must adapt or die. The business world is replete with examples of corporations that failed to adapt and are no longer in existence. Western Union telegrams, Woolworth's five and ten-cent stores, Sharper Image stores, Commodore computers and Lehman Brothers investment bank are just a few examples of once successful dominant businesses that failed because they became stagnant and were overtaken by competitors. Companies using new technology and evolving marketing techniques to capture markets and displace predecessors, like WalMart in retailing, Zappos in footwear, Volkswagen in cars, and others, were late entrants into existing markets that eventually surpassed competitors. Big pharma, beware, the same could happen to you.

Big Pharma Fines

As an analyst of the healthcare industry, I frequently examine details about companies that could provide an early indication of changes in their status. I recently examined the fines and settlements the five largest grossing U.S. pharmaceutical companies paid in the last five years to see if there is any hint there about future performance.

Pharmaceutical companies generally do a good job of obeying laws and regulations to avoid fines, but when they do transgress, the fines can be huge. Among the largest pharma fines are Pfizer's $2.3 billion fine for illegally marketing Bextra, Abbott's $1.6 billion fine for off-label marketing of Depakote, Johnson & Johnson's $1.2 billion fine for mitigating the

severity of side-effects of Risperdal, Eli Lilly's fine of 1.4 billion for off-label promotion of Zyprexa and Merck's $950 thousand fine for off-label marketing of Vioxx.

Fines for misdeeds are a way to incentivize companies and individuals to perform in a desired manner. If the fines are too low or irregularly applied, they have little or no impact. If they are too high, people to avoid the activity. For example, a shopper paying a one dollar fine for a parking meter violation would see the fine as so trivial that meter time limits would be ignored, whereas a $1,000 fine might cause shoppers to avoid going into the community that levies such a fine.

… The top five revenue-producers among U.S. pharmaceutical companies paid close to $6.8 billion in fines, equivalent to the gross domestic product of Tajikistan (number 142 on the World Bank list), but revenue for these companies in one year alone topped $196.9 billion, equivalent to the gross domestic product of Peru (number forty-nine on the same list).

To put the impact of the fines into perspective, the total fines for five years were equivalent to less than 3.5 percent of the revenue of these companies for one year. What is more difficult to determine is how much these companies paid to settle civil lawsuits, which are usually dependent on the recipients of settlements not disclosing the amounts paid.

The question we need to ask ourselves is whether these pharmaceutical companies are acting in accordance with laws and regulations or whether the enforcement agencies are too lax. No one will be able to answer that question without an expensive and time-consuming investigation.

What is important is that as these companies are forced to reduce staff and overhead due to shrinking revenues caused by the patent cliff and generic drug competition, whether they will continue to keep costs of fines at such a low percentage and whether the enforcement

agencies will continue to practice strict oversight. Any significant deviation from this historical norm, could be an indicator of difficulties for a leading pharmaceutical company and should be viewed with caution by investors.

The 5 Things You Should Know When Your Healthcare Claim Is "Denied"[189]

I am often asked to comment on a range of medical treatments – from new drugs to medical devices and procedures. Investors will inquire about a new treatment or procedure to gauge the likelihood of a product's success, or to understand if there is a market for a particular treatment. But recently, and with greater frequency, I have been getting calls from individuals detailing obstacles they face to receiving medical treatment. Many of these calls concern costly and essential treatments or procedures, and with growing frequency, these callers have been denied reimbursement by their insurance companies.

Unfortunately, this is not an uncommon practice in the healthcare industry and with or without Obamacare this trend will continue. In fact, according to AARP, 200 million claims are rejected every year, and there are a range of reasons for an insurance provider to deny a claim. Based on some research, we have identified five things you can do to have an insurance claim approved, even after it has been denied.

1. Identify why your claim was denied. There are many reasons insurance companies can deny a claim. The first step is to find out why your claim was denied. Call your doctor, insurance company or hospital as soon as you receive your Statement of Benefits to find out why your claim was denied. Here are some of the common reasons for denial:

[189] Steve Brozak, "The 5 Things You Should Know When Your Healthcare Claim Is "Denied"," *Forbes.om*, October 26, 2013, http://www.forbes.com/sites/stephenbrozak/2013/10/26/the-5-things-you-should-know-when-your-healthcare-claim-is-denied/#79922a344ba7.

- Incomplete or inaccurate insurance information
- Lack of pre-certification or prior authorization
- Non capture of tests or procedures
- Diagnosis and procedure coding errors and omissions
- Past timely filing limits
- Insufficient medical necessity
- Co-Pay, Deductible, Patient Portion amounts

Keep in mind that many denials are recoverable given the proper tools. AARP reports about half of denials that were independently denied were appealed successfully.

You are not the first, and you will not be the last person to have a treatment claim rejected by an insurance company. As long as you're calm and organized, you should be able to find a way to alleviate, if not resolve your situation.

2. Enlist the support of advocates. Doctors, hospitals and even health insurance companies can help to reverse your denial. Many hospitals employ social workers who assist patients in dealing with healthcare insurance companies, or obtaining Medicare and Medicaid benefits for those who qualify. These social workers operate as proxies, to qualify patients for benefits that pay for hospital bills. They are employed by the hospital to help patients capture any and all benefits that may be used to pay their bills. Often they are linked with the charity care department of the hospital, because if patients cannot acquire insurance reimbursement, they may become eligible for charity care to help pay bills. If this resource is available, you will want to introduce yourself and explain your case. You should be polite and engaging. Help them understand the validity of your claim. You will want them in your corner to direct you in submitting the correct paperwork.

While you're recruiting your forces, get your doctors onboard as well; they will need to plead your case directly to your insurance company. If your claim was denied due to incomplete or inaccurate information, your doctor may simply need to clarify or correct the claim submission. But, if your claim was denied because of *insufficient medical necessity* or *lack of prior authorization,* your doctor may need to write a *letter of medical necessity.* Such a letter specifies your diagnosis, recommended treatment, and the length of treatment time. Essentially, it lets your insurer know exactly how necessary this denied treatment is for your condition. Templates and examples of letters of medical necessity are available online so that you can familiarize yourself with this type of document.

3. Apply, reapply, re-reapply. It might not make sense to most of us, but insurance companies are trying to spread risk and keep as much money in their organization for as long as possible as they "adjudicate a claim." Eventually, they have to pay up and add their payment to you, as their loss on their balance sheet. They use auditing software, often called "claim review programs" to sift through millions of submitted claims. Others have dubbed this software "denial engines" because their intent is to lower the amount of money paid to physicians and hospitals. These auditing programs work by finding technical errors in billing codes that all doctors, hospitals and clinics, among others, submit for payment. The programs use data-mining technology and can even be tuned to capture a predetermined percentage of financial return. The program's algorithms vary by insurer, therefore the odds of denial or approval are not exact. Shown below are examples compiled by the *American Medical Association,* showing the difference between denial metrics of companies like Aetna AET -0.46 percent, Cigna CI -0.05 percent, Humana HUM +0.28 percent, UnitedHealth Group UNH +0.45 percent and more.

Payer	% of claims requiring rework	Overall rework cost per claim
Aetna	7.13%	$1.68
Anthem	14.30%	$2.64
Cigna	5.45%	$1.25
HCSC	14.85%	$3.32
Humana	7.57%	$2.29
Regence	20.49%	$2.28
UnitedHealthcare	5.36%	$2.13

Figure 3. Administrative Burden Index. The American Medical Association's National Health Insurer Report Card (NHIRC) documents the claims revenue cycle activities of the major commercial health insurers and Medicare. The NHIRC provides metrics on the timeliness, transparency and accuracy of claims processing of these payers in an effort to educate physicians and the public, and to reveal opportunities for improvement.

Regardless of these differences, there is one sure thing – the more times you re-apply, the higher your odds of approval become. If your claim was denied on a technical basis, such as a coding error or untimely filing, reapplying once will likely solve your problem. If your claim was denied on the basis of a coverage issue, such as insufficient medical necessity, you may need to reapply more than once with additional paperwork, such as a letter of medical necessity. After several re-submissions on your behalf, it becomes less advantageous for an insurer to deny your claim versus someone else's new claim, and thus more likely for your claim to be approved. So, don't give up.

4. File everything electronically and keep records. You need to keep a digital paper trail as a reference when dealing with your insurer. Conduct as much of the correspondence between yourself, your insurer, and your doctor or social worker via e-mail. Snail mail is fine, too, as long as you keep copies and logs. Make sure to ask specific, detailed questions that will not be ambiguous to a third party reader should they look into your case. Ask questions like how your claim was filed (whether digitally or physically), and ask for copies of that filing. The more proactive you are with your due diligence, the more likely you are to get a positive result from your insurer. This is because companies, such as Automatic Data Processing,

Inc ADP +0.02 percent or ADP, have developed electronic-claim-filing software with the explicit goal of addressing insurance companies' denial algorithms. According to ADP, their *AdvancedMD*Medical Billing Claim Inspector software "automatically runs more than 3.5 million edits on each claim for CCI, HIPAA, LCD and carrier-specific requirements before the claim is submitted." Specific issues are identified and tools provided to quickly produce a clean claim. As a result, *AdvancedMD* customers' claims are accepted at a rate of ninety-five percent or better. Whatever filing system was used, be sure to ask for digital copies of all documents and e-mails. Remember, companies can profit from consumer ignorance, so don't let this potentially disorderly process stop you from getting your claim approved. A well-kept electronic trail will decrease your chances of a second or third denial.

5. Become aware of the price of the treatment that you were denied. The more informed you are as a healthcare consumer, the better the system will work for you. It's important to understand why your insurer would want to deny a particular treatment. The answer will almost definitely lie with the price of the procedure. Until recently, prices have been difficult to come by. However, several Websites that can aid in obtaining pricing information have recently come online. They include, but are certainly not limited to:

- Federal Database of National Health Care Costs
- FairHealthConsumer.org
- HealthBlueBook.com
- NewChoiceHealth.com
- SaveonMedical.com

Become aware of both the price of the procedure that was denied and the price your insurer will cover, allowing you to negotiate how and how much of the difference you will

pay with your physician or hospital. One insurer, Aetna Inc., has had the insight to make pricing information a bit easier for their clients to obtain. Aetna Inc. has a Member Payment Estimator Tool, which provides cost estimates for more than 550 commonly used health services. If you are insured by Aetna, one step in having your claim approved is that much easier. If not, hopefully your insurer will catch up soon.

If these tactics only work partially, and you're left with a large bill that charity care won't cover, remember, you still have leverage. At the end of the day, physicians and hospitals would rather receive some payment than lose all of it. So be prepared to negotiate.

Digitized Health Records

New technology and technology applied to new purposes always has both beneficial and deleterious effects. Television has destroyed newspapers and disturbed family cohesiveness. The automobile has given humans mobility that was never before possible but increased deaths through collisions, fostered urban and suburban sprawl, increased pollution and global warming and caused families to become separated.

Computers and networking have increased productivity, made mobile offices possible so that people can work anywhere, enabled ordinary office workers to do things formerly requiring highly skilled specialists and made online commerce possible, but people can no longer escape their work to depressurize, personal information has become widely available, and new opportunities for classic crimes have been created.

In the healthcare arena, digitization of personal health-related information will yield the same mix of benefits and liabilities. Teams of doctors will be able to quickly and effectively collaborate on an individual case. Distance will no longer be a factor in choosing a

consulting physician. Robotic surgery could just as easily be performed a continent away as in the next room. As increasingly mobile people move from place to place, they will have access to their complete medical history so that doctors in their new location will be able to understand intricacies of your medical profile. Rooms full of paper files that are vulnerable to fire and flood will no longer need to be retained.

But there is a reason we call computer information as having been encoded. It is code – sophisticated code to be sure but code nonetheless. Ever since Champollion decoded Egyptian hieroglyphics in 1822, it has been axiomatic that "any code, which has been made by man, can be broken by man." As we have seen from recent code breaking for nefarious means of computer code used by retailers, large corporations and the federal government, the axiom is true today with computer code just as it was with the Japanese Naval Code prior to World War II.

If you live in the United States, it is inevitable that your health information will be placed on at least one digital computer. It will place the aggregate of your private health information at risk of being hijacked. But it is likely that much of your health information is already available to anyone who wants to track you. Your doctor's prescriptions have been carefully monitored by large pharmaceutical companies for decades. When information on an MRI, X-Ray or CT Scan is reported to your doctor it is usually sent via e-mail. Hospitals keep extensive records of every admission or emergency room visit that include income verification, insurance coverage, prescriptions and any procedures, including surgical operations that have been performed on you. So the information is already out there. Consolidation programs are available and anyone who really wants to know about you can find out. However, universal, digitized health records will make it easier. The risks are that

people with ulterior motives will gain access to your records – for extortion, to get information for future employment or promotions, to determine credit risk or to sell un-needed stuff to vulnerable people. A whole new service is likely to emerge, one that guarantees protection of your private medical records, just as services to protect you from identity theft have come on the market. Some people and some businesses will be victimized, just as Target shoppers and customers of other large businesses have had their private information used for criminal purposes. Some people may benefit by having access to the information. Whatever the case, most people will be unaffected and, over time, as the technology matures, law enforcement will develop equally innovative and capable programs to stop the malfeasance.

The BitCoin theft is a perfect example of the leapfrogging of criminal and law-enforcement technology. Thieves who stole a half billion dollars of BitCoins will be unable to use the same technology to steal BitCoins again, because both private and public law enforcers have closed that door. In the process they were alerted to other ways thieves could be attempted to steal BitCoins. Will they ever be one-hundred percent effective? No, but they will make a break-in of BitCoin archives (and healthcare archives) so difficult as to be unattractive to virtually all potential crooks and character assassins.

Prophet's Death

When Arnold Relman died on June 17, 2014 the voice of a prophet for the medical community was silenced. Like Cassandra, the prophet of Greek mythology, who was doomed never to be heard, Dr. Relman spoke out about what he called the "medical-industrial complex" that he felt was placing profit above professional standards, yet the prophet against runaway profit was ignored.

Within the memory of many people still alive is the image of the doctor with a little black bag, visiting homes of sick people to deliver caring and cures. When medicine morphed from a highly respected profession where a person could make a living into one in which the practitioner could get wealthy, the little black bag, the care and the sacred relationship between doctor and patient began to erode. Today, many doctors don't even visit their patients in the hospital, because such hospital visits no longer make economic sense.

The consequences of the erosion of trust between doctor and patient are not just emotional. Each new drug must outperform a placebo before it can be considered for approval because the mind is often stronger than the body. So too with relationships, where the patient's confidence in a doctor can have significant impact on the speed and completeness of recovery, or at least make the patient feel better emotionally.

The changes in the relationship began to be noticeable in the 1960s. According to Dr. Relman, physicians and hospitals to saw great opportunity for wealth accumulation based on increased frequency and size of fees that could be collected from private insurance, and later, Medicaid and Medicare payments. The increased flow of money fueled accelerated development of new drugs and medical devices. They, in turn, drove the further commercialization of medicine by providing an opportunity for more doctor visits, more diagnostic tests and more costly prescription medicines. Drug companies saw the opportunity and changed their pricing model from cost-based to value-based pricing. Then pharmaceutical prices soared to the point where a secondary market (generic drugs) became attractive and profitable.

Doctors and patients have become strangers to one another with severe economic impact. It is much easier to agree to cutting the fee of a stranger than a trusted caregiver, and

increasingly, our doctors are becoming strangers. Since most people have little understanding of medical practice, the physician controls consumption and all physicians tend to operate similarly.

If you can't tell one practitioner from another based on quality of care, personality or likelihood of a cure, then price becomes the main criterion. When prices became uncomfortably high, insurance companies were able to place themselves between caregivers and patients to control costs, and, in the process, have added billions of dollars to the national cost of medical care.

In his essay, *The Health of Nations*, Dr. Relman says, "we now live with a seriously defective medical care system, based more heavily on market incentives than the health care regime of any other country in the world. The consequence is that the U.S. pays more per patient for healthcare than any other country on earth and physicians see themselves more as competitive business people than as caregivers." If you are wealthy, you can afford the best care in the world. If you are poor, elderly or live in a rural area, you must take what you can get. The overall consequence is a mediocre system at best.

The U.S. government has incrementally inserted itself into the healthcare industry. Government rarely attempts to fix a problem unless it becomes irreconcilable. Regulations that govern safety requirements for the workplace and transportation, environmental laws and financial market regulations were not implemented until circumstances in those businesses became untenable. Many of Dr. Relman's concepts were incorporated into the Patient Protection and Affordable Care Act, but it remains to be seen whether this complex law will achieve the desired outcome or if it will successfully gain control of medical cost and quality in the U.S.

The healthcare community of doctors, hospitals drug companies and insurers still has time to avert a massive government restructuring of healthcare, but the clock is ticking and unless more attention is paid to how the patient feels, it is likely that strict regulations will be imposed, then Dr. Relman's prophecy, warning against a medical community ruled by marketplace fundamentals and focused on profit will finally be heard.

In the more than three decades since Dr. Relman spoke out about greed replacing idealism in medicine, esteem for doctors has diminished, trust in medical institutions has dwindled, the drug business became a highly profitable industry that is now combining and contracting.

When "take this pill and call me in the morning" replaced the attentive physician sitting with a sick patient through the night, the bond between doctor and patient morphed into customer and consultant.

The generalist who saw patients, delivered babies and performed surgery is now a rare species. Primary care physicians have become traffic directors. Radiologists are invisible to patients. Surgeons are impersonal automota who meet the patient a few days and often a few minutes before a procedure.

When medicine became an "institution"; when hospitals became a place where you are treated by strangers; when doctors ration their time to eight or twelve minutes and drug companies market a wide array of exotic and expensive medicines, price becomes the decision-making criterion.

Physicians who perform surgical procedures or invade the body with a diagnostic tool can still earn a lot of money. However, primary care physicians, pediatricians and

psychiatrists, the specialists that rarely if ever hold a knife, yet who are the gatekeepers of the U.S. medical system struggle along.

Roche and InterMune Beckon Pharma's Summer of Discontent[190]

"Now is the winter of our discontent" was how Shakespeare characterized the despair of King Richard III of England. If Shakespeare were writing about the desperation of big pharma today, he would probably just change the season to summer and call it a day.

As evidenced by what we are seeing, the pharmaceutical industry is going through a fundamental transformation, driven by the need to grow the investor value of earnings per share. The dominion of blockbusters, downsizing, consolidation, acquisition, and tax inversions is symptomatic of the earnings-per-share imperative. More than $260 billion was spent in deals by pharmaceutical, biotechnology and medical products companies through June 2014. The amount spent is the highest on record and more than twice that of the first six months of 2013. And Roche Holding AG (RHHBY), a $246 billion company, has entered into the fray.

Yesterday it was announced that Roche and InterMune, Inc. (ITMN), a $5.8 billion company agreed to a merger. InterMune is a company with a new first-in-class drug, Esbriet® (pirfenidone) that is under review by the FDA, with approval to be decided by November 23. Pirfenidone is intended to treat Idiopathic Pulmonary Fibrosis (IPF), a disease in which the alveoli (small air sacs of the lung) gradually become scar tissue (fibrotic), reducing the patient's ability to breathe and usually causing death within five years.

---

[190] Steve Brozak, "Roche and InterMune Beckon Pharma's Summer of Discontent," *Forbes.com,* August 24, 2014, http://www.forbes.com/sites/stephenbrozak/2014/08/25/roche-and-intermune-beckon-pharmas-summer-of-discontent/#40f276fc256d.

Pirfenidone is a small molecule drug taken as a pill that delays progress of the disease by reducing scar tissue formation and inhibiting inflammation. Pirfenidone also has demonstrated activity in fibrotic conditions of the kidney and liver as well as the lungs.

What makes this merger striking is not that InterMune is the first company that Roche has recently acquired. Roche has been an active buyer in the pharmaceutical asset market since its Genentech acquisition five years ago. Even as recently as early August, Roche acquired the privately-owned, Denmark-based biopharmaceutical company Santaris Pharma for up to $450 million. Santaris is noteworthy because it created the Locked Nucleic Acid platform, which has been instrumental in creating medicines to treat a variety of otherwise difficult to treat diseases.

As notable as Roche's acquisition of InterMune is, it is book-ended by its withdrawal of the rumored bid for the forty percent of Chugai Pharmaceutical Co. Ltd. (CHGCY) that Roche did not already own. This highlights the fluid nature and the fast tempo that we are continually seeing in the new global pharmaceutical order.

In this new order, the acquisition of Genentech five years ago and majority ownership of Chugai should satisfy investors, but Roche realizes it also must acquire approved or soon-to-be-approved products to produce immediate revenue and completely control its assets to please investors. That is why InterMune with its pirfenidone asset is so important. While pirfenidone can't be a replacement for the cancer mega-blockbuster Herceptin, which lost patent exclusivity this July, it has the potential to break the billion-dollar barrier, focusing on patient populations of fewer than 200,000 people in the U.S. and Europe, and that is the critically important conclusion to draw from this deal.

There has been a major shift in pharmaceutical strategy. A line of demarcation has been drawn between old blockbusters and new blockbusters. Old blockbusters commanded a premium price, treated large numbers of people, and were close to being affordable. Those old blockbusters targeted problems like osteoporosis, rheumatoid arthritis, high blood pressure, diabetes, acid reflux and cancers.

Most of the old blockbusters have lost exclusivity and by definition can no longer demand premium prices given generic availability. We are now witness to a new generation of blockbusters. These drugs target diseases that affect small numbers of people and the companies that own them can charge extremely high prices. Some drugs, many of which treat orphan diseases with less than 200,000 patients, can cost as much as a hundred thousand dollars or more each year for the life of the patient. But the pricing for Sovaldi, a drug from Gilead Sciences Inc. (GILD) that treats Hepatitis C, a disease with a much larger population, raises a troubling question. Sovaldi is priced at $1,000 a pill for a total treatment cost of $84,000. With the acceptance of Sovaldi's price by major insurance carriers, we must ask, what influence will Sovaldi's price have on pricing for a broader range of pharmaceuticals?

Even though in 2014 we have seen a record number of mergers and acquisitions, initial public offerings and enactment of new healthcare legislation, the question still remains how to solve the demand for earnings-per-share growth by pharmaceutical industry giants. We have seen that no Shakespearean drama can rival the investment banking scripts being presented to pharmaceutical boards of directors daily. And so, our summer of discontent is sure to be followed by a bleak autumn and more than five hundred years after the death of Richard III, his winter of discontent is likely to return.

Retrophin, Gilead, And Our Healthcare Values[191]

Have you ever wondered how our society values innovation, how it rewards breakthrough discoveries? Most people say that it's the price we place on new drugs that shows how much we value the breakthrough. Supposedly our willingness as a society to pay more and bear extraordinary costs for newer drugs rewards a company for the development costs, risk and, ultimately, the breakthrough it makes. That leaves very little room for bargain hunting in our healthcare system until a generic substitute appears on the market. However, examining the price to the value of goods and services we exchange in society is rarely a rational process. Sometimes, though, it's all too rational as can be evidenced in the recent pricing of a new drug and the re-pricing of a nearly thirty year-old generic drug.

Earlier this year Gilead Sciences, Inc. – a proven cutting edge biotech, an innovator of new medicines, and an acquirer of companies with risky product candidates who then assumes the responsibility to complete clinical trials and commercialize the drug if approved – delivered with a new drug called Sovaldi. It's more than just a treatment. For the majority of patients who receive Sovaldi, it's a cure for Hepatitis C, a chronic disease that eventually destroys the liver leading to complications that could cost well over $600K to treat. Eventually this results in total organ failure and an agonizing death for many patients.

Gilead set the price for Sovaldi at $84,000, which was met with a great deal of controversy and indignation from insurance companies and members of Congress alike. In this instance Gilead is doing what we want our biotech and Big Pharma companies to do: Be

[191] Steve Brozak, "Retrophin, Gilead, And Our Healthcare Values," *Forbes.com*, September 12, 2014, http://www.forbes.com/sites/stephenbrozak/2014/09/12/retrophin-gilead-and-our-healthcare-values/#69d47264fca4.

innovative and cure disease. And for that, $84,000 is a very small price to pay for a cure. Some analysts built models that priced and justified Sovaldi as high as $500,000 for a full course of treatment.

In cases where diseases can't be cured, we manage them on a day-to-day basis and make those diseases chronic illnesses. That's what Hepatitis C used to mean for people afflicted with the virus, a chronic disease. Most new breakthroughs, ones for which we pay some of the highest prices in the world for, only treat to manage disease. Let me be clear: Gilead's drug doesn't manage Hepatitis C; it eradicates it.

Recently a small company called Retrophin, Inc. (RTRX) licensed a generic drug called Thiola in May 2014 from Mission Pharma, a San Antonio, TX based company. Originally approved in 1988 by the FDA, Thiola is sold as 100 mg tablets used to treat a chronic illness called cystinuria. With approximately 20,000 patients in the U.S. with cystinuria, this rare disease is a lifelong affliction for which there is no cure. Patients are usually diagnosed with the disease at a very young age and have an abnormally high concentration of an amino acid called cystine present in their urine. The excess cystine crystallizes regularly into stones that painfully travel through the kidneys, ureters or bladder. Imagine having a kidney stone form or pass once a month, tearing through your organs as it tracks its way out of your body.

Thankfully the drug Thiola helps patients to manage the disease by taking anywhere from five to ten tablets a day to regulate the amount of cystine in their urine. At a cost of about $1.50 per tablet, the cost of Thiola was reasonable and affordable. But Retrophin has just increased the price to $30 a tablet, which represents a nearly 2000 percent increase in price of a single tablet. Keep in mind that Retrophin hasn't conducted any new trials, made any new

claims about the drug, changed its formulation or delivery mechanism. As the only supplier of the drug to the U.S., Retrophin has increased the price for the drug just because it can.

Even though it's a generic drug that any company with development capability could bring to market, there are no alternatives for Thiola on the market. There are also no other pending applications at the FDA for any other companies to bring their version of this twenty-six year-old product to market to compete with Retrophin's drug. This means that patients have to either purchase the drug from Retrophin at a cost of $54,750 to $109,500 per year with the help of health insurance companies like UnitedHealth Group Incorporated or Humana, or seek care elsewhere in the world where the drug is still cheap and in steady supply.

So how is Retrophin turning patients into commodities like barrels of oil without any of the same outrage from insurance companies and Congressional leaders that Gilead received? It probably has to do with the disproportionate attention the media and insurance companies have paid to Gilead's decision to price a new drug that treats a larger patient population.

The reality is that there are so few patients with cystinuria in the U.S. that the amount insurance companies spend yearly for Thiola on these patients is a fraction of their total drug spend. Compared to the number of plan members they provide coverage for with Hepatitis C, for whom health plans could easily spend hundreds of millions a year versus the thousands of dollars they spend on care for their members with cystinuria, it's even more inconsequential. But this might change when insurance companies realize a sudden 2000 percent increase in spending for patients with cystinuria. At ten pills a day, a plan with, say, one-hundred patients afflicted with cystinuria will now have to pay approximately $10,950,000 instead of the roughly $547,500 per year for the same patient population the

previous year. It's more than likely, however, that insurance companies will remain focused on populations with higher spend rates where they can control a greater percentage of their total drug spend, even though some analyze and control spending on the smaller populations with the same degree of rigor.

On average, the cost for caring for a single patient with cystinuria using generic Thiola will probably increase from $2,737.50 per year to $54,750 per year for the rest of his or her life. Gilead will cure your Hepatitis C with a new drug for just under $30,000 more. Now that's what I call a bargain.

I'm Shocked, Shocked to Find That Pharma Is Paying Doctors![192]

As a healthcare analyst anytime I decide to share my judgment on a company or its technology, I must make a disclosure of any relationship between myself and that company. This includes any stock I may hold in that company. It's part of a series of complex laws established to safeguard people's wealth and life savings to ensure transparency and allow investors to receive objective views as they make investment decisions. Doctors regularly engage in similar activities on behalf of drug companies. They stand up before fellow physicians at dinners or weekly meetings at local hospitals to share their judgment on a drug product; the difference is they have no such disclosure requirements despite the fact that they may be rewarded handsomely for their time.

Yesterday a provision of the Affordable Care Act (ACA) went into effect referred to as the Sunshine Act. As part of the provision, the government released a trove of information

[192] Steve Brozak, "I'm Shocked, Shocked to Find That Pharma Is Paying Doctors!," *Forbes.com*, October 1, 2014, http://www.forbes.com/sites/stephenbrozak/2014/10/01/i-am-shocked-shocked-to-find-that-pharma-is-paying-doctors/#94738f15a87e.

through the Open Payments reporting system that may turn out to be the most important facet of the ACA if we actually pay attention to the data and its implications.

Open Payments requires that drug companies report anything of value that is paid to healthcare professionals and teaching hospitals. The objective is to create transparency in the relationship between healthcare manufacturers and healthcare providers. Placing such relationships in the light is a step toward assurance that prescribing information is made solely on medical criteria and best practice.

What can be gleaned from an initial analysis of the data is just how the drug industry gains an advantage by compensating more than sixty percent of licensed doctors in the U.S. The payments are for duties that include giving speeches and other forms of consulting that can often add up to significant fees. These doctors are tasked with creating a favorable relationship between the healthcare manufacturers and other doctors who prescribe their medicines.

Dr. Shantanu Agrawal, who is in charge of the program, said, "Open Payments does not identify which financial relationships are beneficial and which could cause conflicts of interest." This implies that some of these transactions do cause conflicts of interest and that making all the payments visible will discourage inappropriate transactions.

In any other profession self-serving relationships between industry and providers would be disclosed, but until today the relationship between healthcare manufacturers and health service providers has been opaque. Today, for the first time, the Open Payments tracking program reveals how a significant portion of our healthcare dollars are spent. And the amount is huge. Today's report showed 4.4 million payments to healthcare providers valued at nearly $3.5 billion for only five months in 2013.

When the first Open Payment report was made public, a quick snapshot showed a small reporting subset that included four companies which had paid more than $23 million for a category titled "services other than consulting, which includes serving as a faculty member or a speaker at a venue other than a continuing education program." What those four companies spent showed that:

- AstraZeneca PLC AZN paid more than $8.9 million to 4,369 doctors in payments ranging from $1,000 to $6,000;
- Forest Laboratories a subsidiary of Actavis PLC ACT paid more than $7.5 million to 4,870 doctors in payments ranging from $1,000 to $150,000;
- Amgen Inc. AMGN paid more than $4 million to 769 doctors in payments ranging from $1,000 to $125,000;
- Eli Lily and Company LLY paid more than $2.8 million to 1,174 doctors in payments ranging from $1,000 to $120,800.

If these types of payments were being made to decision makers in any other industry, they would be challenged as speaker fees. In New Jersey we would call it pay-to-play. In general we hold our physicians to a higher standard than other professions, but it must follow that there is something wrong if money is exchanging hands between our drug industry and physicians without adequate disclosure.

The Sunshine Act is a major step forward in illuminating the dealings between drug manufacturers and healthcare providers with potential conflicts of interests. But I see two potential shortcomings to the Open Payments system itself that must be addressed. The first shortcoming is the assumption that one stroke of the pen will stop and prevent further threats

to the integrity of the healthcare system. In any situation where billions of dollars are at stake, great resources will be used to skirt the purpose of the system.

The second shortcoming in the Open Payments reporting is the lag in the data and its potential for inaccuracy. A once-a-year report is better than nothing, but gives little information for real-time operational decisions on our healthcare system. The report is a panoramic view of activity over a prolonged period of time that is inscribed at one point in time and is unchanging. The earliest data for this, the first year's report, was gathered thirteen months before it was released. In subsequent years, the earliest data will go back fifteen months. Such information is interesting from a historical perspective but may be less useful in the timely correction of any potential conflicts.

In the final analysis, Open Payments is a significant and solid first step in solving the transparency issue that our healthcare system desperately needs. It is vital to each individual in literal matters of life or death. But it is still a first step and as it is put into practice, further action will be needed to assure continuous data enhancement. The Sunshine Act maybe our best ray of hope to encourage that the best medical practices are the future standard for each patient.

Meningitis Outbreak: Restoring Confidence in the Drug Industry[193]

With as many as 14,000 people exposed to tainted steroid injections, resulting in more than 200 infections and fifteen deaths, and more expected in the coming weeks, the drug

[193] Steve Brozak and Henry Bassman, "Meningitis Outbreak: Restoring Confidence in the Drug Industry," *ABCNews.com*, October 16, 2012, http://abcnews.go.com/Health/Wellness/meningitis-outbreak-restoring-confidence-drug-industry/story?id=17484794.

delivery system is once again coming under scrutiny and has been threatened with loss of confidence.

In the shameful steroid contamination scandal now continuing to evolve, the New England Compounding Center appears to have exploited an astonishing loophole. Compounding pharmacies are supposed to mix custom combinations of drugs from already manufactured materials when ordered by a doctor. Some compounding pharmacies will pre-mix certain recipes. They call it "anticipatory compounding." In the case of the fungus-tainted steroid, the New England Compounding Center mixed a batch of 17,000 doses. Massachusetts Gov. Deval Patrick has said that the company was operating outside the limits of its state license.

"What they were doing instead is making big batches and selling them out of state as a manufacturer would," Patrick said Wednesday at a news conference.

Every few years a major scandal revolving around patient safety brings us closer to a profound question: How can this continue to happen?

Some of the past headline pharmaceutical failures have resulted from negligence, lack of oversight or self-recognized problems. Other problems, like the current steroid tragedy and the distribution of phony heparin just a few years ago are caused by rogues.

Every industry has its offenders and rogues. The world of asset management had Bernie Madoff; Washington lobbyists and political advisors had Jack Abramoff; and football coach Jerry Sandusky is now deservedly serving thirty to sixty years in prison. Yet, even the most stringent oversight can't identify every potential problem and no government can post police at every corner to assure that rules and laws are obeyed.

Drug development and delivery is a long and tortuous process. It starts in a laboratory, where basic scientific knowledge is enhanced and ends when a pharmacist fills a prescription or a patient takes an over-the-counter medication off the drug store shelf.

Science that results in a new drug advances in steps. Building scientific knowledge is like building a brick wall. If the bricklayer has to personally inspect every brick before placing it in the wall, progress is delayed. If the bricklayer assumes all the bricks are solid but some are not, the wall could be seriously weakened or even collapse. In the pharmaceutical world, each brick in the process of developing and delivering a drug must be reliable or people's health, and potentially their lives, are in danger.

The painful reality is that there are many gaps in the reliability and accuracy of the drug development chain. Not only is the end of the chain sometimes tainted, but increasingly, so is the beginning.

Peer-reviewed publications are the standard of excellence in the scientific world. They are the reliable source of progress for each of the disciplines they represent. When peer-reviewed publications publish and then retract a report, it is because something in that report was inaccurate. In a recent issue of the prestigious journal Proceedings of the National Academy of Sciences, the authors reported that there has been a ten-fold increase in retracted scientific papers since 1975.

The authors, who reviewed more than 2,000 reports, concluded that 67.4 percent of the retractions were due to misconduct, including fraud, suspected fraud, duplicate publications and plagiarism. Only 21.3 percent were attributable to error.

Some people believe that this precipitous rise in retractions is caused by sloppy work in a competitive publish-or-perish environment, or that the rate of errors is the same as it

always was, but that detection is more frequent because of increased sophistication of computer systems that detect errors. But computer searches that can detect errors after publication should also be able to detect errors before publication.

Not long ago, you could trust that information in a scientific journal or presentation was truthful. Scientists may have made mistakes in procedure or evaluation, but you could believe they were telling the truth as they understood it. Increasingly, this is not so today. The Department of Health and Human Services' Office of Research Integrity Division of Investigative Oversight reports that it handles approximately 200 allegations of research misconduct each year.

Not that long ago, you could walk into a drug store and be pretty certain that the non-prescription drug you took from the shelf or the prescription drug you received from the pharmacist was pure. Increasingly, this is not so today.

We are now facing questions of integrity and failure of self-regulation, which are the underpinnings of scientific credibility. In previous eras, the scientific community was relatively small and concentrated in Western Europe and the United States. Scientists in a particular field knew one another and read each other's reports. Peer pressure kept most honest and accurate. Data was shared among researchers. Scientists would repeat experiments to verify the accuracy of each other's results. Peer-reviewed publications would make information available to all in a field and government regulation could catch mistakes before they affected the general public.

Science has always been competitive and it is becoming more so. Today, academic researchers are increasingly competing for scarcer government grants. Industrial scientists and corporate laboratories are being put under tremendous pressure because of continuing cost-

cutting initiatives and increasing demands for productivity. The scientific community has become huge, spanning countries that were never before centers of scientific advancement, and the pace of scientific progress has made it impossible to track all advances in a discipline, even in some that are highly specialized.

In a competitive world, where pursuit of patent protection is king, scientists are loath to share data. Peer-reviewed publications have failed to detect fraud and mistakes, while rogue companies and sometimes established name-brand enterprises escape government oversight through loopholes in regulation or the inability of the government regulators to be everywhere.

Though the systems for insuring the credibility of scientific reports and the safety of the drugs we take work most of the time, most is not enough when lives are at stake. There will always be loopholes and regulators will never be able to spot unsafe situations before problems arise. Large fines and factory closings only stop bad drugs from reaching the public after the damage has done. For some companies, billion dollar fines could well become just another cost of doing business that is passed along to customers and shareowners.

The step mentioned in the title may be opening the door to a new era of transparency. GlaxoSmithKline, a large international pharmaceutical company, is taking a radical approach to delivering safe and reliable drugs. After Glaxo was fined $3 billion for misbranding a drug to treat depression in patients under eighteen and withholding safety information about a diabetes medicine, the company said it learned from its mistakes.

… Glaxo CEO Sir Andrew Witty outlined new measures for the company to more openly share its intellectual property and knowledge, and to help stimulate R&D into diseases that most affect the world's poorest people. The company will make clinical research data that

is often closely held, available for review by qualified researchers once a drug has completed the approval process or has been abandoned.

Witty committed to releasing information about 200 of Glaxo's experimental drug compounds that have shown signs of fighting tuberculosis, a huge global health threat for which progress has been stymied. He also pledged that the company will support independent research into other diseases of the developing world.

Glaxo's announcement was a good first step. It may not provide for total transparency, but in an era when billion dollar blockbuster drugs are losing exclusivity, when pharmaceutical competition has never been greater and large drug companies are downsizing to cut costs and maintain margins, Glaxo's initiative is counter-intuitive. Yet it is beneficial for the company as well as its customers.

Glaxo has the potential to take that all-important first step in maintaining confidence in a system that cannot exist without it. Hopefully, by setting an example for the rest of the research and pharmaceutical business, other developers and manufacturers will follow, thereby reducing the need for and cost of government regulation, which is paid for by customers, shareowners and taxpayers.

CHAPTER FOUR

STEM CELLS AND CANCER

The articles of this section focus on 1) how the ban on human embryonic stem cell research, although later lifted, held back the progress of regenerative medicine and 2) challenges and misconceptions in the delivery of cancer therapy and diagnostics. Seventy percent of treatment is based on the "best-guess" model—specific, sensitive and efficient diagnostic tools in cancer will significantly improve survival and quality of life. Structured funding is necessary to reboot regenerative medicine development, improve early detection of diseases, and increase precision in therapy.

The Day Science Died

U.S. leadership in advanced medical science ended on August 9, 2001, when President George W. Bush announced restrictions on human Embryonic Stem Cell (hESC) research. The decision to restrict the number of hESC lines and to halt government funding of hESC research resulted in duplicate hESC research facilities-one for funded research and one for non-funded research. It doubled the cost of hESC research and had the effect of encouraging leading scientists in the field of hESC research to take their work elsewhere.

Within weeks of President Barack Obama being inaugurated, the ban on hESC research was lifted. Under ordinary circumstances, lifting the ban would have been enough. But, as anyone who reads a newspaper or owns a television set knows, these are not ordinary times.

The financial markets have been devastated by the worst downturn since the Great Depression. Government spending is focused on rescuing public and private institutions that

are crucial to economic recovery. Advancing science is nice, but given current circumstances, not viewed as essential. But the issue is as much advancing medical treatment and business opportunities as it is advancing science.

The path from scientific hypothesis through basic research to advanced research and ultimately product/service development is tortuous. The attrition rate is high, so large numbers at the input stage result in relatively small output. Venture capitalists and institutional investors will only invest in technology that has reached a promising stage. In biotechnology, significant in vitro proof-of-concept results are necessary to attract venture capitalist investment. Attracting investment by a large pharmaceutical company often requires successful clinical studies or demonstrated revenue.

Senator Arlen Specter (R-PA) along with Senator Dick Durbin (D-Ill.) took a significant step toward stimulating scientific input that will result in revenue potential when they inserted a $10 billion increase in funding for the National Institutes of Health (NIH) over the next two years into the economic stimulus recovery bill (H.R. 1) passed just a few weeks ago. Of the $10 billion, $3.1 billion is designated for capital improvements and research on comparative effectiveness of health treatments. $1.5 billion is designated "to support additional scientific research…" The remaining $5.4 billion is undesignated in the bill, and probably will be shared by existing programs.

Nature[194] reported in 2006 that the average cost of an NIH grant is $400,000 per year, which would mean that the additional $1.5 billion would fund approximately 3,750 new grants over the next two years. Some of these grants will undoubtedly go to hESC research projects, many will go to other research areas.

[194] *Nature* 443 (October 26, 2006): 894-895.

Under ordinary circumstances, this stimulus funding would be seen as a significant step toward advancing medical science. But, over the past eight years, many scientists and scientifically-oriented companies have taken their work outside the U.S.

Geron is one example of a U.S.-based company that has received significant funding from another government to do offshore hESC research. In May 2008, the company received additional funds totaling US$7.2 million over two years, for a collaboration with the University of Edinburgh to develop hESC-derived hepatocytes for the treatment of liver failure and for use in cell-based assays, as well as to develop osteoblasts and chondrocytes for the treatment of musculoskeletal disorders such as osteoporosis, bone fractures and osteoarthritis.

To understand the significance of the last eight years of benign neglect in hESC research, we need to look back to the last great technology surge. The U.S. through grants, tax breaks and industrial R&D funded much of the breakthrough discoveries in computing and telecommunications during the 1960s, 1970s and 1980s. The surge in new capabilities fostered swarms of new companies that generated tremendous wealth for U.S. entrepreneurs. Thousands of new businesses, some of which became fabulously successful, were formed and the U.S. economy benefitted from being the host nation for many of them.

We believe biotechnology holds the promise of being the next great technology surge. However, because the U.S. discouraged hESC research as a matter of public policy for eight years, much of the fundamental R&D work moved elsewhere. Germany, South Korea and Great Britain are well-known for their efforts in hESC research. Less visible is work that is suspected to be taking place in China and elsewhere.

We believe hESC biotechnology can be a wealth-builder. When biotechnology start-ups succeed, the rewards can be gigantic, but the failure rate is high. We don't believe a bailout is the answer because that will encourage government oversight, which will discourage innovation. We believe that a way to encourage investment in small biotechs at little cost to taxpayers is to give new investors a tax credit for their willingness to take risk. Encouraging investment through a tax credit will give biotechs an advantage in the competition for investors and foster innovation by making capital available for new technology.

There are many examples of beneficial tax legislation and tax credits already on the books--hiring new employees from affected groups, buying a fuel-efficient vehicle or making an "angel investment" if you live in certain states. In 1997, Congress passed a law that gave investors in Qualified Small Business Stock a fifty percent exclusion on tax in stock held more than five years.

We believe a meaningful tax incentive would be beneficial to the biotech industry, would eventually benefit the larger pharmaceutical industry, would yield more breakthrough drugs for sick people and would foster continued U.S. leadership in pharmaceutical R&D. This small investment through preferential tax treatment would yield tremendous return for individuals, investors and the economy as a whole.

Unless the U.S. takes extraordinary steps to recapture the momentum of research, this country will lag in the development of new hESC technology. As we have seen with other technology surges, the country where the R&D takes place is usually the country that reaps the most benefit -- from startup companies to new technology initiatives in established companies. $1.5 billion is a good start, and would be sufficient for a continuing program, but more needs

to be done to foster research and encourage the formation of new businesses in the potentially lucrative hESC field.

Nuclear Medicine Meltdown Threatens Heart and Cancer Patients
Shortage of Isotope Technetium-99 Has Big Implications for Patients[195]

It is time to add a new phrase to the dictionary of disasters: Technetium-99 -- also known as Tech-99 or Tc99m. If you, or someone you know, suffers from heart disease, cancer or a score of other medical conditions, a shortage of Tc99m could be life-threatening.

Tc99m is the radioactive material used in four out of five of the twenty million nuclear medicine procedures performed in the United States every year, and it is now in critically short supply.

The fifty-two-year-old nuclear reactor that produces close to half the world's supply of Tc99m has been shut down and may never reopen. Compounding the problem, Tc99m cannot be stockpiled because it has a short half-life. Doctors and hospitals that use this material must be re-supplied every sixty-seven hours to have a continuous supply.

If Tim Russert, the late host of Meet the Press, had received a nuclear stress test instead of a less accurate echo stress test he might be alive today. If the forty-first president, George H.W. Bush, had not been tested using Tc99m, his diagnosis of Graves Disease might have come later, after significant medical problems had progressed.

---

[195] Stephen Brozak and Larry Jindra, M.D., "Nuclear Medicine Meltdown Threatens Heart and Cancer Patients Shortage of Isotope Technetium-99 Has Big Implications for Patients," *ABCNews.com*, June 15, 2009, http://www.wbbsec.com/attachments/142_Nuclear%20Medicine%2006-15-09.pdf.

The Society of Nuclear Medicine will hold a press conference Monday at its annual meeting to discuss "the latest developments surrounding the international medical isotope crisis." Ironically, the Society announced yesterday that it would bestow its Nuclear Pioneering Award on the three men who innovated the heart test that uses Tc99m.

The award announcement read, "Millions of heart attack patients and other potential sufferers who have undergone a noninvasive nuclear imaging test with the isotope technetium-99 can thank [these] three innovators."

Worldwide, there are five old, high-energy Uranium 235 reactors that produce virtually all of the raw material from which Tc99m is made. They are in Canada, Belgium, South Africa, the Netherlands and France. These high-energy nuclear reactors run on Uranium 235, are forty to fifty years old and have been closed down several times over the last few years.

Chalk River Problems Deal Huge Blow to Isotope Supply

The only reactor in North America that makes the raw material for Tc99m was closed in mid-May. It is located on the Chalk River, 115 miles northwest of Ottawa, Canada. There is no hard information about when or whether the Chalk River reactor will ever reopen. When it was closed, it was expected to be reopened in three months, then eight months—and now some people—including Jean-Luc Urbain, president of the Canadian Association of Nuclear Medicine—question whether it will ever reopen.

The remaining reactors cannot make up for the shortage caused by the Chalk River shutdown, even while running at full capacity. To make matters worse, the South Africa reactor is now closed for scheduled maintenance, adding to the short supply of the

isotope. And in July, when the South Africa reactor is scheduled to reopen, the Dutch reactor is scheduled to close for a few months.

The price of Tc99m has already increased significantly and it is sure to rise further in the coming months. Some Canadian news reports have claimed that hospitals could expect to pay $80,000 to $200,000 more per year for isotopes. More importantly, it may not be available when and where patients need it.

We must now take steps to preserve and increase the limited supply of this critical material. First, we must recognize there is a shortage of Tc99m that is likely to last for a long time. Second, we must acknowledge that the United States should control the availability of its supply of this product.

We need to get the most benefit from a limited supply by using it efficiently. Radioactivity continues around-the-clock. The mother isotope from which Tc99m is made does not sleep, and we must take advantage of this twenty-four-hour-a-day characteristic by identifying hospitals where all patients within geographical regions can receive tests that are scheduled throughout the day and night.

We can maximize the benefit of a limited supply by standardizing dosages. Some tests that use TC99m in off-label applications have no standard dosage. We need to encourage the FDA to set standards for TC99m and accelerate approval of tests that use minimal dosages of this critical material as soon as possible.

Tech-99 Shortage Exposes Weaknesses in U.S. Medical System

We can create a U.S. supply of TC99m. The U.S. needs to allocate the funds necessary to convert an existing reactor or build a new reactor from which the source of Tc99m can be produced. This will free the U.S. from foreign sources and reduce delivery

time of an isotope with a limited lifespan while eliminating international border inspections and delays.

The National Academy of Science and professional societies such as Society for Nuclear Medicine and the American College of Cardiology have called for building a U.S. reactor to produce this critical medical diagnostic for years. The best candidate for conversion of an existing reactor is the U.S. Department of Energy research reactor at the University of Missouri.

Finally, we must ask ourselves what other weak spots exist in the U.S. medical system. We take for granted the availability and affordability of most medical procedures and supplies in the U.S. Yet there is little public awareness of the vulnerabilities in our medical system. Over the past few years we have seen other surprise vulnerabilities -- to anthrax and influenza. It is unlikely that the shortage of Tc99m is the last problem we will encounter. Let's take the step of finding out where all the vulnerabilities are. Without such awareness, we become prey to a new, unexpected tragedy, as we were on 9/11 and the day Katrina hit New Orleans.

Proton Therapy

There are only seven of them in the U.S. They cost more than $100 million. They are larger than a football field. But they hold promise to be a significant new tool in treating cancer for thousands of people.

What we are talking about is proton therapy facilities. Sometimes they are called Proton Generators, other times Linear Accelerators, but whatever they are called, they are products of high-energy physics that generate finely-targeted radioactive beams on tumors to

treat cancer. Proton therapy was approved for cancer treatment in 1988 and thus far only 67,000 people worldwide have been treated using this approach, 30,000 in the U.S.

Radiation therapy, in the form of X-Rays or radiation from different isotopes has been used for decades. The first X-Ray therapy for cancer was attempted as early as 1897.

Radiation destroys cancer at the atomic level. In effect, the radiation scrambles the DNA of the cancerous cells, reducing their ability to survive.

When someone undergoes radiation therapy, energized charged particles, such as protons or other forms of radiation, pass near the electrons that orbit around an atom's core.

The positive charge of the protons attracts the negatively charged electrons, pulling them out of their orbits, which is called ionization. Ionization changes the characteristics of the atom and consequentially the character of the molecule within which the atom resides. DNA molecules are especially susceptible to damage from radiation.

The cells try to heal themselves by developing enzymes to rebuild the injured DNA; however, if damage from the radiation is too extensive, the enzymes fail to adequately repair the injury.

Both normal and cancerous cells go through the same repair process, but cancer cells are less capable of repairing the molecular injury. As a result, cancer cells sustain more permanent damage and subsequent cell death than the normal cell population.[196]

If X-Rays are a shotgun approach to treating cancer, proton therapy is a sniper-rifle approach. If sufficient x-ray radiation is directed at a cancer, it will be controlled. But, standard devices radiate healthy tissue as well as cancerous tissue. Consequently, a less than-desired dose is frequently used to reduce damage to healthy tissues and avoid unwanted side

[196] *The National Association for Proton Therapy*, http://www.proton-therapy.org/howit.htm.

effects. The power of protons is that higher doses of radiation can be used to control and manage cancer while significantly reducing damage to healthy tissue and vital organs.

Though there are only thirty or so Proton treatment centers worldwide, there are close to a half-dozen manufacturers of the equipment. Among the leaders in Proton therapy are well-known medical device manufacturers like GE, Hitachi, Siemens and Phillips, which have agreements with specialty firms like, Varian and the Swedish company Elektra. There are also a couple of less well-known companies that specialize in Proton therapy installations such as TomoTherapy, Accuray, Still River, which is developing a smaller device and IBA (IBAB) the leader in installing Proton therapy facilities.

Proton therapy has the potential to become a killer technology, or as the business schools might call it, a disruptive technology. It is more effective than current radiological cancer treatments and in those areas where proton therapy has become available, it has displaced conventional radiation therapy as the treatment of choice for many types of cancer.

As of when this article was written, there are seven operating proton therapy centers in the U.S. with five centers under development and one being planned.

Operating Proton Centers:
James M. Slater, M.D. Proton Treatment and Research Center at Loma Linda University Medical Center
Francis H. Burr Proton Center at Mass. General Hospital
Midwest Proton Radiotherapy Institute at Indiana University
The University of Florida Proton Therapy Institute
M.D. Anderson Cancer Center's Proton Center, Houston
ProCure Proton Therapy Center, Oklahoma City, located at the INTEGRIS Cancer Campus
The Roberts Proton Therapy Center at University of Pennsylvania Health System

Proton Centers under Construction:
Hampton University Proton Therapy Institute
Northern Illinois University Proton Therapy Center
CDH Proton Therapy Center, a ProCure Center, Warrenville, Illinois
ProCure Proton Therapy Center in partnership with Princeton Radiation Oncology Group and CentraState Healthcare System, Somerset, N.J.

Proton Center in Development:
South Florida Proton Center

There are two ways to generate the protons for proton therapy – using a cyclotron or using a linear accelerator. Earlier systems used cyclotrons and newer ones tend to use linear accelerators.

Proton therapy is now being used to treat head and neck area, lung, prostate, bladder, spinal cord, gastro malignancies, and ocular tumors, among others. Plasma therapy is particularly suited to eye surgery because the tumors are so small and damage to surrounding area can cause significant loss of sight. Some proton therapy sites, such as University of California at San Francisco treat only ocular tumors. Proton therapy offers an alternative to removing the eye of a young person with retinoblastoma.[197]

A Fall for Stem Cells[198]

Injunction Halting Stem Cell Research Funds May Have Far Reaching Consequences

This fall could be an historic season for stem cells. Public debate on government funding of embryonic stem cell research and significant advances in adult stem cell technology will cause the press to shine a light on the technology.

---

[197] Additional information and online sources on this topic
Short pulse lasers http://www.extreme-light-infrastructure.eu/Hadron-therapy-for-cancer-treatment_5_5.php
Proton is a form of hadron. Hadrons are made up of multiple quarks.
Gantry is delivery end of system.
Varian (note not approved by FDA) http://www.varian.com/us/oncology/proton/
Laurence Livermore and Tomotherapy https://publicaffairs.llnl.gov/news/news_releases/2007/NR-07-06-06.html.

[198] Stephen Brozak, Larry Jindra, M.D., "A Fall for Stem Cells," *ABCNews.com*, August 27, 2010, http://abcnews.go.com/Health/Wellness/stem-cell-injunction-impact-research-industry/story?id=11491225.

Stem cells are the most promising pharmaceutical or biotechnology prospect since the discovery of antibiotics. Several companies that are developing stem cell-based medical treatments are poised for major breakthroughs in treatment of life-threatening events, such as heart attacks, strokes and spinal cord injury. Other treatments for a wide range of medical problems are in earlier stages of development.

The summer of 2010 was hardly over when the story begun to unfold. A Washington, DC district judge, issued a temporary injunction halting all federal funding for basic research into embryonic stem cell technology. The injunction states there is a legitimate basis for arguing the matter in court. A full hearing will soon decide the final outcome.

Basic research is the first domino in the line that leads to medical breakthroughs, and until that first domino falls they all stand. If upheld, the decision to withhold federal funds could choke off virtually all embryonic stem cell research in the U.S. because basic research advances the science that leads to development that produces medical breakthroughs.

Judge Lamberth's decision was more about public consensus than science. It was another attempt to decide the appropriate and acceptable direction for research and development in the embryonic stem cell arena.

This is not a unique kind of controversy. Science is always implemented and advanced based on public consensus. Think of any scientifically-based program that has been implemented in recent times – nuclear power, pollution control, seat belts, health warnings on tobacco products – these significant changes only were implemented when the majority of our population agreed they were needed.

The judge's ruling reflects the lack of awareness in the U.S. around research and development of embryonic stem cells. There are two basic classes of stem cells, based on where

they originate. Adult stem cells come from various parts of a fully-developed human. Embryonic stem cells are harvested from the earliest stage of fetal development.

Lack of Understanding Impacts Stem Cell Investments

Public consensus has been reached on advancing adult stem cell technology. Most people believe it is ethical and permissible. Public consensus has not yet reached about whether it is ethical to advance embryonic stem cell technology. The sad fact is that many people who have a position on the matter, and even many sophisticated investors, have little understanding of the difference between the two.

Adult stem cell companies have made great progress toward developing significant medical therapies. They should be unaffected by this controversy. Access to federal funding, financing, clinical programs and investment should continue without interruption. Whether they come from bone marrow, adipose tissue (fat) or umbilical cords, these cells have been a rich resource of new medical promise.

The financial markets have yet to recognize the full potential of these companies. Venture capital is hard to come by. Initial public offerings and secondary offerings by companies with solid technology have floundered.

Following Judge Lamberth's ruling, we saw a drop in stock prices for all stem cell companies, and then a slight recovery. We believe that investors pulled out of stem cells in general because they couldn't differentiate between adult and embryonic cell companies.

For those investors who have knowledge of the stem cell arena, we believe that now is the time to invest because prices are attractive and visibility of advances can be expected as soon as this autumn. Such advances, along with articles in peer-reviewed publications, clinical trial

reports and third-party verifications, will pave the way for a more appropriate reckoning of stem cell stocks in the financial markets.

At some point, possibly in the near future, a breakthrough stem cell medical treatment for a severe condition will be reported. When that happens, those who invested wisely today will be the cover story for financial magazines tomorrow.

Patient Beware: When Stem Cells Harm
A Case for Accelerating Regenerative Medicine [199]

Early in March 2012, seventy-seven-year-old Richard Poling entered a clinic in Bonita Springs, Fla., for a stem cell treatment to help with age-related heart and lung conditions.

Poling, an avid golfer and family man from Indiana, had sought several conventional therapies to alleviate his suffering with unsatisfactory results and was desperate for a treatment that would allow him to enjoy the pleasures of life again. Shortly after receiving his alleged treatment, however, Poling went into cardiac arrest at the clinic and died. According to investigators, the alleged stem cell treatment Poling received was not approved by the FDA.

According to multiple reports, the local cardiologist who conducted the treatment removed fat cells from Poling's abdomen and sent them to a lab that claimed to process and isolate adult stem cells from a patient's own fat. A few hours later, a second procedure was allegedly performed at the same clinic in which Poling had the stem cells injected back into his bloodstream for their regenerative properties. The entire process took one day, and during the hours between the procedures, Poling enjoyed lunch out with his family.

---

[199] Stephen Brozak, Salman Punekar, M.D., and Emad Samad, "Patient Beware: When Stem Cells Harm A Case for Accelerating Regenerative Medicine," *ABCNews.com*, April 2, 2012, http://abcnews.go.com/Health/patient-beware-stem-cells-harm/story?id=16042857.

Poling was the second patient to die under the same doctor's care in the last two years after receiving the supposed stem cell therapy. The physician was already under order by the state of Florida to cease performing any further stem cell treatments pending further review, but the doctor allegedly continued performing various stem cell procedures -- until his license was revoked and suspended after Poling's death.

With all the marvels of modern medicine, there are still medical needs that remain unmet by our conventional health care system. When that happens, desperate people like Poling search for alternatives anywhere they can find them. One of these alternatives is stem cell therapy, a science that is no stranger to controversy.

The problem lies in that most stem cell therapies are not FDA-approved, and thus the market is under-regulated and consists of products that lack standardization and legitimacy. The lack of approved products has generated a gray market for stem cell therapeutics—one that is dangerous and can be deadly.

Even though the United States has taken a passive approach to stem cell therapy as compared to its European and Asian counterparts, there are several U.S. companies vying for FDA approval as they develop stem cell therapies for indications such as heart disease, neurologic disorders and ophthalmologic diseases. While these companies spend hundreds of millions of dollars individually—billions collectively—to conduct groundbreaking research and development, rigorous safety studies, and extensive human trials to establish meaningful uses of their medical technologies, the majority of their studies occur overseas where they are sure to receive swifter review and eventual approvals.

Many patients will go to any lengths for treatment, travelling to another country for more cost-preserving procedures, or travel to receive a treatment not available in one's home

country. Medical tourism isn't practiced by just our very sick. Recently, we have seen an increase in news stories of star athletes who have travelled abroad to receive stem cell therapies to recover from sports injuries. This could inspire younger high school and college athletes, driven by hopes for professional careers, to seek similar treatments from illegitimate stem cell practitioners, with catastrophic results.

Problems arise when patients travel to places where regulation is not paramount and where treatment is questionable to begin with. A simple Internet search reveals that there are many companies willing to sell "stem cell therapies" for virtually any indication in the form of injections, pills and creams without proven scientific basis or medical merit. We have seen physicians claiming that any autologous procedure, one in which the patient's own tissue are used to isolate adult stem cells, are safe to use when adequately processed.

There is no telling, however, without any studies as to the purity of the cells being hawked by today's stem cell alchemists whose concoctions may contain useless cells, such as fat cells that could prove deadly if injected into the bloodstream, or worse, a population of malignant transformed cells that could be cancerous.

This is when we start to see morbidity and mortality associated with these treatments. Stem cell therapy is just the latest in a slew of modalities that will cause patients harm if we, as a nation, cannot bring standardization and regulation to an entire industry.

No responsible party will advocate that the FDA regulate the stem cell industry with less scrutiny and vigor than it does for other therapeutics. However, the FDA may become more responsive after a company has established defensible safety and efficacy profiles for its stem cell therapy.

Once a Phase I safety study has been inspected and the data has met the standards evaluating the chances of adverse events, the therapy should be launched into an accelerated approval process with abbreviated timelines, allowing our sickest patients swift access to safe medical technologies with extraordinary promise. The FDA could allow marketing approval for the treatment and allow remaining questions to be thoroughly answered after the market launch. This is not unlike the culture embodied in the oncology review division of the FDA, which has a culture of fast-tracking treatments that show tremendous results in trials to aid physicians treating our sickest cancer patients in highly controlled environments.

The seriousness of this situation cannot be understated. There are legitimate companies developing products that have real potential to create groundbreaking technology that can offer treatment for conditions that now have had little to no options. Bear in mind these are therapies that have been investigated and validated thoroughly in trials and retrials for close to two decades in multiple animal and human studies. It would be better to have a few years of well-supported products approved by the FDA that have not answered all the questions than several more years of charlatans conjuring stem cell therapies from their basements.

Stem Cell Quandary - Why Is Large Pharma Missing in Action?

One new technology, stem cells, holds the promise of dramatically changing the practice of medicine. With effective stem cell treatments, cancer and heart disease can be prevented and cured, paraplegics can walk, the blind will see and the deaf will hear.

Stem cell treatments will be worth billions of dollars to their developers and even at very high prices per treatment, the overall cost of medical care will shrink. Companies that

develop these treatments are likely to recognize revenue from them for decades, because each stem cell line will be unique.

With all these potential benefits, one would think that those businesses most likely to benefit from owning stem cell therapies - big pharmaceutical companies - and those businesses most likely to suffer from not owning stem cell therapies - the same big pharmaceuticals - would be pouring research and development money into stem cell therapies. Sadly, that is not the case.

The overall preponderance of research and development money for stem cell therapies is coming either from the Federal Government or investments in smaller, development-stage companies. While large pharmaceutical companies are promoting investment in themselves based on dividends to shareowners, smaller companies are carrying the technology forward but are stifled because of the difficulty of attracting investors to development of game-changing, breakthrough medicine.

Ironically, less is happening than those companies, both large and small, would have you believe. Investors who are willing to take a risk on this new technology are unsure which companies to choose. It is difficult for the non-scientist, investor to sort out the claims from performance. Gatherings of multitudes of companies, each claiming to be at the forefront of stem cell research and development give the impression of breakthrough progress, while some of them are laboring to develop incremental steps forward.

Even the Catholic Church is claiming a stake in stem cell progress by holding its Second International Vatican Adult Stem Cell Conference. One would think, with the church's concern for the sanctity of human life, it would be holding its tenth, twelfth or twentieth such symposium.

Meanwhile, large pharmaceutical companies are focusing their development efforts on ultra-orphan drugs where the requirements for success are lower and the promise for reward greater. All this is taking place while there is a great deal of well-placed concern about the rising cost of healthcare in the U.S.

Stem cell therapies hold the promise of saving lives while improving quality of life and drastically reducing healthcare costs. Proposed solutions to the rising cost of healthcare are focused more on cutting costs than achieving breakthroughs. Trimming costs will slow the rate of growth, but unless we are willing to allow large numbers of people to go untreated, or find a revolutionary new way of treating disease, healthcare costs will continue to inundate our economy.

Stem cell research and development should not be the endeavor of a small segment of the medical research and development community but it should be the primary development effort of both large and small pharma. Yet big pharma, with its enormous resources is almost absent from the table.

Big pharma is crucial to development of such a radically new medical methodology because big pharma has the personnel with the development and manufacturing skills to advance the science and the regulatory experience to husband new medical approaches through the arduous clinical trial and regulatory process.

Big pharmaceutical companies have the financial resources to support development of those companies focusing on stem cell research and development, but for how long? As blockbuster drugs lose their exclusivity, the amount of cash these huge companies can generate diminishes. We have already seen significant downsizing, relocations and cost-cutting to maintain profits and pay dividends.

If big pharma fails to board the bus, they could be left in the dust. One breakthrough technology could spawn a new generation of pharmaceutical companies that overtake the old, chemical and biological medicine manufacturers. Without these huge companies investing in their own development programs or partnering with smaller companies that hold promise for new therapies, they could become obsolete.

The Three Things Ken Burns Gets Wrong About Cancer[200]

Rather than focusing on the noble quest of a few scientists and physicians, we must face the reality that cancer is a business

It's almost mandatory that any documentary or news segment describing a new treatment for cancer must pulse with the twin themes of tragedy and hope. The camera follows patients through hospital corridors and rooms as their narratives unfold within the story of a potential cure. The audience waits with the family and patient, hoping for a positive outcome while hooked into the drama of personal catastrophe. Doctors appear in their obligatory white coats, either interacting with patients or seated in carefully staged studies. The latest Ken Burns documentary, *Cancer: The Emperor of All Maladies*, captures and surpasses these hallmarks of the genre.

As an analyst of the health-care industry, I am continuously reminded that real scientific discovery is wonderfully random and human behavior is exactly the opposite in how woefully predictable it is. Viewing the PBS series … left me without what I believe

[200] Stephen G. Brozak, "The Three Things Ken Burns Gets Wrong About Cancer," *Bloomberg.com*, April 3, 2015, http://www.bloomberg.com/news/articles/2015-04-03/the-three-things-ken-burns-gets-wrong-about-cancer.

is a current real-world assessment of the state of cancer. Viewers get only a fragile hope for a positive future.

The statements by experts recorded for the series try to instill a tone of mortal combat in their efforts, but the reality of military efficiency in the so-called war on cancer is unfortunately missing in action. Instead, we face dispassionate decisions made by clinicians to justify clinical trials in which patients receive the perception of treatment to measure a drug's efficacy.

Three well-known axioms of science and medicine are overlooked or glossed over in this documentary series.

1. Most advances in cancer therapy are incremental.

That means patients have cancer-free intervals or see overall survival extended by months. To defeat cancer, however, more than incremental change is necessary. A novel approach and perspective are critical, and Ken Burns includes several breakthrough narratives that have a common theme: "young" researchers with brilliant new concepts who defy conventional wisdom and battle the system until their views become the accepted norm. This scenario unfortunately flies in the face of how cancer research is now funded. According to National Institutes of Health studies, research funding for scientists and physicians under age thirty-five has declined almost eighty-five percent since 1980, while funding for research by those over age sixty-six has increased 700 percent. Innovation may not be the sole province of the young, but even the director of the NIH, Francis S. Collins, has been critical of the folly in this trend.

2. Cancer is a megabusiness that resists change.

The world of cancer is a medical-industrial complex of pharmaceutical and biomedical companies, physicians, nurses, hospitals, and even charitable organizations. The financial costs of cancer are also crushing. According to the NIH, cancer cost the U.S. an estimated $263.8 billion in medical expenses and lost productivity in 2010. The sums are so huge that the participants in the cancer complex protect themselves and each other with precision. The notion of waiting for better and cheaper treatments defies the reality of the business of cancer, which has little if any incentive to bring down costs that would result in slower revenue growth.

If you don't believe me, just look at what is happening with chemotherapies. Older, cheaper drugs that are still used as our primary tool against cancer are completely unavailable in some parts of our country due to a vast drug shortage. No matter what new therapy comes out on the market, chemotherapy is usually the first treatment given to patients. Despite their age, chemotherapies are unfortunately the best weapons we have to knock out cancer initially in a patient's body. None of the companies presented in the Burns documentary want to make chemotherapies because the drugs are so old that they can charge only hundreds of dollars a dose, far from the tens of thousands of dollars commanded by a new drug. Manufacturers can't make enough money off of essential chemotherapy drugs to justify making them.

3. Mergers, acquisitions, divestitures, and corporate relocations are a big part of the cancer story.

Completely missing in the PBS series is acknowledgement of the impact corporate structures have on R&D. The frequent reorganizations and restructuring of businesses often

disrupt research funding, with promising programs delayed and sometimes shut down completely. This pattern plays out when a small biotech company announces a promising new therapy and is acquired by a larger biotech or pharma. The same may occur when a university announces a clinical breakthrough and licenses the program to a large pharmaceutical company, only to have it lost or shelved amongst hundreds of other once-promising therapies.

The Burns documentary does devote some attention to how we apportion the majority of cancer funding to late-stage treatments that have little promise of efficacy. Such a fiscally irresponsible approach would not be tolerated in any other discipline or business. The series highlights the drama of massive interventional therapy that culminates in the rejoicing of a lucky few survivors while offering almost boring descriptions of routine diagnostics, which identify cancer in its early or even formative stages and gives treatment options the best chance of success.

The series concludes with a few suggestions, one of which was that we might ameliorate the mortal threat of cancer by transforming it into a manageable chronic disease, which would be a source of even greater predictable revenue for the cancer industry. Even if turning cancer into a chronic disease is the inevitable future for cancer treatment, the prospect ignores the reality that achieving such a metamorphosis is an insurmountable and unresourceable approach to managing the disease given the state of our health-care system.

I believe that rather than focusing on the noble quest of a few scientists and physicians, we must face the real issues of cancer, which are scientific, economic, and social. We need to acknowledge that cancer is a business, that the present excitement

about immunotherapy is another example of scientists jumping on a bandwagon with the hope that a cure is just around the corner. And we must question the amount and allocation of funding on the prospect for success if a radically new therapy shows promise. Only by focusing a public discussion on difficult issues such as these can we turn the present fragile hope for a positive future into a realistic prospect for a better outcome for all of us.

CHAPTER FIVE

THE BACTERIAL AND VIRAL CONUNDRUM

Our best defense against infectious disease is failing us as bacteria ramp up resistance to existing antibiotics. Investment in novel antibiotics and developmental platforms is essential to outsmarting them. Additionally, many of the following articles focus on how to prepare for sudden epidemics that threaten public health or challenge healthcare infrastructure. This is best exemplified in the articles about the 2014 Ebola outbreak. They may serve as templates in the Zika pandemic or future pandemics.

Controlling Ebola

Containing a widespread disease such as Ebola Virus Disease (EVD) is becoming practically impossible. With no vaccines or anti-viral drugs that are effective against Ebola, the only recourse is to implement non-pharmaceutical strategies. Each strategy can be helpful in controlling the disease and each has its own shortcomings.

Strategy 1 – Containment/Social Distancing

Containment

Containment requires that once a case appears, a geographical area is cordoned off, the people within that area treated and isolated until the incubation period passes. Containment also requires that people exposed to the disease, who are possible carriers, be isolated until they show symptoms or until the incubation period passes.

Containment must be universally applied or it is useless. If a few, infected people escape the containment area, efforts are meaningless.

Social Distancing

Social distancing is the practice of imposing distance between people. The strictest enforcement requires people to not gather in large groups, restrictions on public transportation, closing of schools, suspension of athletic and other public events and other interventions to reduce contact between people. calls for avoiding crowds and limiting large gatherings of people.

Social distancing is an extremely disruptive and expensive intervention. It requires closing schools and daycare centers, which would result in parents staying home to take care of children, creating a secondary impact on businesses. Theaters, arenas and other places where people gather would be closed. Public transportation would be curtailed causing further economic hardship. But people will need to go to public places to buy food, seek medical care, or escape the tedium and monotony of days under confinement.

Home Confinement

This intervention requires people to stay home if they are sick and in its extreme application it requires all people in a designated area to be confined to their homes. If one person in a family is sick, another would be required to stay home to care for the sick person. If the sick person is moved to a care facility, family members will be quarantined until the incubation period passes. Maintaining a quarantine requires tremendous logistical support to provide food and medical care. How and by whom they are to be resupplied needs to be decided. National Guard units, the historic resource for states during domestic emergencies, are not trained in isolation techniques and their members may be reluctant to expose themselves to a deadly disease. Prisons, nursing homes and other group living facilities will be

in dire straits very quickly, and if infection enters one of those institutions, it will run through it like wildfire.

Schools

Dismissal of students from school may lead to the second-order effect of workplace absenteeism for child minding. Subsequent workplace absenteeism and loss of household income could be especially problematic for individuals and families living at or near subsistence levels. Workplace absenteeism could also lead to disruption of the delivery of goods and services essential to the viability of the community."

Workplace

Some businesses will close down by choice. Others will close because of staff absenteeism. The consequence will be lower revenue, decreased ability to meet payrolls and pay for benefits. It will also result in less availability of essential goods and services.

Transportation

Travel on trains, airplanes and buses could be restricted or suspended. This strategy has been validated by a study that showed the 2001-2002 influenza season was delayed because of the total restriction of U.S. air travel following the September 11, 2001 attacks. Of course, any restriction of public transportation would need to be evaluated carefully to assure that the disruption caused by curtailing public transportation would outweigh the disruption caused by the threat of Ebola.

Jails, Prisons and Penitentiaries Pose a Problem

If the Ebola becomes established in the U.S., jails, prisons and penitentiaries could become breeding grounds that would hasten spread of the virus. One sick prisoner could infect large numbers of other prisoners and guards. Prisons are closed institutions. They are often over-crowded. People live in close proximity. There is opportunity for cross-infection from guards, visitors and released inmates. Many prisoners today are immuno-suppressed due to HIV/AIDS and hepatitis infections, which is likely to make them more susceptible to Ebola Virus Disease.

Strategy 2 – Vaccine

Current plans estimate that an Ebola vaccine will be available in limited quantities by January 2015, but best estimates indicate the vaccine will be widely available in 2016.

Five companies have announced plans to start human testing of an Ebola vaccine, including GlaxoSmithKine (GSK), Johnson & Johnson (JNJ), Inovio Pharmaceuticals Inc. (INO), NewLink Genetics Corp. (NLNK), and Profectus Biosciences Inc.

GSK is conducting a Phase I clinical trial to determine safety of its vaccine. GSK acquired its vaccine last year as part of its $324 million purchase of Okairos AG. GSK intends to have 10,000 to 15,000 doses available by January for health-care workers on the front lines of the Ebola outbreak. GSK said it will need six months to figure out how to eventually produce hundreds of thousands of doses.

JNJ has been developing a vaccine for about a decade. JNJ acquired this vaccine when it acquired Crucell. JNJ plans to start human testing of its vaccine in March. J&J expects to

have one hundred thousand doses available by January first and more available doses through the course of 2015. The company expects having more than a million on hand by 2016.

Strategy 3 – Anti-Viral Medications

No approved anti-viral medication is available. Several companies have been mentioned that are developing drugs that may be effective against Ebola. Among them are Tekmira, Sarepta, BioCryst, NewLink, Mapp Biopharmaceuticals (makers of ZMapp).

Economic Impact

The economic impact of a significant Ebola threat could be disastrous. Mandated interventions would disrupt retail businesses, transportation, entertainment, manufacturing and a host of other industries.

How the Business Environment Could Change

During a past New York City transit strike, a city of eight-million people ground to a halt. Businesses of every size from local delis to Fortune 100 headquarters were closed or severely hampered. Schools shut down and people who lived in one part of the city were stranded in another.

Imagine the impact if all essential services – sanitation, police, fire, medicine and food distribution – ground to a halt, not for a few days but for weeks. Imagine if a twenty-four-hour curfew or restriction on group gatherings were imposed. Imagine such shutdowns occurring not just in one large city, but in every community across the United States.

Such shutdowns would affect not just rank-and-file workers, but all levels of leadership, including C-level leaders. Even if rank-and-file employees were available for work, businesses would need either to go into hibernation mode, where resources are protected and preserved until the storm passes, or radically change the way they do business.

Some businesses already have begun anticipating a pandemic. A few weeks ago HSBC announced that it had begun preparations for conducting business with large numbers of employees home sick or caring for family members.

Other Businesses that Could Change

Other businesses could potentially undergo similar radical changes. Any industry that depends on large groups gathering for commerce would be susceptible to change. Industries such as entertainment, transportation, vacation and sports could experience significant disruptions during a flu pandemic.

The $447.6 billion grocery store network is an example of an industry that could be ripe for change. Food processing has become increasingly centralized over the past century to improve productivity and lower costs. After processing, food is transported by rail or truck to regional distribution centers, then to local stores and supermarkets for sale to consumers. Since fresh food is highly perishable, considerable costs are incurred in expedited storage, shipping and handling. Because the points of purchase are so widely distributed, real estate, transportation and personnel costs are high in a business with historically low margins.

Some food chains have instituted phone and Internet ordering for delivery from a central warehouse, but the concept has been slow to catch on. For many people, shopping at a

supermarket is both a chore and an adventure. If going to the supermarket were to become a life-threatening activity, that pattern might change.

Ebola, Coming to a Community Near You

Ebola is a frightening disease. Just the name sounds ominous. But the real threat from Ebola is greater than the name. Last week, Doctors Without Borders reported that West Africa's ongoing surge of Ebola is "out of control." As of last Thursday, close to 400 people have been killed by the latest outbreak in West Africa.

Ebola virus disease, also known as Ebola hemorrhagic fever can be deadly. Since it was first identified in the Democratic Republic of Congo in 1976, two-thirds of those diagnosed with the disease have died of it. In all, there have been 2,387 identified cases, resulting in 1,580 deaths.

Ebola does not always have to be fatal. With proper care, there is a good chance for healthy people to recover. No vaccine and no drug treatment specifically for Ebola virus is currently available. The preferred treatment for the disease is supportive care and treatment for complications.

That care is simple, yet effective. It includes lots of fluids, usually given intravenously from bags of saline solution. Such bags are a staple of modern medical care. They are found, almost universally, beside practically ever hospital bed in the U.S. But the simplest of hospital supplies, saline solution is in short supply.

Baxter International and Hospira Inc. supply 90% of the saline bags used in the U.S. A shortage of saline solution has existed since last December, highlighting the vulnerability of

a hospital supply system that can't even provide the most basic and widespread treatment for a vast array of medical problems.

A shortage, like the current one for hospital-quality saline solution, is always caused by multiple, unexpected events. It all began last January with a higher than expected outbreak of influenza in the U.S., which required more people to be hospitalized and administered fluids. The shortage was increased by the annual suspension of manufacture in late December. A crisis was finally created when manufacturing defects in the finished product were discovered and much of the supply had to be destroyed.

Ebola is caused by a virus. It is transmitted, either by contact with the blood or bodily fluids of an infected animal such as a monkey or fruit bat. Once a person is infected it may be passed on to someone else, but requires close contact or fluid exchange during the time the infected person is showing signs of the disease.

The disease incubates for anywhere from two to twenty-one days. People cannot transmit the disease to someone else until symptoms begin to appear. They begin with a fever, throat and muscle pains, headaches, nausea, vomiting and diarrhea. Then the disease takes a different turn with decreased liver and kidney functions and bleeding.

In an era when global travel is ubiquitous and diseases take longer to incubate than intercontinental travel, a disease like Ebola is especially dangerous. It has a high mortality rate, can be spread from person to person by handling fluids or being in close contact and there is no specific cure for the disease, other than bed rest and fluids.

The Federal government under the Biodefense Advanced Research and Development Authority, known as BARDA, is funding the development of preventives and treatments for several diseases that could threaten our society either as widespread and deadly epidemics or

as biological weapons. BARDA has a fund, established by Congress to support development and purchase stocks of vaccines and medicines for a variety of highly threatening diseases, such as influenza and dengue.

A number of companies have novel approaches to prevention and treatment of such that, if they get out of control, can be life-threatening to large populations. Among them are two small biotechnology companies, Sarepta Therapeutics and BioCryst Pharmaceuticals. Both are developing RNAi technology that could be effective against hemorrhagic diseases like Ebola and Marburg.

The nightmare scenario is one that undoubtedly keeps public health officials around the world up late at night. It is the prospect of a runaway deadly disease that easily can be passed from one person to another through exposure, especially among people who live and work in close proximity. Ebola poses just such a threat. It is now out of control in densely populated areas of West Africa, among people who are recruited for menial work in Europe and the Middle East.

Ebola takes up to twenty-one days to incubate, during which time, the victim has no symptoms, feels normal and cannot transmit the disease to someone else. Once the disease becomes apparent, it is likely those infected with it will pass it to others with whom they are in close contact – fellow workers in dormitories, close family members or even supervisors with whom they come in contact. A pocket of the disease could develop before it is discovered and escape any boundary established to cordon it off because its invisibility during incubation makes a cordon ineffective. The consequence could be widespread infection that establishes itself before the extent of the epidemic is discovered.

In a medically sophisticated world where complex treatments for deadly diseases are administered multiple times daily, it is alarming that the simplest and most effective treatment for so many medical purposes, a bag of saline solution, could be in such short supply. The shortage of this and other necessary medical supplies endangers large numbers of patients, including potential victims of deadly outbreaks, like Ebola. The shortages may just cause patients in industrialized nations to be triaged based on age and pre-existing medical conditions. Those in less well-developed nations may just suffer and die.

Ebola Has Landed[201]

The amount of real time media coverage two American Ebola patients have received has been extraordinary. It may even be the most attention any medical condition has received by the modern media. Meanwhile, in Africa, the current Ebola outbreak is spreading despite local efforts to control the disease, highlighting our misunderstanding of real and imagined disease threats. The disease is now a serious healthcare challenge in four West African countries—Guinea, Sierra Leone, Liberia, and most recently, Nigeria. In the eight days between July 24 and August 1, 285 new cases of Ebola were identified in Africa and 118 people died.

The two Americans infected with Ebola are making progress towards recovery, which reflects how focused treatment and technology can fulfill the vision of what we want healthcare to be. Unfortunately, the experience among patients in Africa reflects the usual

[201] Steve Brozak, "Ebola Has Landed," *Forbes.com*, August 5, 2014, https://www.google.com/url?q=http://www.forbes.com/sites/stephenbrozak/2014/08/05/ebola-has-landed/%2324e050d65c2b&sa=D&ust=1461915775494000&usg=AFQjCNEAHwS5JlZGzThPlubfOhimi9S1Ww.

reality of disease progression – rampant disease and dire outcomes. Dr. Margaret Chan, Director General of the World Health Organization, admitted, "This outbreak is moving faster than our efforts to control it."

The World Health Organization has allocated $100 million to combat the spread of Ebola. It is a totally underwhelming amount given the geographical extent of the threatened area and the large number of people who have already been exposed to the disease. The U.S. needs to allocate significant resources to keep Ebola out of the U.S. and this means addressing it in Africa, while it is containable. The containment protocols espoused over the weekend by CDC officials for the U.S. are to identify and to isolate the patients' family, friends and other contacts until the incubation period has passed in the U.S. Without the same approach in Africa, all our vigilance and infrastructure may only allow the U.S. to more successfully treat the disease than other countries, but we will not be able to stop its coming to our shores.

Returning to the two treated Americans, they received an experimental drug named ZMapp which had previously only been used on monkeys. It was developed by the biotech firm Mapp Biopharmaceutical, Inc. Dr. Kent Brantly was the first of the Americans to be treated with ZMapp. He is the voluntary medical worker in Africa, who arrived in Atlanta, GA over the weekend and was immediately taken to a special wing of Emory University Hospital. Nancy Writebol, a medical missionary, who is due to arrive at Emory Hospital today, is the second person treated with ZMapp.

ZMapp is a serum that is administered in three doses and was produced using a three-mouse monoclonal antibody that has been developed in specially-designed tobacco plants. Mice that were exposed to fragments of the Ebola virus developed antibodies against the disease. The antibodies that the mice produced were extracted and used to treat patients. To

allay any concerns of "exotic" technology, the use of monoclonal antibodies has a long and successful history. Mouse antibodies are even a component of one of the first biological anti-arthritis drugs, Remicade, developed by Centocor Biotech, Inc., which is now part of Johnson & Johnson (JNJ). On the tobacco side, there is also a great body of knowledge surrounding use of tobacco plants to grow drugs. However, a rush to invest in the world's largest tobacco company, Altria Group Inc. (MO), would most likely be premature at this time.

While the technology for the new Ebola treatment is impressive, the Ebola realities are sobering, with more than 1,603 cases and 887 deaths having been reported thus far. But, it is almost certain the disease is more extensive than reported. Dr. Chan reported that frightened patients had left hospital isolation wards, leading to many cases that have not been reported. As a consequence, there may be many more cases that have been treated privately by families in remote villages, distant from government and medical observation, leading to even broader distribution of the disease than previously believed.

The transfer of the two American patients to the U.S. has raised concerns about the disease escaping the Emory Hospital confines and infecting people in the U.S. In assessing real risks, these two patients, who were intentionally brought to America with Ebola are being handled too carefully for there to be an accidental transmission. However, given the current trajectory of events and global travel patterns, there is a high likelihood that others will become infected in America. In that scenario, the current Ebola surge, like a firestorm, will spiral out of control and feed on itself to the extent that it becomes self-sustaining. In the four countries where the disease is now present and in many of their neighboring states, the political systems are unstable, the public health infrastructures fragile and the general population has too few resources to adequately isolate and care for the sick. How we respond

to Africa and the Ebola threat today directly affects what happens here tomorrow. If the Ebola epidemic does not burn out there, it will become a different kind of problem and then we will have more than just perception to deal with here.

Stopping Ebola: Mali Matters; Maine and Manhattan Don't[202]

This has been an attention-grabbing week for Ebola in America. Starting with the diagnosis last Thursday of Dr. Craig Spencer, a physician who returned to New York City from West Africa, and continuing with the involuntary quarantine in New Jersey of Kaci Hickox, a nurse who had similarly returned from abroad, the nation has been transfixed by the perceived risk from a tiny group of health-care professionals. Hickox made headlines today by going for a bike ride after leaving New Jersey's quarantine for her home state of Maine.

It's time to look beyond Manhattan and Maine. The most frightening event from last Thursday didn't concern a humanitarian-minded doctor from Harlem—it was confirmation by the World Health Organization that a two-year-old girl in Western Mali had Ebola. The virus appears to have crossed the border into yet another country that may not have the resources to contain it. The announcement was preceded just hours earlier by a strikingly different and misleading message given by the WHO's assistant director general: "There is reasonable confidence right now that we are not seeing widespread transmission of Ebola into neighboring countries."

Problems with public-health messaging are emblematic of our continuous misunderstanding of this vicious disease. Weeks earlier, the Centers for Disease Control had

---

[202] Steve Brozak and Anne Marie Noronha, "Stopping Ebola: Mali Matters; Maine and Manhattan Don't," *Bloomberg.com*, October 30, 2014, https://www.google.com/url?q=http://www.bloomberg.com/news/articles/2014-10-30/stopping-ebola-mali-matters-maine-and-manhattan-dont&sa=D&ust=1461915775490000&usg=AFQjCNGuvlPnnzTy1unlCZ0Sfkz0LR7_gA.

assured Americans repeatedly that our "superior health-care infrastructure" was fully capable of handling any Ebola cases on our soil. While a full blown epidemic in the U.S. is implausible, the fragility of our health-care system was exposed with a series of grave missteps involving the Thomas Duncan case in Dallas and then again by the unchecked travels of Dr. Spencer immediately after his return from treating Ebola patients.

Health organizations are currently operating off of a long list of hypotheses. We do not know the true numbers of asymptomatic patients, those with Ebola who don't run fevers or give other signs. Nor do we know how long it takes to incubate without symptoms or the most efficacious way to treat the disease.

This brings us to the most troubling issue yet to be addressed with the Ebola threat. Given the inaccurate assurances of our government about Ebola and its fumbled response thus far, we can only speculate on what would happen if and when an outbreak occurs anywhere else. Since Ebola has traveled to the U.S., there is a high probability it has also traveled to other parts of the world undetected or unreported. The recent case of the child who traveled through Mali is a reminder that the virus sees no borders. If our data and understanding of Ebola are insufficient—or worse, wrong—it's only a matter of time before we experience far more serious incidents. Will individuals delay notifying authorities, like Spencer, or refuse quarantine, like Kaci Hickox?

The WHO has been very vocal about the epidemic in West Africa and has concentrated its efforts toward vigilance in spite of its logistical limitations. But it cannot take meaningful action against Ebola. The WHO is a bureaucratic group of "thought leaders" that need widespread financial and political support before accomplishing anything of measure. The format the organization typically utilizes involves more than 200 key opinion leaders to

discuss an issue with a normal two-year time frame to prepare properly for action. This is clearly not an option with Ebola.

As we wrote in *Bloomberg Businessweek* last month, no known therapeutics or vaccines can currently address this outbreak. Proving efficacy and safety of any treatment will be an incredible obstacle given historical constraints. Even if any treatments were widely available, no infrastructure exists in West Africa for their efficient administration. Although President Obama recently appointed an "Ebola czar" to oversee U.S. efforts, the key to stopping the disease will be to establish effective quarantine zones in West Africa and expansive health-care delivery systems. The inability of the health-care systems in West Africa to handle an overwhelming surge in patients has been a major contributing factor to Ebola's spread.

To pull off an effective response requires greater military familiarity than medical prowess. The best way to prevent a global pandemic is to attack Ebola at its point of origin. Only a military presence can establish an infrastructure that will allow for restabilization of the affected countries. To slow Ebola's exponential growth, concentric circles must be drawn around hot spots, establishing zones where containment and medical efforts should be the most vigorous. Control can be returned to local authorities once the virus is gradually cleared from the infected areas. If control is not soon established in the affected regions, then, as a simple tactical matter, Ebola threatens to become a ubiquitous menace and exponentially more difficult to eradicate.

We are still focused on the wrong aspect of the virus. Ebola in Manhattan is a sensational story; Ebola in Mali is neglected and is a harbinger of a potentially much bigger problem than currently believed. We need to stop Ebola at the source, as CDC Director Tom

Frieden has stated, but the source is not a quarantine tent in New Jersey. The developed world has learned the price of hubris and of postponing action, and now we must learn from past mistakes quickly while we still have time.

Why the Ebola Crisis Won't End Without Military Intervention[203]

Ebola has evoked our worst nightmares as it continues to outrun containment efforts. The staggering death toll of the disease, projected to rise exponentially, means the modern world faces a global crisis on par with the plagues of history. Unlike seven centuries ago, there are viable options to fight the disease on a global scale. The longer the world takes to exercise those options, however, the less effective and more costly they will become.

Most people expect that some biotech company will eventually create a vaccine or antiviral, and the high-tech cure will swiftly arrive where it is most needed. Countless Hollywood blockbusters have implanted such fictions in our psyches. Unfortunately the pace of science is much slower, even in the face of mass loss of life. It's true that we have sophisticated manufacturing facilities, but only because of U.S. government spending over the last decade by such agencies as BARDA(Biomedical Advanced Research and Development Authority) and NIAID (National Institute of Allergy and Infectious Diseases) to address the threat of deadly pathogens. These facilities will become critical to our "mopping up" efforts later on. First, however, we must accept that Ebola is a threat to the entire world.

---

[203] Steve Brozak and Anne Marie Noronha, "Why the Ebola Crisis Won't End Without Military Intervention," *Bloomberg.com*, September 16, 2014, https://www.google.com/url?q=http://www.bloomberg.com/news/articles/2014-09-16/why-the-ebola-crisis-wont-end-without-military-intervention&sa=D&ust=1461915775502000&usg=AFQjCNFubQSVQhHDLD6acEc8yK5Bl0nl3A.

As the U.N. General Assembly meets on Tuesday, we must come to terms with the fact that a highly coordinated military intervention is absolutely necessary and inevitable. The U.S. and its allies must be obliged to muster a ready force of 15,000 within thirty days, with almost as many health-care personnel to deal with patients and medical screening. Even prior to this, a secured air-bridge system must be initiated while commercial air travel continues to shut down. An air-bridge will be essential to continue uninterrupted transport of health-care workers, medical supplies, and food.

Why is such an organized and robust strategy required? Reports from Liberia indicate that the situation is desperate. Hospitals have become quarantine zones for the dead and soon-to-be dead. Medicine is no longer even being used on people infected with Ebola. It is especially clear that the Liberia's government is incapable of managing a response; even elected officials have fled the nation. Doctors and nurses have either perished from Ebola or have left the country due to a lack of support and concern for their safety.

Amid the collapse of health-care infrastructure, it is only a matter of time before total chaos descends. The number of infected people is spiraling out of control, with estimates of human infection unreliable. In past outbreaks, transmission contacts in remote areas were counted by the tens; today's infected contacts can reach the hundreds in an urban setting.

The early symptoms of Ebola—fever, chills and flu-like illness—mimic several other diseases, including malaria. Those who may seem to have the disease are put into wards with patients who really do have Ebola. The impending onset of the hot rainy season will make it even more difficult for remaining health-care workers to adhere to wearing full biohazard suits. This will only aggravate the exponential rise in the number of sick and dead: Some

models predict over 100,000 deaths by the end of the year if the rest of the world continues to drag its feet.

Even if Ebola doesn't mutate to become more infectious, we must accept that this virus is no longer an African problem—so far away geographically that it's hard to imagine it touching our own lives. A single passenger on a ship or an airplane could spread the virus to another continent. The Ebola crisis is a natural disaster, like a tsunami or earthquake. But unlike natural disasters with limited global consequences, Ebola is perpetual with far-reaching implications. What we must realize is that Africa is our neighbor and Ebola's global spread is no longer the stuff of fiction.

Five Actions Our Government will take when Ebola Infects 5,000

1. Form a response team that can fly anywhere on short notice. The team should be equipped with supplies and personnel to begin treating, isolating and quarantining regions at the first appearance of a deadly communicable disease, like Ebola. The team would establish proper care facilities, care for patients, train local staff, track down other exposed people and work with local governments to educate, impose and enforce isolation and quarantine.
2. Accelerate development of multiple Ebola drug candidates and a vaccine. The FDA, EMA and other national drug agencies should move suitable drug candidates to primate testing and, if shown to be effective with no severe side effects, into human Phase I clinical trials as quickly as prudent. For those candidates that appear to be beneficial, companies should be helped to advance manufacturing process capability so that in a dire emergency, drugs can be made available to large groups.

British drug maker GlaxoSmithKline will start clinically testing an Ebola vaccine as international health workers struggle to contain an outbreak of the deadly disease. Glaxo will partner with the National Institutes of Health (NIH) to start a Phase I trial, giving the vaccine to a limited number of patients to test its effectiveness, in the next few months.

3. TSA and Customs and Immigration will become Ebola Screeners. Passports will be checked. All who traveled in the infected areas will be detained, a la Ellis Island in 1900s checking for trachoma and conjunctivitis. Because of our modern international transportation system, infected and exposed people can travel to the four corners of the earth before disease fighters are even aware of a threat. Containment to a small geographical area can be impossible for all practical purposes. When there is no treatment for the disease, as with Ebola, isolation, hydration and palliative care, combined with quarantine of people who could have been exposed, are the only means of combating the disease.

4. If and/or when Ebola or other life-threatening diseases arrive in the U.S., there is an encyclopedic set of rules, regulations and resolutions that give the Federal Government broad powers, including police powers, to impose and enforce strict quarantine and isolation. Many of these rules inhibit Constitutionally-mandated personal freedoms. We all need to be aware of the extent of these rules so they can be implemented when needed and not implemented for inappropriate purposes.

5. Poor coordination and lines of responsibility by government agencies will become obvious and the subject of news coverage. FEMA, CDC, NIAID, BARDA and Public Health Service will compete for control, boast about successes and blame

other agencies for failures. All this while the President makes speeches and Congressional leaders blame each other for the situation.

The Last Straw
(A Report on the Threat of an Influenza Pandemic)[204]

The Current Pandemic Threat

Within the last four days, a new strain of influenza has appeared that has caused 103 deaths in Mexico thus far. What is certain is that this strain has genetic components from a number of sources, including human, swine, and avian. Twenty cases have been confirmed in Texas, California and Kansas with, as yet, no U.S. deaths. Possible cases are being evaluated in Europe, Israel and New Zealand. What is also certain in addition to the health repercussions is that a deadly influenza pandemic at this time can only act to aggravate the current global recession to what degree is the only uncertainty.

This report characterizes the potential economic threat of an influenza pandemic, evaluates the current defenses for an influenza outbreak and describes some of the grim consequences of a severe influenza pandemic to individuals, world society and the economy.

Where We Stand

The world is in the midst of a quickly evolving potential medical emergency. What the newly emerged virus does is out of our hands. How the world reacts will determine how badly we are affected.

---

[204] Steve Brozak, *The Last Straw (A Report on the Threat of an Influenza Pandemic)* (Clark: WBB Securities, 2009).

On Thursday, April 23, 2009 an outbreak of a new strain of influenza in Mexico that resulted in several deaths was announced. The next day several outbreaks were suspected in Texas, California, Kansas and New York City and later confirmed as the same strain as the Mexican Swine flu.

By Sunday afternoon, April 26, eighty-one deaths and 1,300 infections were reported in Mexico. twelve cases were confirmed in the U.S. with no deaths. We don't know for certain why the mortality rate is different in Mexico than the U.S. but there are a number of theories. One theory is that many more people than reported thus far have come down with this disease in Mexico and the inevitable result was that some of them died, while not enough people in the U.S. have been diagnosed for a mortality to show up. Another theory is that conditions in Mexico City, a crowded city of twenty-million people with terrible air pollution, may have predisposed people to being more susceptible to complications arising from flu. In more simple terms a comparator might be that living in Mexico City could be the equivalent of smoking a pack and a half of cigarettes a day, thus making people's respiratory system more vulnerable to complications from influenza. Yet another theory is that intervention and emergency care in the U.S. is higher quality and sought earlier than in Mexico City. The final theory is unlikely since only one U.S. victim thus far has been briefly hospitalized.

Dr. Richard Besser, the Acting Director of the Centers for Disease Control and Prevention, announced that the Department of Health and Human Services declared a public health emergency in the United States. He said, "That sounds more severe than really it is. This is standard operating procedure." Declaring an emergency allows the government to free up federal, state, and local agencies and their resources for prevention and mitigation; it allows the federal government to use medication and diagnostic tests that

might not otherwise be available, particularly for very young children; and it releases funds for the acquisition of additional antivirals.

The federal government now has fifty million treatment courses of the antiviral drugs Tamiflu® and Relenza® in the Strategic National Stockpile. Individual states have additional stockpiles of antivirals available to add to the national stockpile. The federal government is releasing twenty-five percent of its available medication, making them available to all of the states, but particularly prioritizing the states where there are confirmed incidents of the flu. In addition, the Department of Defense has procured and strategically prepositioned seven million treatment courses of Tamiflu.

Pandemic influenza outbreaks have arisen on average once every thirty years. Whether this strain evolves into a pandemic is unknown at this time. How deadly it will ultimately become is also unknown at this time. It could blow over or blow up. We don't know. What we do know is whether or not this influenza strain becomes a worldwide pandemic, based on the averages from the past, the world is overdue for an influenza pandemic, and Mother Nature has a nasty habit of meeting her averages.

Prior to the outbreak of the Mexican Swine Flu strain, the World Health Organization (WHO) assessed the threat of a flu pandemic as level three on a six-stage scale, shown on the next page. With the rapid and widespread outbreak of this virus, it is likely that the threat level will be increased.

Following is the chart that WHO uses to illustrate the current status of the flu threat worldwide.

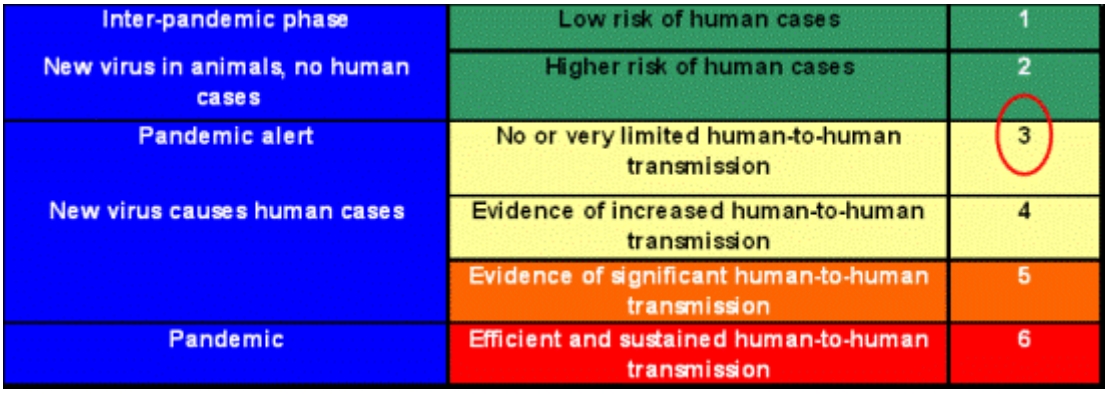


Figure 4. WHO Worldwide Flu Threat. Available at WHO.int.

Like other acts of nature, a severe influenza pandemic is both a medical disaster and an economic disaster. To date, U.S. federal, state and local governments as well as businesses have focused on the medical impact of a flu pandemic without giving much attention to the economic impact. In March 2007, a private agency, The Trust for America's Health (TFAH) issued a report outlining in detail the economic impact of an influenza pandemic on a state-by-state basis and tracked a flu pandemic's impact on twenty industries.[205]

Today, most scientists and public health officials predict an influenza pandemic is inevitable. Some are planning for a catastrophic event, while others are planning for a moderate or mild event. Surviving the medical challenges of a severe pandemic would be one challenge. Economic survival after the pandemic would be another.

How Flu Will Impact the U.S. Economy

The impact of any influenza pandemic depends on the rate of infection and severity of disease, two factors that are unknown with the current threat at this time. During the Bush

[205] "Pandemic Flu and the Potential for U.S. Economic Recession," *Trust for America's Health*, March 2007, http://healthyamericans.org/reports/flurecession/FluRecession.pdf.

administration, the Congressional Budget Office and the President's Homeland Security Council gave a gross estimate of economic impact of a pandemic. They estimated approximately a five percent decline in the Gross Domestic Product (GDP), which would be equivalent to approximately $500 billion, which is about the same as a mild post-World War II recession.

We believe the CBO estimate understates the probable economic impact of a "severe" flu pandemic. In our report, *Flu Scare, Investors Beware*, published December 8, 2005, we offered an industry-by-industry assessment of economic impact from an influenza pandemic. That analysis concluded that the U.S. economic impact could be as high as $800 Billion.

Patient care, insurance and lost work costs for a pandemic could be catastrophic. Costs to the economy based on infection and five percent death rate are shown in the table below. Lost work costs are based on the assumption that the age of all flu patients will be between twenty to sixty-four years old. As the potential impact of a flu pandemic becomes more predictable, these costs are almost certain to become more precise.

Table 6. FLU Patient Care, Insurance and Lost Work Costs

FLU Patient Care, Insurance and Lost Work Costs					
Sickness Rates	25%	30%	35%	40%	45%
5% Death	$ 450,746,775,000	$ 594,985,743,000	$ 631,045,485,000	$ 721,194,840,000	$ 811,344,195,000

Economic impact on stricken individuals or caregivers would be significant. Below is a rough estimate of the economic impact of influenza per infected person if treated at home, in a hospital or if the disease results in death.

Table 7. Economic Cost Per Average Case of Avian Flu per Survivor with No Hospitalization

Absentee Cost by employer	$371 (7 days @ $100 per day for 53% of those ill.)
Absentee Cost of caregiver by employer	$186 (7 days @ $100 for half the population of the 53% of those who become ill)
Lost productivity by patient's employer	(Not computed)
Lost productivity by caregiver's employer	(Not computed
Medical Cost to Insurer	$80 (2 doctor visits and no hospitalization)
Prescription Drug Cost to Insurer	$100
Total Loss Per Patient (no hospitalization)	$737
Added Hospitalization Costs	
Additional Absentee Cost by employer	$371 (7 days @ $100 per day for 53% of those ill.)
Additional Caregiver Absentee Cost by employer	$186 (7 days @ $100 for half the population of the 53% of those who become ill)
Medical cost (7 days hospitalized)	$14,000
Disability payments (6 months @ $500)	$3,000
Total Added Cost per Hospitalized Patient	$17,557
Added Cost per Mortality	
Additional Absentee Cost by employer	$742 (14 days @ $100 per day for 53% of those ill.)
Additional Caregiver Absentee Cost by employer	$371 (14 days @ $100 per day for 53% of those ill.)
Medical cost (21 days hospitalized)	$42,000
Life Insurance Payout	$8,985 ($15,000 payout for people 20 + years of age
Total added cost per mortality	$52,098

The U.S. gross domestic product, which stood at $14.2 trillion[206] in 2008, will be affected by any influenza pandemic. The question is which industries will be affected most and what will be the total impact? If a flu pandemic were to reach disaster proportions, the effect on the economy would be disastrous, thereby negating practically any investment strategy. If the impact of a flu pandemic is manageable, then strategic investment decisions could be made to minimize loss and position investors for recovery.

Industries Temporarily Impacted

Examples of industries that are likely to be only temporarily affected by a flu pandemic are real estate and durable goods manufacturing, because as the economy recovers from a pandemic, the need for these purchases will be restored to their pre-pandemic levels. Other industries, such as broadcasting, hospitality and food services are unlikely to ever recover lost revenue. A simple example of this kind of permanent loss is that people who are sick and don't go to a restaurant for dinner on a given night will not go out to eat at two restaurants in one night when they get well again.

Industries Permanently Impacted

In March 2007, a private agency, The Trust for America's Health (TFAH) issued a report outlining, in detail, the economic impact of an influenza pandemic on a state-by-state basis and tracked a flu pandemic's impact on twenty industries.[207]

---

[206] Bureau of Economic Analysis, U.S. *Department of Commerce*, http://www.bea.gov/bea/dn1.htm.

[207] "Pandemic Flu and the Potential for U.S. Economic Recession," *Trust for America's Health*, March 2007, http://healthyamericans.org/reports/flurecession/FluRecession.pdf.

WBB Securities (WBB) used two sources to size the economic impact of an Influenza pandemic. They are the analysis of select industry groups by the TFAH and a separate analysis of thirteen other industry subgroups by WBB. For the WBB analysis, we conservatively computed lost revenue for the selected industries over a twelve-week period, which is the length of time the U.S. government has estimated activities may be closed or curtailed during a severe flu outbreak. Based on this estimate, these thirteen business classes would lose $325.149 billion of revenue, which would probably never be recovered.

Our analysis includes twelve of the thirteen TFAH industry groups in the following table. These industries account for a $283.261 billion loss of GDP.

Allowing for an $11 billion overlap of these two lists, the total impact in this illustration alone would be $562.552 billion. Analysis across the entire economic spectrum would likely show a greater overall loss.

Table 8. Illustrated GDP Loss in Selected Industries from a Severe Flu Surge

Illustrated GDP Loss in Selected Industries from a Severe Flu Surge						
Affected Industries	Annual Revenue (Billions US$)	WBB/TFAHLost Revenue Percentage for 1 year	WBB Lost Revenue Estimate (Billions US$)	Trust for America's Health Estimate (Billions US$)	Discount for Overlap (Billions US$)	Total Economic Impact (Billions US$)
Agriculture, forestry, fishing, hunting	119.066	2.5%		2.977	1.0	1.977
Flowers, seeds, potted plants	17.1	12.5%	2.14			2.140
Mining	213.574	2.5%		5.339		5.339
Gasoline and oil	185.9	12.5%	23.238			
Construction	593.535	2.5%		14.838		14.838
Manufacturing	1,496.541	2.5%		37.414		37.414
Wholesale trade	733.090	2.5%		18.327		18.327
Retail trade	828.634	2.5%		20.716		20.716
Transportation & warehousing	362.247	16.7%		60.676	5.0	55.676
Purchased local transportation	11.8	20%	2.36			2.36
Purchased inter-city transportation	51.0	20%	10.2			10.20
Finance & insurance	1,011.548	2.5%		25.289		25.289
Educational services	113.082	2.5%		2.827		2.8270
Arts, Entertainment, Recreation	117.921	20%		23.584	5.0	17.584
Admission to spectator events & amusements	32.1	25%	8.026			8.026
Pari-mutuel net receipts	4.9	25%	1.225			1.225
Radio/TV advertising revenue	17.9	25%	4.475			4.475
Accommodation, food services	337.957	20%		67.591		67.59
Food for off-premises consumption	628.7	25%	157.175			157.175
Food and beverages	390.0	25%	97.5			97.50
Alcoholic beverages	40.8	20%	8.16			8.16
Other Services (non-government)	294.611	1.25%		3.683		3.683
Barber shops, beauty parlors, health clubs	42.6	25%	10.65			
Totals	7,644.606		325.149	283.261	11.0	562.521

Insurance – A Special Situation

With 227 million people covered by private health insurance, based on 1998 data,[208] it is likely that the insurance industry, particularly health insurance, will experience a severe financial burden even in a moderate pandemic scenario. Whether insurance companies set aside sufficient funds, or if they have the resources to set aside sufficient funds, for such a contingency is an important question for which answers are not readily available.

Insurance carriers generate $495 billion in revenues annually. Assuming a twenty percent profit rate they generate $100 billion in profits annually from premiums. In a pandemic, we estimate a conservative impact of thirty percent of insurance company annual premiums, which equates to a GDP loss of $148 billion.

The assumption is that the insurance industry could sustain a tremendous number of claims in a short period of time during a pandemic surge. We have seen during other catastrophic events that insurance carriers don't always have the liquidity to cover large numbers of claims from regional catastrophes.

Human Impact of Pandemic Flu

Pandemic Influenza could have significant impact on the entire world population. The chart below shows the U.S. death rate over an extended period of time. While impact on that death rate by widely feared diseases like Polio and HIV have little apparent impact on the overall death rate, the death rate for the entire country spiked in 1918 as a result of the Spanish Flu epidemic.

---

[208] *Statistical Abstract of the United States*, http://www.census.gov/prod/2001pubs/statab/sec03.pdf.

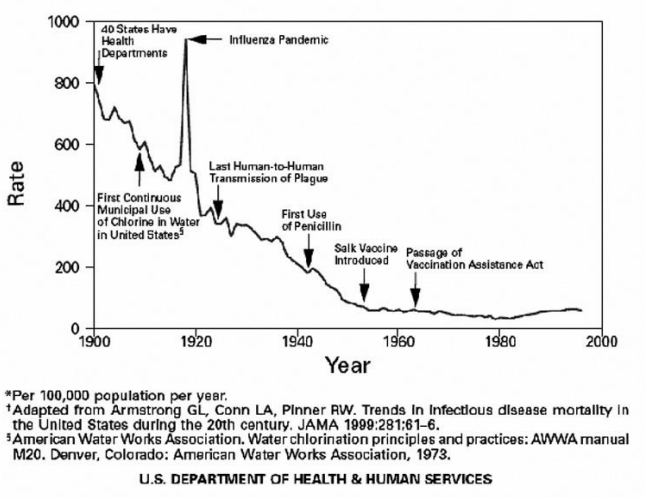


Figure 5. Influenza Pandemic.

Potential Death Rate Depends on Severity of Disease

Predictions of the impact of a pandemic flu vary widely. However, even the most conservative estimates predict tremendous human suffering. As many as 7.4 million people could die in the next worldwide influenza epidemic according to the U.S. Centers for Disease Control and Prevention. In high income countries alone, predictions call for up to 233 million outpatient visits and as many as 5.2 million hospital admissions, with the greatest impact in low-income countries because of different population characteristics and already strained health care resources.[209]

The Centers for Disease Control (CDC) says that in the U.S., without vaccination, a medium-level pandemic could affect up to thirty-five percent of the population (103.25 million people), causing up to 207,000 deaths, 734,000 hospitalizations, forty-two million outpatient visits and another forty-seven million people being sick.

[209] *World Health Organization* Web site, www.who.int/csr/disease/influenza/pandemic/en/.

Other reports are grimmer. Michael T. Osterholm, writing in the May 2005 issue of the *New England Journal of Medicine* reports that if a pandemic were to strike today with the same impact as the 1918 flu, "there could be 1.7 million deaths in the United States and 180 million - 360 million deaths globally."[210]

How Flu Kills

One of the many tragic aspects of the 1918 influenza pandemic was the large proportion of healthy, young people who succumbed to it. It is estimated that eight to ten percent of all young adults died during the onslaught. The death rate spiked among young adults because their immune systems over-reacted and overwhelmed the patients.

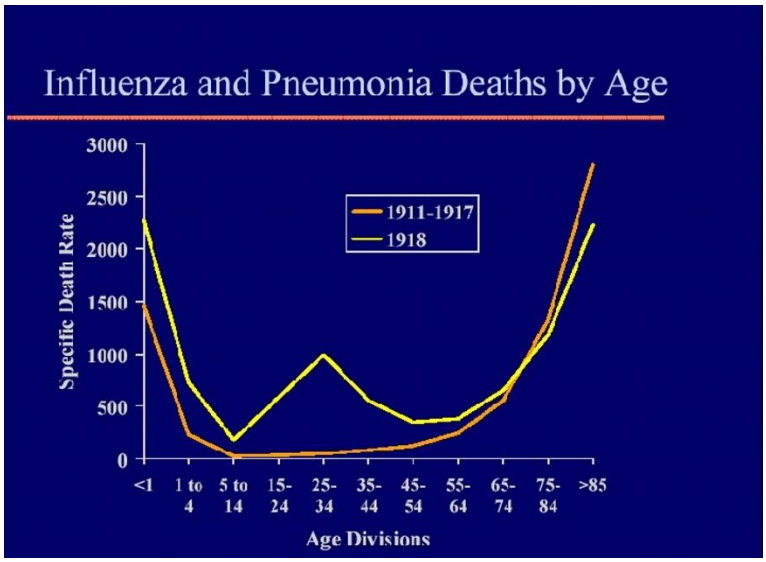


Figure 6. Influenza and Pneumonia Deaths by Age. Available at CDC.gov.

[210] "Preparing for the Next Pandemic," *New England Journal of Medicine*, 352, no. 18 (May 5, 2005).

Flu symptoms include: Rapid onset of disease, secondary infection, sore throat, inflammation and fever, headaches and bone pain. Here is how each of those symptoms is caused by the body's response to a flu infection.

Rapid Onset

Since a virus cell cannot reproduce on its own, it must form a bond with an animal cell. When virus cells invade the human body, they attach themselves to the epithelial lining of the respiratory tract, which stretches from the throat down to the minute air sacs (alveoli) where fresh air infuses blood with O_2 and waste gases, like CO_2, are evacuated from the blood.

About ten hours after the first virus bond is formed, the human cell bursts open, releasing between 1,000 and 10,000 new virus cells. At even the lowest rate of multiplication (10^3 every ten hours) a single virus cell can become one million virus cells in less than three days. This explains the rapid onset of viral diseases.

Secondary Infection

While the virus is duplicating inside the respiratory system, it is releasing chemicals that inhibit the release of interferon, the first line of defense against viruses, making the infected person more susceptible to other infections like bacterial pneumonia.

Sore Throat, Inflammation, Fever and Aching Bones

By attaching to epithelial cells, using them to incubate virus cells and then causing them to explode, even mild viruses can strip the throat of epithelial cells, thus making it sore.

When an infection gets a toehold, the patient's white blood cells respond by releasing specialized proteins called "cytokines." There are many different types of cytokines and each is highly specialized. Some cytokines some attack invaders directly, some act as messengers to other cells such as the cytokines that stimulate the production of more white blood cells in bone marrow, which may cause aching bones. Some cytokines can affect the hypothalamus, deep inside the brain, driving up the body's temperature because some diseases do not tolerate high temperature.

Respiratory Congestion and Asphyxiation

When a killer flu attacks the body, the normal, measured and appropriate responses of the body can over-react. The healthier the immune system, the stronger the reaction can be. This over-reaction, called cytokine storm, can kill quickly and dramatically, especially among people in the twenty-five to thirty-four age group as was experienced in 1918.

In cytokine storm, the capillaries that supply blood to the alveoli expand, flooding the air-sacs with white blood cells, antibodies, other elements of the immune system and more cytokines. More fluid pours into the lung. Pink glassy membranes called hyaline membranes line the alveoli. The fluid that coats alveoli to facilitate oxygen replenishment disappears. Then areas of the lung become tangled in cell debris, fibrin and collagen (blood clotting factors). Proteins fill the space between lung tissue cells. Eventually, portions of the lung become totally blocked, cease functioning and the patient can die.

Setting the Parameters

There are two variables to the potential impact of an influenza pandemic – rate of infection and rates of mortality and morbidity among those infected. The following chart demonstrates the kind of human impact seasonal flu, a mild influenza pandemic, and one comparable to the 1918 flu could have.

Table 9. Factors that Could Impact Death Rate

Severity	Available Vaccine Doses	#U.S. Infected People	#U.S. Hospitalized	# U.S. Deaths
Seasonal Flu (Base Line)	70 mm	40 mm	1 per 400 cases 100,000 200,000 150,000=median	36,000
1999 U.S. Study	20mm	91mm	700,000	100,000-200,000
CDC Moderate Estimate	20mm	35%-94.5 mm	734,000	207,000
Spanish Flu Death Rate	20mm	35%=94.5 mm	50%=47.25 mm	5%=4.725 mm

Variability of Severity

As a conservative planning estimate, if the per-case flu death rate were one percent, higher than the CBO estimate, or 3½ percent of those infected, it would result in another 900,000 deaths. Of the three flu pandemics in the Twentieth Century, the Spanish Flu of 1918-1919 was the worst. It is widely used as a reference point for what a "severe" flu would be like. However, nationwide causes of death weren't kept in the U.S. until 1880, so it is impossible to determine if the 1918 pandemic was an 'out-of-the-ordinary' or a 'to-be-expected' event.

Differences in Age Distribution – Greater Over 65-year-old Population

In calculating the impact of a 1918-like flu pandemic on people over sixty-five, we applied the same illness rate (thirty percent) as the total population for the fifteen million healthy people over sixty-five. This resulted in a total of 4.5 million infected by a pandemic flu. If they were to die at twice the rate of the adjusted death rate for the entire infected population, or 6.6 percent, it would account for 297,000 deaths among healthy people age sixty-five and older.

Using the same calculation for immuno-suppressed people over sixty-five, we anticipate a higher infection rate, conservatively estimated at 1.5 times the overall infection rate or forty-five percent. Even at the same death rate as healthy people over sixty-five, additional deaths in this group would total 617,760. When both groups are added together, the result is a total of 914,760 additional deaths in a flu pandemic due to old age.

The U.S. population distribution is different today than it was in 1918. In 1918 there were only 4.8 million people or 4.7 percent of the population alive at ages sixty-five and older. Today, the sixty-five and older population accounts for 36.3 million people (12.4 percent of the total population) or three times what it was eighty-six years ago.

People who survived to age sixty-five and beyond in 1918 were unusual. They had very high resistance to disease and much stronger constitutions than people at the same age today. They were leaner, stronger and in many cases more isolated than older people today. So it is probable that the case rate and the death toll among the aged would be higher today than it was in 1918.

In 1918, the percentage of older people who came down with flu was relatively low, but the case death rate was relatively high. Since fewer people lived to old age, the impact of the 1918 flu did not disproportionately affect older people.

Immuno-Suppression

More than 100 million people are living today with suppressed immune systems that put them at greater risk from a flu infection. If the death rate among the 100 million who are immuno-suppressed were twice the adjusted rate of the flu death rate for the overall population, it would account for an additional 330,000 deaths.

Many diseases that made people more vulnerable to death in 1918 are no longer threats today. Diseases such as pertussis (whooping cough), tuberculosis, diphtheria, diarrhea and appendicitis are either virtually non-existent, or non-life-threatening events in the U.S. today.

Significant numbers of people who are alive today as a result of modern medical intervention would be at increased risk during a flu pandemic. Many of these people survive with reduced immuno-suppressive systems because the drugs that keep them alive also suppress their ability to resist disease.

Following is the number of people living with selected medical conditions that suppress their immune systems.[211]

- Obesity……. 59 million
- Cancer…….13.9 million (6.7 million over 65)
- Asthma……13.6 million (2.7 million over 65)
- Emphysema …….. 3.1 million (3.1 million over 65)
- Diabetes…… 14.0 million (5.7 million over 65)
- Kidney Disease….. 3.0 million (1.2 million over 65)
- Liver Disease…… 2.5 million (0.4 million over 65)
- Living with HIV/Aids..1.0 million
- Kidney Transplants…… 870,000 (70% of 125,000 transplants in last 10 years)
- Liver Transplants…… 150,000 (70% of 22,215 transplants in last 10 years)
- Heart Transplants….. … 90,000 (70% of 14,000 transplants in last 10 years)

[211] *Summary Health Statistics for U.S. Adults: National Health Interview Survey*, 2003, http://www.cdc.gov/nchs/data/series/sr_10/sr10_225.pdf.

Population Density and Mobility

Today, most of the U.S. population is in urban or suburban communities and it is a mobile society with thousands of people en route to a distant destination on any given day. The combination of today's increased density and mobility could add to the number of people infected in a pandemic flu. At an additional five percent infection rate and a 3.3 percent death rate, increased density would result in 368,000 additional deaths.

The total U.S. population in 1918 was approximately 103 million people. Today's U.S. population is close to three times that number. In 1918, the U.S. was largely a rural country with people in remote communities who only gathered together on Sundays and market days.

During the 1918 flu, the hardest hit locales were the growing cities: Philadelphia, Baltimore, New York, and even relatively small towns like Lawrence MA. In 1918, spread of influenza was accelerated because of the mobility of military and civilian populations due to World War I.

A World Without Old People

With thirty-four million people in the U.S. who are sixty-five-years-old or older,[212] the prospect of an elder tragedy in the event of a flu pandemic becomes very real. Many older people are already living with compromised immune systems. Add to their age and immune system vulnerability the threat of influenza and the result is a recipe for major disaster among this group of people.

[212] "Interim State Population Projections," *U.S. Census Bureau Population Division,* 2005.

The potential for high death rates among the elderly comes not only from the flu itself but from disruption of essential services in eldercare that could cause additional and catastrophic death rates from lack of care.

In the year 2000, 2.5 million older people were receiving long-term care, either in nursing homes or through home health care. (1.5 million living in nursing homes; .9 million receiving home health care).[213]

It is possible that more than two-thirds of the Nursing Home residents, or a million people, could die during a flu pandemic. Some would die from the effects of the flu itself, but many more are susceptible to dying of neglect. If you add to this a conservatively higher death rate of twice the overall prediction (five percent versus 2.5 percent) and a total of close to 2.7 million older people could die during a flu pandemic.

Nursing homes are already critically understaffed. A three-state survey of nursing homes conducted in 2000 showed that fifty-four percent of the homes were below standards in number of aides per patient and twenty-three percent had LPN and RN staff shortages.[214] The same report stated that seventy-five percent of all California Nursing Homes failed to meet quality standards.

Thirty-eight percent of people sixty-five and over live with a severe disability and forty-seven percent of those aged sixty-five and over have Alzheimer's disease or another form of dementia.[215] People with these conditions need help with routine activities such as bathing, dressing eating, toileting, transferring and continence. Home Health Care patients are not much

---

[213] *The MetLife Market Survey of Nursing Home & Home Care Costs*, September 2004.

[214] "Nursing Home Statistics," *AHCA,* www.efmoody.com/longterm/nursingstatistics.html.

[215] *The MetLife Market Survey of Nursing Home & Home Care Costs*, September 2004.

better off. Of the .9 million receiving home health care, more than 553,000 require care for bladder, bowel, or bladder and bowel incontinence.[216]

In 1999, 4,138 deaths in nursing homes were attributable to starvation, dehydration or bedsores, according to a study by the St Louis Post-Dispatch. With nursing home residents' lives threatened from neglect under normal circumstances, we can only imagine how horrific life in these institutions could become in the midst of a pandemic flu surge with staff absenteeism, food unavailability and medical supply shortages. Those on life support systems will be in dire straits if interruption in critical services such as electricity, natural gas and water occur.

Federal Government Plans

The U.S. Centers for Disease Control has developed a set of guidelines for combating an influenza pandemic. The guidelines are based on lessons learned in previous pandemics, including the 1918 Spanish Flu. The major assumption is that a flu surge will last between six and twelve weeks.

CDC seeks to accomplish three goals:

1. Reduce the impact of a surge through social distancing and antiviral administration as soon as the first cases appear.
2. Reduce the death rate at the peak of the surge.
3. Extend the length of time the surge lasts to spread out its impact.

[216] "Characteristics of Elderly Home Health Care Users," *National Center for Health Statistics, CDC*, http://www.cdc.gov/nchs/products/pubs/pubd/ad/301-310/ad309.htm.

The government has devised five strategies for battling an influenza pandemic, each of which is limited, because without a vaccine or a one hundred percent effective anti-viral, success cannot be guaranteed.

Defense 1 – Containment

The theory of containment says that once an index case appears, a geographical area can be cordoned off, and the people within that area treated and spread of the disease stopped.

In the case of the current flu threat, containment has already failed. The virus causing the current outbreak has already been identified in several U.S. locations and perhaps locations elsewhere in the world. Barring a mutation or going into a dormant state with the onset of Spring in the Northern Hemisphere, it is likely that this virus will spread worldwide.

Defense 2 – Vaccine

This is a new virus. It will take six to eight months to prepare enough vaccine to have impact. It is possible that the virus will have run its course by the time a vaccine is available.

Defense 3 – Anti-Viral Medications

Reducing viral loads is a laudable goal. However, it may not be sufficient to eradicate an influenza pandemic. Antiviral medication needs to be administered early in the course of the disease to save lives. Otherwise the viral load can be too great and overwhelm the patient.

Governments, businesses and individuals around the world have invested hundreds of millions of dollars in Tamiflu and Relenza. Early reports say that both Tamiflu and Relenza have impact on this virus strain but Amantadine HCL, an older anti-viral, is ineffective against this virus.

Defense 4 – Reduce Deadly Symptoms

One factor that a new severe influenza strain would have in common with the 1918 pandemic virus, is that the new strain could induce called cytokine storm.

Medicines available today that could conceivably control cytokine storm have severe side effects that could enhance the deadliness of influenza if administered to very sick people. For example, TNFα blockers, like Remicade®, Humira® and Enbrel® shut down the entire auto-immune system, thereby leaving patients susceptible to secondary infections that could cause even more damage to the victims.

Defense 5 – Slow the Spread

Social Distancing is at the heart of the CDC's non-pharmaceutical intervention plans. The CDC outlines four pandemic mitigation interventions for individuals, communities, educators and businesses:

1. Isolation and treatment (as appropriate) with influenza antiviral medications of all persons with confirmed or probable pandemic influenza. Isolation may occur in the home or health care setting, depending on the severity of an individual's illness and /or the current capacity of the health care infrastructure.

2. Voluntary home quarantine of members of households with confirmed or probable influenza case(s) and consideration of combining this intervention with the prophylactic use of antiviral medications, providing sufficient quantities of effective medications exist and that a feasible means of distributing them is in place.

3. Dismissal of students from school (including public and private schools as well as colleges and universities) and school-based activities and closure of childcare programs, coupled with protecting children and teenagers through social distancing in the community to achieve reductions of out-of-school social contacts and community mixing.

4. Use of social distancing measures to reduce contact between adults in the community and workplace, including, for example, cancellation of large public gatherings and alteration of workplace environments and schedules to decrease social density and preserve a healthy workplace to the greatest extent possible without disrupting essential services. Enable institution of workplace leave policies that align incentives and facilitate adherence with the nonpharmaceutical interventions (NPIs) outlined above.[217]

Social Distancing would be implemented on an escalating scale depending on the severity of the outbreak. Below is a list of actions the government would recommend based on severity.

[217] "Interim Pre-Pandemic Planning Guidance: Community Strategy for Pandemic Influenza Mitigation in the United States," *CDC, Division of Health and Human Services*, February 2007.

	Pandemic Severity Index		
Interventions* by Setting	**1**	**2 and 3**	**4 and 5**
Home **Voluntary isolation** of ill at home (adults and children); combine with use of antiviral treatment as available and indicated	Recommend†§	Recommend†§	Recommend†§
Voluntary quarantine of household members in homes with ill persons¶ (adults and children); consider combining with antiviral prophylaxis if effective, feasible, and quantities sufficient	Generally not recommended	Consider**	Recommend**
School **Child social distancing**			
-dismissal of students from schools and school based activities, and closure of child care programs	Generally not recommended	Consider: ≤4 weeks††	Recommend: ≤12 weeks§§
-reduce out-of-school social contacts and community mixing	Generally not recommended	Consider: ≤4 weeks††	Recommend: ≤12 weeks§§
Workplace / Community **Adult social distancing**			
-decrease number of social contacts (e.g., encourage teleconferences, alternatives to face-to-face meetings)	Generally not recommended	Consider	Recommend
-increase distance between persons (e.g., reduce density in public transit, workplace)	Generally not recommended	Consider	Recommend
-modify postpone, or cancel selected public gatherings to promote social distance (e.g., postpone indoor stadium events, theatre performances)	Generally not recommended	Consider	Recommend
-modify work place schedules and practices (e.g., telework, staggered shifts)	Generally not recommended	Consider	Recommend

Figure 7. Pandemic Severity Index. Available at CDC.gov.

Planning also calls for curtailing public transportation in the event of a runaway pandemic flu outbreak. Travel on trains, airplanes and buses will be restricted, not to stop the spread of flu but to slow it down. This strategy has been validated by a recent study that shows the 2001-2002 flu season was delayed because of the total restriction of U.S. air travel following the September 11, 2001 attacks. Of course, any restriction of public transportation would need to be evaluated carefully to assure that the disruption caused by curtailing public transportation would not outweigh the disruption caused by an influenza pandemic.

The CDC describes some of the second- and third-order consequences to implementation of social-distancing strategies. As an example, the CDC plan says:

> Dismissal of students from school may lead to the second-order effect of workplace absenteeism for child minding. Subsequent workplace absenteeism and loss of household income could be especially problematic for individuals and families living at or near subsistence levels. Workplace absenteeism could also lead to disruption of the delivery of goods and services essential to the viability of the community.

When social distancing is implemented, commerce will come to a halt, lowering revenue and decreasing the ability of businesses to meet their payrolls. At the same time, "workplace absenteeism for child minding" of up to twelve weeks will exhaust vacation and personal leave allowances, leading to personal income interruptions. Thus, economic imperatives could work to offset the government's containment strategy, forcing people to decide between financial disaster and physical disaster.

Failure of "Slow-the-Spread" Strategy

Current strategy both internationally, through the World Health Organization, and domestically, through U.S. agencies such as Health and Human Services (HHS) and Department of Homeland Security (DHS), is to slow the spread of an pathogenic influenza outbreak through non-pharmaceutical intervention, administration of a pre-pandemic vaccine and anti-viral medications to key people, and waiting until sufficient quantities of strain-specific vaccine can be produced and administered to protect the majority of the population.

Under this approach, initial outbreaks would be contained and fought while the region surrounding the first cluster of sick people would be quarantined in what the GAO report describes as a "geographically defined containment zone." Samples of the contagious virus would be made into vaccine and distributed to the general population.

In the current circumstance, the virus has already escaped containment, so the opportunity for a slow-the-spread strategy is diminished.

Health of the Healthcare System

A study, out of Johns Hopkins University, shows that if a catastrophic influenza pandemic strikes, the healthcare system is likely to cease functioning. The failures are liable to be seen first at the lowest levels and will then percolate upward from below.

The study, titled *Local Public Healthworkers' Perceptions Toward Responding To An Influenza Pandemic*, reports that clinical staff (nurses, dentists, physicians) are more likely to show up for work during a flu pandemic than technical support staff (computer operators, clerks, etc.).

A flu surge is expected to last for weeks. On day one the doctors and nurses are likely to show up at the local hospital. If the doctors and nurses, who are the top of the healthcare pyramid, find a marginally functioning base with limited numbers of X-Ray technicians, phlebotomists to draw blood, orderlies or aides to move patients from one place to another, clerks to enter data, and food service people to feed either staff or patients, doctors and nurses will become frustrated and are likely to drop out.

The aftermath of Hurricane Katrina serves as a vivid example of how professionals and other service staffs can react in a crisis. Here is how the scenario could unfold. Professionals and dedicated service staff people initially show up to meet the crisis. They find tremendous gaps and shortages in the support systems they need to do their jobs. They continue to do the best they can for a few days, until the frustration level becomes so high that they become demoralized by the futility of the situation and their inability to make a beneficial difference.

As other studies have shown, those with family obligations, especially those with sick family members, begin staying home also, and eventually, the treatment facilities degenerate into buildings where no meaningful healthcare can be delivered.

All of these factors point to the potential for a severe healthcare crisis during a major influenza pandemic.

The Challenge of Creating a Strain-Specific Vaccine

If the current virus threat were to become dormant, efforts would be directed to creating a vaccine for this specific threat. In the U.S., federal government officials have set a goal to "vaccinate all persons in the United States who choose to be vaccinated."[218] The timing for making enough doses available for 300 million U.S. residents is six months. However, the GAO report points out that "only one manufacturer's entire seasonal influenza vaccine production facilities are located completely within the United States." Therefore, our destiny is not completely in our hands and it may be necessary for manufacturers to make and package billions of doses of vaccine to meet a worldwide demand before the domestic U.S. goal can be met.

The genetic structure of influenza constantly shifts. The consequence of the shifting variations of flu strains and sub-strains makes flu samples harvested from patients a valuable commodity. The virus itself is the raw material that must be used to create a vaccine that can fight it. And since the virus is constantly shifting, vaccine manufacturers must have the most up-to-date virus samples to assure that the vaccine they create to fight of a flu pandemic is effective.

---

[218] "Draft Guidance on Allocating and Targeting Pandemic Influenza Vaccine," http://www.pandemicflu.gov/vaccine/prioritization.html.

What About Avian Influenza H5N1

The threat of a pandemic from a strain of the Type A H5N1 influenza virus remains as worrisome today as it did before the new Swine flu strain appeared. The H5N1 virus continues to be a deadly disease. A thirty-three-year-old Egyptian woman died from the H5N1 strain of bird flu, the third death from the disease in Egypt this week, the health ministry announced.

The woman, from Kafr el-Sheikh province, was the 26th person to die in Egypt from the strain since it was first identified in the Arab world's most heavily populated country in 2006. If the new virus strikes before or instead of H5N1, the planning for the H5N1 virus will have yielded tremendous benefit.

Influenza Outbreak
Raising the Stakes[219]

This report discusses some of the economic and medical aspects of the recent announcement by the World Health Organization raising the Flu threat level to the highest category plus questions and answers about the current flu threat.

On Wednesday afternoon, April 29, the World Health Organization (WHO) raised the worldwide influenza threat level to five on a scale of six. This event occurred less than a week from the time the world became aware of a new strain of Type A (H1N1) influenza that was infecting people in Mexico and the U.S. WHO Director General, Margaret Chan indicated the seriousness of the situation when she said in her announcement, "New

[219] Steve Brozak, *Influenza Outbreak Raising the Stakes* (Clark: WBB Securities, LLC, 2009).

diseases are, by definition, poorly understood. Influenza viruses are notorious for their rapid mutation and unpredictable behaviour."

On Thursday afternoon, April 30, Mexico's president ordered a partial shutdown of the country. He instructed government offices and private businesses, not essential to the economy, to stop work beginning Friday.

WHO's action and the steps taken by the Mexican government, in our opinion, indicate significant concern. Mexico is taking a short-term measure to attempt social distancing through a quarantine that is intended to stop the spread of the influenza. Strict compliance by the Mexican people will be necessary for this measure to have impact on the disease.

The action by WHO is a longer-term measure. We believe WHO took into account the presence of another, active and deadly flu strain, Avian Flu Type A (H5N1), which is present in Asia, Europe and North Africa when it decided to increase the threat level. At the same time, physicians in the Northern Hemisphere are still seeing new cases of seasonal flu.

Unpredictability in flu virus is a significant cause for concern. The Spanish Flu of 1918 began as a benign virus in the Spring, became dormant over a summer, and reappeared in the Autumn as a deadly disease. Both the H5N1 and the H1N1 strains have the capability of turning quickly into a deadly strain of influenza virus, much as the Spanish Flu of 1918 did.

If the H5N1 and H1N1 strains were ever to enter a single host, such as a pig or a human, they could mix, in a process known as genetic resortment (or reassortment),

yielding a highly contagious and deadly virus. This is a remote possibility but one that could become a worst-case scenario.

Behavior characteristics of the H5N1 and H1N1 strains are mirror images of one another. The H5N1 influenza strain has been watched closely for several years. It is highly lethal but not easily transmitted between humans. There are approximately 421 known cases of H5N1 and 257 deaths—more than sixty-one percent of those infected. The newly emerging H1N1 strain is easily transmissible but appears to be relatively mild with approximately 1,300 suspected cases and approximately one hundred reported deaths-close to eight percent of those infected.

Each virus reacts differently to the currently available antivirals, Relenza® from GlaxoSmithKline (GSK), Tamiflu® from Roche (RHHVF) and Amantadine and Rimantadine, members of an older generation of antiviral drugs. Relenza and Tamiflu are the antivirals in the Strategic National Stockpile of fifty million courses of antivirals.

Both Relenza and Tamiflu appear to be effective against the H1N1 Flu but have limited effectiveness against the more deadly H5N1 Avian influenza strain. Amantadine and Rimantadine, appear to have some effectiveness against H5N1 but have been shown to be to be ineffective against H1N1.

Today's announcement raising the pandemic threat level is more than a paper exercise. It has both significant medical and economic impact. The 1918 Spanish Flu was the worst influenza pandemic the world has seen. It killed 675,000 people out of a population of 105 million in the U.S. HHS predicts that a severe flu pandemic today could result in up to 1.9 million dead in the U.S. and initial economic costs near $200 billion.[220]

[220] Thomas A. Garrett, "Pandemic Economics: The 1918 Influenza and Its Modern-Day Implications," *Federal Reserve Bank of St. Louis Review*, March/April 2008.

WHO describes Phase 5 as "Larger cluster(s) but human-to-human spread still localized, suggesting that the virus is becoming increasingly better adapted to humans, but may not yet be fully transmissible (substantial pandemic risk)." The recommended response is intended to "Maximize efforts to contain or delay spread, to possibly avert a pandemic, and to gain time to implement pandemic response measures."

The HHS has its own criteria for designation of a Phase 5 threat level. In the U.S., pandemic planning, the definition of a Phase 5 threat is when flu is spread throughout the U.S. If, in the case of the H1N1 virus, the number and locations of cases continue to grow at the present rate, such a determination could come within days.

The economic impact of a U.S.-declared domestic Phase 5 flu threat level would be significant. Mandated interventions would disrupt retail businesses, transportation, entertainment, manufacturing and a host of other industries. The interventions called for in a Phase 5 scenario call for:

1. Isolation and treatment with antiviral medications of all persons with confirmed or probable pandemic influenza. Isolation may occur in the home or healthcare setting, depending on the severity of an individual's illness and/or the current capacity of the healthcare infrastructure.
2. Voluntary home quarantine of members of households with confirmed or probable influenza case(s) and possible prophylactic use of antiviral medications.
3. Dismissal of students from school (including public and private schools as well as colleges and universities) and school-based activities and closure of childcare programs, coupled with social distancing.

4. Use of social distancing measures among adults in the community and workplace, including, for example, cancellation of large public gatherings and alteration of workplace environments and schedules to decrease social density and preserve a healthy workplace without disrupting essential services.

Questions and Answers About the Current Influenza Threat

Question 1… What new lessons have we learned about flu thus far?

The world is just as vulnerable economically from a flu scare as it is medically from a flu outbreak. We have already observed impact on tourism, travel and other industries.

Though the current H1N1 Swine Flu outbreak may be mild, it demonstrates the world's vulnerability to a severe flu outbreak. We are learning that the outbreak began with an initial case in early March, but awareness of the disease's presence only developed in late April. That delay allowed the virus to spread over great distances, thereby avoiding the first line of defense, which is containment.

Question 2…What has been re-learned that was known before?

Flu can strike from any geographical region. While we were watching the Avian Flu outbreak in Asia, a Swine Flu strain developed in Mexico and went undetected for close to six weeks.

After fourteen days without intervention, confinement is impossible, according to some experts. As was learned in 1918, once an influenza strain gets into enough people, given a modern transportation system, its spread is unstoppable. This is because influenza is undetectable for several days after infection and before symptoms appear. The only way to

isolate and eliminate the virus is to stop it before too many people get infected. Unfortunately, the H1N1 virus was not detected until it had spread outside a single geographical zone, where containment might have been possible.

The world lacks the necessary tools to combat an influenza surge. Medical science has made great strides since the influenza pandemic of 1918, but we are still left with much the same tools to combat influenza as were available then.

There is no universal influenza vaccine. A single vaccine formula stops all smallpox, whooping cough, plague and a wide variety of other, once-deadly diseases. To be effective, flu vaccine must be modified to meet the differing characteristics of each flu strain.

Vaccines are unavailable for newly emerged flu strains. It takes six to eight months from the time a new flu strain appears until sufficient quantities of vaccine are available to inoculate large numbers of people. Vaccine creation and manufacturing relies on sixty-year-old, egg-based technology and there are insufficient manufacturing facilities available to produce both seasonal flu vaccine and pandemic vaccine simultaneously. New vaccine manufacturing technology that will speed the process has been under development for a number of years, but is advancing slowly.

No highly-effective and universal anti-viral drug is available. Currently available antivirals are vulnerable to the quickly changing characteristics of influenza viruses.

There is no highly effective mitigant that can be given to patients with severe cases of flu to reduce symptoms and improve likelihood of survival. The most deadly aspect of a killer flu infection is over-reaction by the human body's inflammatory system, called hypercytokinemia or cytokine storm. This phenomenon has been widely reported in scholarly journals and elsewhere. (See figure 8 below from *New England Journal of Medicine*.) Yet no

large-scale effort to create a cytokine storm mitigator has been initiated. The U.S. government and others are focused solely on creating vaccines and stockpiling antiviral medications, both of which have limited usefulness in a fast-changing flu environment.

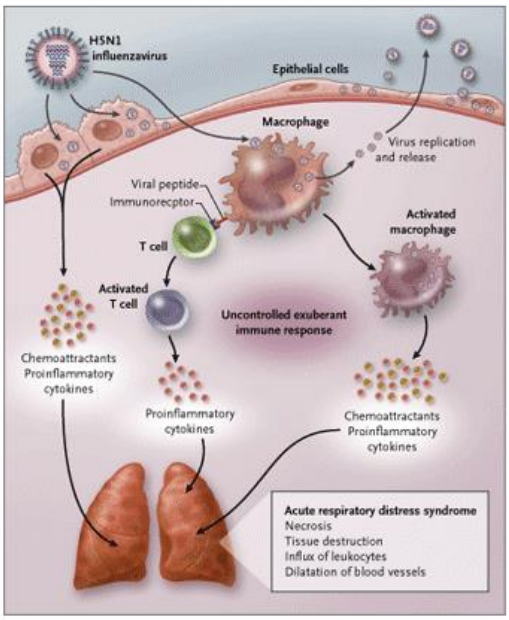


Figure 8. H5N1 Influenzavirus. From New England Journal of Medicine.

Question 3… What defenses are available against an influenza outbreak?

No reliable and effective defense against a severe flu outbreak is available. Defenses available to combat a flu surge today are frighteningly similar to those of 1918, when VapoRub®, now owned by Proctor & Gamble (PG), was the therapeutic of choice. The objective of current defenses is to treat those who are sick and slow the spread of the disease until a strain-specific vaccine can become available, which will probably take six to eight months. Since a flu surge lasts approximately six weeks, the first surge of a newly emerged flu will be long-gone before a vaccine is available.

These are the defenses currently available to combat a flu surge:

- Social Distancing – This practice calls for avoiding crowds and limiting large gatherings of people. Public transportation would be curtailed, schools would be closed and public events canceled. We are already seeing schools closed in regions where outbreaks have occurred.
- Quarantine and/or Isolation – If you are sick, stay home. If someone in your family is sick, that person should stay home and you should too.
- Personal Hygiene – Wash your hands, cover your mouth when you cough or sneeze, keep well rested.
- Antivirals – The U.S. government, state governments, and governments around the world have invested millions of dollars in these drugs. Relenza from GlaxoSmithKline and Tamiflu from Roche are the primary antivirals in use today. They appear to be effective against the H1N1 Flu but have limited effectiveness against the more deadly H5N1 Flu. Amantadine and Rimantadine, members of an older generation of antiviral drugs, appear to have some effectiveness against H5N1 but to be to be ineffective against H1N1.

Question 4… What about Avian Flu (H5N1)?

Avian (bird) flu, otherwise known as Influenza A (H5N1) is still an active threat. As spring approaches in the Northern Hemisphere, flu becomes dormant. However, in the Southern Hemisphere autumn is beginning, a time when flu begins to surge.

The human experience with Avian Influenza H5N1 has, in some ways, been the reverse of the experience with the current H1N1 Swine flu strain. With Swine flu, we have had many

suspected cases (1,300 or more) and relatively few deaths (~100), whereas with the Avian Influenza we have seen 421 diagnosed cases with a very high percentage of deaths, totaling 257, or more than fifty percent.

Question 5… What if Avian Flu and Swine Flu were to combine?

It is not out of the question. A combination of a highly transmissible influenza strain with a highly fatal one is a nightmare for epidemiologists. If the H5N1 and H1N1 varieties ever had the opportunity to mix in a commonly susceptible animal, such as a pig or a human, the resulting strain could be highly communicable and highly fatal.

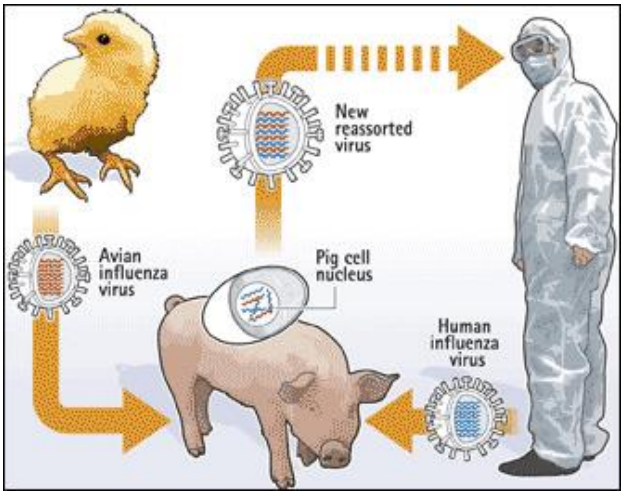


Figure 9. Animal-Human Virus Transmission. From Harvard Public Health Review, Winter 2006.

Question 6… Will H1N1 become a killer flu like the 1918 Spanish Flu?

We don't yet know; influenza strains can change very quickly, but there are some chilling similarities. The 1918 flu was an H1N1 virus. The first flu surge appeared in the March/April timeframe. The first flu appearance was relatively benign, infecting large numbers of people but killing relatively few. The 1918 flu spread around the world relatively quickly due

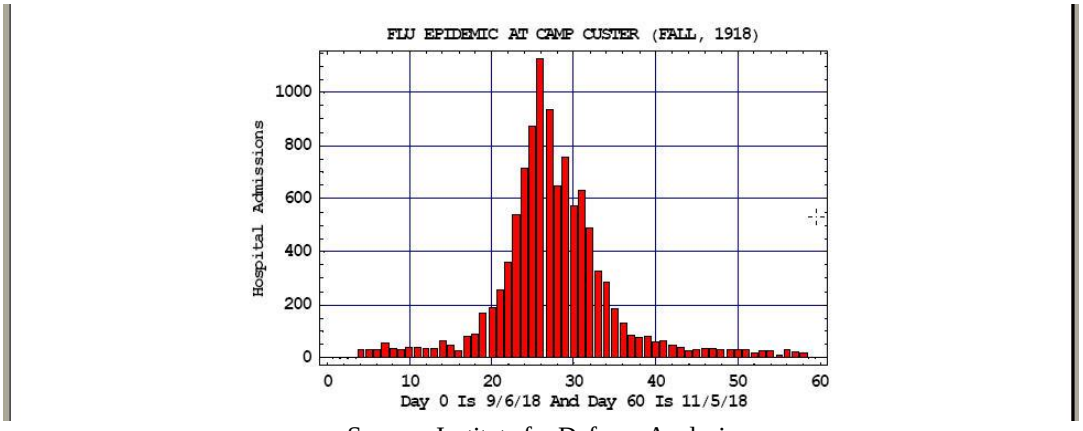
to increased movement of people associated with World War I. The flu went into a latent period during the summer of 1918 and reappeared in the Autumn in an area replete with pig farms and a nearby dense population.

The 1918 flu became the deadliest pandemic since the Black Plague. It was a rare event. Whether a 1918-like flu will reappear is unknown, but the possibility is worrisome, hence the preparedness that has been underway for several years.

Question 7… What is the likely course of this outbreak?

The current surge is likely to last forty to sixty days. We are now at day seven. The highest number of cases will be diagnosed around day twenty-five and the number of deaths should peak about ten days later.

Following is a chart showing infections during the 1918 Spanish flu. Hospital Admissions and deaths lag the trend of infections by about ten days.



Source: Institute for Defense Analysis

Figure 10. 1918 Spanish Flu Infections. From Institute for Defense Analysis

Question 8… What should I do to prepare?

At this stage, watchful waiting is called for. It would be prudent to have a supply of food sufficient for a couple of weeks in the house, just in case the virus takes a turn for the worse and people need to stay home to care for someone who is sick or a quarantine is imposed. Everyone should have a thirty-day supply of prescription medications on hand. And to quote the book, *A Hitchhikers Guide to the Galaxy*, "Don't Panic!"

Question 9… Should I buy enough Tamiflu to treat my family?

This is a decision between you and your God. The CDC does not recommend getting Tamiflu in advance of needing it. There are questions about effectiveness of Tamiflu, about the morality of acquiring a medicine that may be in short supply and needed by people who are desperately ill. No one is certain whether such action is warranted at this time since most people who contract the current H1N1 virus seem to recover without problems and Tamiflu is of questionable effectiveness against H5N1. There is also the concern that if large numbers of people take Tamiflu or Relenza when unnecessary, the virus may have an opportunity to adapt to it and it will become ineffective.

Influenza Outbreak
A Call to Action[221]

Thus far, the current Type A (H5N1) Swine Flu outbreak is serving more as a warning than a threat to life in the U.S. As of Sunday morning, there were 226 confirmed

[221] Stephen G. Brozak, Lawrence F. Jindra, M.D., and Daniel Mallin, Ph.D., *Influenza Outbreak A Call to Action (Clark:* WBB Securities, LLC, 2009), http://www.wbbsec.com/attachments/119_WBB%20Swine%20Flu%20050409.pdf.

cases in thirty states with only one death. The Centers for Disease Control (CDC) had announced that twenty-five percent of the supplies in the Strategic National Stockpile (SNS) were scheduled to be delivered to all states in the continental United States. In addition, the Federal Government and manufacturers have begun the process of developing a vaccine against the H1N1 virus and expect to have both H1N1 vaccine and seasonal flu vaccine available by this Autumn.

In our opinion, the world will react to this pandemic flu warning much as it did to the H5N1 Avian Flu threat. There will be immediate alarm. Numerous Web sites will pop up that advise people how to survive in their homes and provide home remedies for treating flu victims. There will be a spike in sales of emergency supplies like batteries, bottled water and candles. Internationally, governments will create new agencies, write new plans and set aside money for marginally effective remedies. After a few weeks, attention will be directed to another news story and people will take for-granted the presence of what could have become a deadly threat in our midst.

Though it sounds glib, the only thing we know for sure is that the current threat will get worse, stay the same or get better. With a sixty-six percent chance that the world will have more time to prepare, it would be prudent to advance preparations for a deadly pandemic that could come at any time.

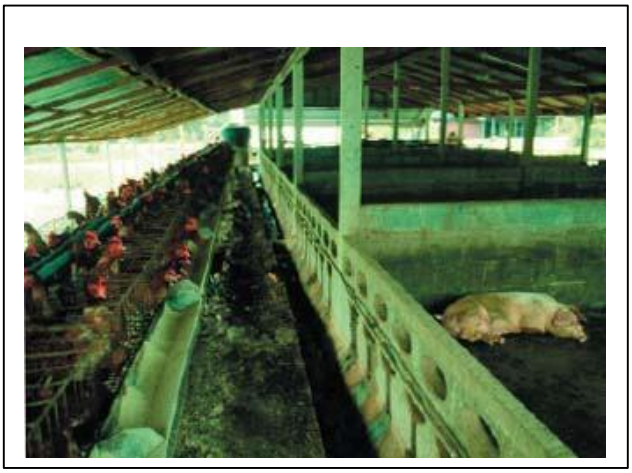
All Pigs Are Equal (Are Some More Equal Than Others)?

The influenza threat level increased two days ago, when Canadian health officials announced that a swine herd in the province of Alberta had been infected with the H1N1 virus by a carpenter who recently traveled to Mexico. Though we don't know the protocols

used in this pig herd, we do know that pigs in North America are treated very differently than pigs in other parts of the world.

Pork is big business. In 2007, the pork industry had sales of $97 billion. U.S. pork producers operate 67,000 farms, and most domestic operations are large-scale. On these large farms, great care is often taken to avoid human-to-animal or animal-to-animal contamination.

In parts of the world outside North America, large-scale agriculture is growing, but backyard farms where a few pigs are raised in rural and in urban areas are common. In these backyard operations, pigs and humans can live in close proximity to one another and with other animals such as chickens and ducks.



Figures 11. from the Food and Agriculture Organization, United Nations.

The opportunity to exchange diseases between species is great in these small, multiple species farms. The situation is exacerbated when people bring their animals to local markets for sale.

With multiple pandemic influenza strains circulating among several species, the opportunity for resortment (genetic reassortment), where multiple species merge, increases. If such a resortment were to occur in humans or swine, and be transmitted between species, a deadly virus could emerge.

Our Vulnerable Medical Delivery System

The world is at the mercy of a virus, among one of the simplest organisms on the planet. Our current defenses and our medical delivery system are incapable of combating a severe influenza threat. We have at our disposal neither a universal flu vaccine, a fast vaccine manufacturing capability, nor an effective, universal therapy for flu patients.

There is a dirty little secret about what could happen in the event of a severe flu epidemic. It is comparable to the financial meltdown that began on March 14, 2008.

On March 13, few people doubted the fundamental soundness of the U.S. and world financial systems. The next day, the Federal Reserve and JP Morgan Chase & Company (JPM) provided Bear Stearns with emergency funding following a depletion in Bear Stearns cash reserves. By March 16, JPM agreed to acquire Bear Stearns for the equivalent of $2 per share. Then, on September 15, Lehman Brothers Holdings, Inc. filed the largest bankruptcy in history and Bank of America (BAC) agreed to acquire Merrill Lynch for about $50 billion.

These events shook the foundation of the world financial system. After the fact, we learned that a small coterie of people knew how vulnerable the financial system had become, but it was not publicly discussed, for fear of creating panic and accelerating disaster.

A similar rude awakening about the vulnerability of the medical delivery system could arise suddenly in the face of a deadly influenza pandemic. Medical delivery is based on

regularity, predictability and minimal variability in rates of disease. A predictable number of people per thousand will get infections, have automobile accidents, suffer heart attacks or come down with diseases. The number of doctors, nurses and hospital beds is derived from this statistical certainty. Even the likelihood of natural disasters like fires, floods and hurricanes is more or less predictable.

Drug delivery for specific diseases operates on a just-in-time principle that takes into account the predictability of demand. Inventories are kept to a minimum to conserve capital and extend shelf life. Manufacturing and delivery chains are created based upon predictable expectations of need.

If a sudden, vicious, new disease, like a highly dangerous flu pandemic were to strike, the system would be overwhelmed. Doctors, nurses, medical technicians and even hospital clean-up crews would be overworked. Only drugs that were stockpiled would be available in the quantities needed to meet the sudden new demand. If those drugs were ineffective, or if there were insufficient quantities to meet the need, there would be little chance of survival.

This is a difficult scenario that few government leaders discuss in public. It is why the flaws of our current flu defenses are a potential mortal threat.

Five Flawed Flu Defenses

Donald Rumsfeld, former Secretary of Defense, is famous for having said "You go to war with the army you've got." What holds true for a military threat also holds true for a medical threat. You meet the threat with the defenses at your disposal. Unfortunately, after six years since the appearance of the deadly H5N1 Avian Flu, little progress has been made in building new defenses to meet a severe flu threat.

Following are the five primary defenses currently available to combat a flu surge. Each of them has serious flaws.

Vaccine – Vaccines work well when they are available. Each year a newly formulated batch of vaccine must be created and manufactured to meet a changing flu threat. According to the Department of Health and Human Services (HHS), two companies currently have influenza vaccine production facilities in the United States. They are Sanofi Pasteur, the vaccine division of Sanofi-Aventis SA (SNY) and MedImmune, the biologics business unit of AstraZeneca International (AZN), although only SNY's entire production process is based in this country.

There is no universal influenza vaccine. A single vaccine formula stops all smallpox, whooping cough, plague and a wide variety of other, once-deadly diseases. Flu vaccine must be modified to meet the differing characteristics of each flu strain.

It takes up to six or eight months to create enough vaccine to meet a new flu threat. The technology now used for flu vaccine production is close to sixty years-old. It uses eggs to germinate the disease from which the vaccine will be made. There may not be sufficient manufacturing capacity to produce pandemic vaccine without delaying seasonal flu vaccine production, and seasonal flu kills, on average, 36,000 people in the U.S. every year.

There are several serious disadvantages to the current vaccine production process in the face of a deadly pandemic flu.

- 900 million eggs and several months are required to produce 300 million doses of vaccine.
- Egg-producing flocks could decline if the flu were Avian based, jeopardizing vaccine production capabilities.
- Eggs cannot be stored. They must be used when they are fresh.

- The virus must be manipulated so it can adapt to grow in eggs.
- People who are allergic to chicken eggs cannot receive vaccines produced from them.

New vaccine technology that will speed the manufacturing process has been under development for a number of years, but is advancing slowly. This "cell-based manufacturing" uses mammal kidney cells to grow the vaccine. The virus is injected into the cells where it multiplies. The cells' outer walls are removed, harvested, purified, and inactivated. Polio vaccine is currently produced using the cell-based method.

There are several advantages to the cell-based vaccine process that make it superior to egg-based manufacturing:

- No eggs are required, so there is no threat to the growing medium in the event of an Avian Flu, no adaptation of the virus is required for the virus to survive in the egg medium and people who are allergic to eggs can receive the vaccine.
- Cell lines can be safely kept frozen indefinitely, increasing the capability to rapidly produce vaccines if an influenza pandemic were to occur.

In March 2005, HHS issued a five-year contract to Sanofi-Pasteur for $97.1 million to develop cell-based influenza vaccine technology and conduct clinical trials, with the goal of obtaining an FDA license for this vaccine. Under this advanced development contract, the company has committed to develop a plan to establish a U.S. cell-based influenza vaccine manufacturing facility, capable of producing at least 300 million doses of a pandemic influenza vaccine over a one-year period.

In May 2006, HHS awarded five contracts totaling more than $1 billion to accelerate development and production of new technologies for influenza vaccines within the U.S. Thus far, little progress has been reported.

Social Distancing – This practice calls for avoiding crowds and limiting large gatherings of people. But it is vulnerable. One sick person in a crowd would threaten to infect anyone nearby. In the event of a threat, where voluntary social distancing was imposed, public transportation would be curtailed, schools would be closed and public events canceled.

This is an extremely disruptive and expensive intervention. When schools close, parents must stay home to take care of children. Parents of toddlers will miss work because day care will be closed along with the schools. Public libraries, movies and other places where people gather could be closed. Airlines, trains, subways, sporting events and plays will suffer economically. But people will need to go to public places to buy food, seek medical care, or escape the tedium and monotony of days confined at home.

Quarantine and/or Isolation – This intervention requires you to stay home if you are sick. If someone in your family were sick, that person would be required to stay home and you would too. Maintaining quarantine will require tremendous logistical support. People will soon run out of food and medicine. How and by whom they will be resupplied has not been addressed. National Guard units, the historic resource for states during domestic emergencies, are either depleted or deployed. Prisons, nursing homes and other group living facilities will be in dire straits very quickly, and if infection enters one of those institutions, it will run through it like wildfire.

Personal Hygiene – This intervention calls for washing your hands, covering your mouth when you cough or sneeze and keeping well rested. It includes the use of personal protection devices, such as masks, gowns, gloves and goggles. Among the U.S. manufacturers of medical masks and gloves are: Johnson & Johnson (JNJ), Becton Dickinson Company (BDX), 3M Company (MMM), Kimberly-Clark Corporation (KMB), Cardinal Health, Inc (CAH) and Lakeland Industries, Inc (LAKE).

This intervention is very difficult to universally enforce and universal adherence is necessary to have an impact. Cruise ships have hand sanitizer stations throughout, yet gastrointestinal and respiratory diseases remain a constant threat.

Antivirals – Effectiveness of antivirals is flawed, neurological side effects could be fatal and the manufacturing process is complex, limiting production capacity.

The U.S. government, state governments, and governments around the world have invested millions of dollars to purchase Relenza from GlaxoSmithKline (GSK) and Tamiflu from Roche Holdings, AG (RHHVF). Gilead Sciences, Inc. (GILD) is the developer of Tamiflu and receives a royalty for sales of the drug by RHHVF. Both of these drugs appear to be effective against the H1N1 Flu but have limited effectiveness against the more deadly H5N1 Flu. Amantadine and Rimantadine, members of an older generation of antiviral drugs, appear to have some effectiveness against H5N1 but to be to be ineffective against H1N1.

One of the shortcomings of Tamiflu is availability of its basic ingredient, shikimic acid. The primary natural source of shikimic acid is the Star anise fruit, which is used in Chinese Five-Spice Powder. Star Anise is grown in four provinces in China and harvested between March and May. (Japanese star anise, which is virtually indistinguishable from Chinese star anise, is highly poisonous.) In 2006, RHHVF purchased ninety percent of the world's

production of star anise. RHHVF has developed a synthetic process to produce shikimic acid but it is expensive and complex.

By 2007, Roche was producing 400 million doses of Tamiflu a year (33 million per month) worldwide and was in the midst of expanding its production plant in Florence, South Carolina, to a capacity of eighty million doses per year (six million per month). The expansion was expected to go online in early 2009.

The Tamiflu Suicide Risk

There are some disturbing side effects that have been reported, especially among children taking Tamiflu. As the drug is used more widely, it is likely we will see additional instances of these side effects.

Reports of self-injury, suicide and delirium, caused the FDA to add a warning to the Tamiflu label in 2008. The warning includes the following. "There have been post-marketing reports (mostly from Japan) of delirium and abnormal behavior leading to injury, and in some cases resulting in fatal outcomes, in patients with influenza who were receiving Tamiflu. These events were reported primarily among pediatric patients and often had an abrupt onset and rapid resolution." None of the cases had any reported psychological or neurological problems before taking the medication.

The Need for a Mitigant

In addition to the lack of a universal vaccine that can be manufactured and distributed quickly when a flu threat emerges, there is no drug available to mitigate the effects of flu on the human body.

Death from flu can be triggered by our body's over-reaction to the virus. This over-reaction is called hypercytokinemia or "Cytokine Storm" and is a primary cause of death from more virulent forms of influenza infections.

When our bodies detect these deadly viruses, T-Cells are dispatched to our lungs, which are the sites of the infection. As more and more T-Cells accumulate in the lungs, they cause a form of pneumonia that can suffocate patients.

Theoretically, Cytokine Storm can be mitigated by reducing the cytokine cascade. But the cytokine cascade is a complex process that is not fully understood. There are hundreds of cytokines, some up-regulate inflammation and some down-regulate inflammation. Knowing how each cytokine works individually, and in combination with others, is crucial to creating an effective drug.

Why Flu is Tough to Stop

Some people say that the flu virus is clever. It is not. It is a very simple biological entity, not even considered a living thing.

A virus is a submicroscopic parasite. It can only live and reproduce within a living cell of a human or other animal. It is composed of a core of RNA, surrounded by a protein coat, a capsid, or outer shell, and a protein coating. A single virion (an individual virus) can create and release thousands of progeny in a ten to twelve hour life cycle.

The huge numbers of offspring and speed of reproduction accelerate the mutation process, called antigenic drift, in viruses. The simple structure of viruses enables them to blend with one another to create a new viral strain in a process called antigenic shift.

Virus genes are composed of eight separate pieces of ribonucleic acid (RNA). Each piece of RNA specifies the amino acid sequence of one and sometimes two of the virus's

proteins. The segmented nature of the RNA allows different flu viruses to easily "mate" with each other to form hybrid strains of virus with bits of RNA from each parent. That is how the H1N1 virus evolved as a combination of a Swine, Avian and Human strain.

Spikes on the surface of viruses are crucial to viral reproductive capability. Viruses have two kinds of probes sticking out from their shells.

- One spike is hemagglutinin and the other neuraminidase. (You can see them in the photo of H1N1 viruses below.) The flu virus uses a hemagglutinin spike to latch on to the surface of a cell in the lungs and punch a hole in it. Then, RNA is released into the host cell where it reproduces new virions.
- The Neuraminidase spike contains a sialic acid molecule on its end that dissolves the outer wall of the host cell so the new virions can escape. Tamiflu inhibits the action of the neuraminidase on the flu virus cells, causing the new virions to be trapped inside the host cell where they eventually die.

There are sixteen different hemagglutinin types and nine neuraminidase types. Virus strains are identified by the version of hemagglutinin and neuraminidase types they contain. Other genetic variations within the RNA create sub-types of virus strains, called clades. Different vaccines must be produced for each hemagglutinin and neuraminidase combination and for variations within those combinations.

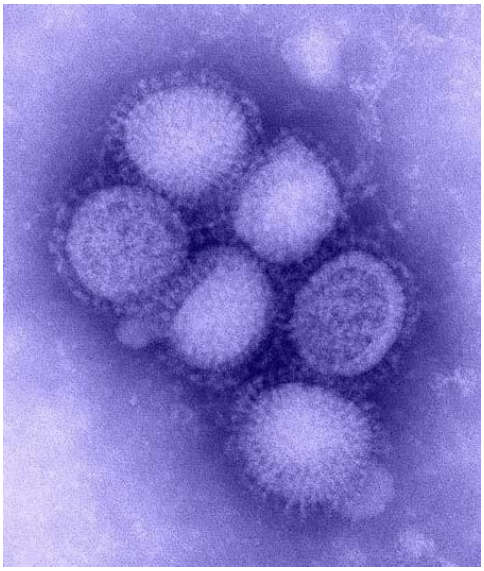


Figure 12. H1N1 Virus. Available at CDC.gov.

The Facts Versus the Truth About Swine Flu
Swine Flu Will Test Health Care, Bedevil Economy[222]

There are the facts and there is the truth. Facts are often debated, because facts depend on how you calculate them. Truth is often ignored because it is often unpopular and usually unpleasant.

Press coverage about the coming unique H1N1 influenza surge has focused thus far on the facts—how many people will get sick and how many will die, how many vaccine inoculations will be available and how many shots will be needed to protect someone from this virus.

[222] Stephen Brozak and Larry Jindra, M.D., "The Facts Versus the Truth About Swine Flu," *ABCNews.com*, September 3, 2009, https://www.google.com/url?q=http://abcnews.go.com/Health/SwineFlu/swine-flu-test-us-health-care-delivery-system/story?id%3D8475278&sa=D&ust=1461915775492000&usg=AFQjCNEtQCRNccojmiXMGTOKOD2jGpFV_Q.

Thus far, most coverage, and the government announcements on which the coverage is based, have ignored two unpleasant truths -- first, that it is unlikely the health care delivery system will be able to respond to a significant flu wave and second, that the economy is likely to be severely affected by a widespread and long-lasting flu surge.

Thus far, government planning to meet these two challenges has been spotty at best. The truth is, gaps in the health care delivery system need to be filled and planning to address the economic impact of a flu surge needs to begin soon.

Challenge to the Health Care Delivery System

The facts are, in 2009 the U.S. health care system would be challenged by a relatively benign influenza surge that would test the federal government's ability to efficiently deliver drugs and vaccines where they are needed. Every level of government and the private sector would need to operate and cooperate to meet the flu challenge and minimize its impact on people's health.

Large numbers of people, over an extended period of time, are expected to become sick during the expected H1N1 flu surge. Sadly, it is possible that many will die. In 2009, two government agencies were bickering over the facts of the expected death toll. … The President's Science Advisory Council issued a report estimating between 30,000 and 90,000 deaths. Later in the week, the Centers for Disease Control (CDC) said the 90,000 number was overstated.

The truth is, estimating the death toll grabs headlines, but it is not as important as planning to minimize the suffering from disease.

We have seen no specific plans for identifying where outbreaks are occurring, how severe they may be, how to determine how much of the critical supplies should be sent to those areas and how they will get into the hands of medical personnel in hospitals and doctors' offices. The truth is, without such plans, needed supplies will be shipped where they are not needed, while places where they are needed will go without.

Too Late to Prepare?

The only way we can affect the suffering from this disease is to assure that the stockpiles of anti-viral drugs (Tamiflu and Relenza) are released by governments in a timely manner and delivered to patients within forty-eight hours of the onset of symptoms, when they can do some good.

The most effective way to prevent the spread of the disease is vaccination, and only limited vaccine supplies will be available starting mid-October, which may be too late to stem the tide. As of today, we have seen no plans for identifying where the vaccine is most needed and getting whatever vaccine is available to people who are at risk in a timely manner.

The facts are, this strain of flu is milder than most, and by every advance indication, the death rate will be relatively low. The facts are, large numbers of people will need emergency medical attention and our hospital emergency rooms are already understaffed and over-committed.

A 2008 report by the American College of Emergency Physicians said, "many emergency departments in the United States are critically overcrowded and unable to respond to day-to-day emergencies, let alone disasters and acts of terrorism." In 2003 and

2004, between forty percent and fifty percent of U.S. emergency departments experienced overcrowding according to the CDC.

The truth is, flu cases will be an additional burden to the normal emergency department loads. During a flu surge, normal emergencies will not cease. People will still have heart attacks, be involved in auto accidents, fall off ladders, deliver babies, be stabbed or shot.

Imagine yourself becoming sick in the middle of the night with a high fever, cough, headache and difficulty breathing. Your spouse takes you to the local hospital emergency room where you encounter twenty to thirty other people sitting on benches hacking and coughing. The expected wait to see a doctor is two to three hours or more and you feel terrible. Will you wait or will you tough it out and go home?

If you decide to wait to see a doctor, there isn't much that can be done to help you. If no Tamiflu or Relenza is available, there may be nothing that can be done to relieve your symptoms because these drugs must be started within forty-eight hours of the onset of symptoms to be effective.

If you are sick enough to be admitted to the hospital, but not deathly ill, there may not be a bed or even a cot available for you. If you are lucky enough for a bed to be available, you are likely to be warehoused in a hallway or other makeshift treatment area.

Challenge to the U.S. Economic System

The truth is, the coming flu surge also will test the economic recovery now in its early stages. The economy will decline as a consequence of a flu surge. If not managed

properly, the decline could become disastrous. Under the best of circumstances, the economic consequences of a flu surge are likely to linger far longer than the disease itself.

We have yet to see any specific estimate of the economic impact of this coming flu surge or any plans for recovering from that impact once the flu passes over us. When the flu strikes, people will stay home. They will miss work, stop going to restaurants and concerts or attending movies and sporting events. They probably won't go to the mall or look for cars and homes. The impact on the merchandizing and production sectors of our economy will be significant.

Taking Action to Minimize Impact of a Flu Surge

The President's Science Advisory Council report called for a single person within the White House to coordinate all efforts across agencies in response to a flu pandemic. We believe that is an excellent idea that should be implemented immediately. There will be no time or ability to establish procedures, or even to create a telephone list of who to call once the flu strikes.

The facts are, H1N1 flu has lingered in the United States at camps and other gathering places over the summer and schools that have reopened early have experienced outbreaks of flu. The truth is, planning for distribution of needed resources to meet a flu emergency should begin immediately, and planning for the economic impact of a long flu surge must be initiated quickly if it is to have any significant impact.

The truth is, preparing to tackle the healthcare challenges of an impending flu surge is not a job for a committee, nor can it be begun during the emergency. A single

point of coordination for flu response should be appointed within the federal government to establish a means for distributing critical supplies where they are needed.

Minimizing the Impact

The truth is, people need to be made aware that the flu will have an impact on the U.S. economy and an economic recovery plan to minimize the financial impact of a flu surge needs to be prepared now. Without such candor and advanced planning, the impact could be exacerbated.

The truth is, we don't know what is going on behind the scenes. If steps have already been taken, or if plans to undertake them have already been made, the American people need to be told the truth about the potential healthcare system vulnerabilities and how they will affect those who become sick. Similarly, we need to be told about the potential economic impact on all of us, and how we can take steps to minimize the economic impact.

Viral Secrets

Recent reports of experiments on the deadly influenza Type A (H5N1) in Wisconsin and Rotterdam, Holland have reignited controversy over control of dangerous information. When scientists produced an easily transmitted mutation of the H5N1 influenza virus. fears of weaponizing this influenza strain grew. The Secretary of Health and Human Services asked scientific publications to withhold publication of the methods used to achieve these results in hopes of discouraging a harmful application of the technology.

Government reaction to these events raises once again, three crucial questions surrounding scientific experimentation. First, are there areas of science, where in the words of the old science fiction movies, "no man ought to go?" Second, can knowledge, once gained be contained? And finally, does society as a whole benefit or suffer from wide dissemination of dangerous knowledge?

Governments and other influential institutions have sought to limit the areas of scientific exploration for centuries. The iconic example is the case of Galileo. The Catholic Church went so far as to threaten excommunication, confine Galileo to house arrest and threaten death if he promulgated his theory that the earth revolved around the sun, opposing the Church's view that the earth was the center of the universe.

Galileo's view of the universe could not be contained and demonstrates that even when a powerful institution controls access to knowledge, the truth cannot be contained. Two other examples illustrate this truth. When the British developed textile mills in the early industrial age, they made it against the law for mill workers to leave the UK. But the American, Francis Cabot Lowell, induced one former mill worker to make his way to America and help engineer textile mills, first in Waltham, and then in Lowell, MA, thus giving birth to the U.S. industrial revolution. The U.S. soon eclipsed the U.K. in textile manufacturing. The second example of a failed attempt to limit the spread of knowledge is more recent. After World War II, the U.S. possessed the world's only atomic weapons. Tremendous security measures were imposed on atomic secrets, even to the point of executing Julius and Ethel Rosenberg for leaking Atomic Secrets to the Soviet Union. But the Russians eventually developed their own bomb, as did Britain and France and in more recent times, China, Israel, Pakistan, India learned how to

build atomic weapons, and today North Korea and Iran are close to becoming nuclear powers in spite of attempts to conceal the knowledge and materials necessary to build a bomb.

The third question seeks to address whether the spread of knowledge, even deadly knowledge, benefits or threatens society as a whole. During World War I, killer weapons using deadly gases such as chlorine (first used by the Germans), and phosgene (first used by the French) were introduced. Within a short time of these deadly gases being used, countermeasures in the form of gas masks were developed and distributed to all troops. During the World War II, gas weapons were not used at all because of the effective countermeasures and because gas weapons could not be confined to injuring only the enemy once they were released.

As we learned during the great influenza epidemic of 1918, biological weapons are even more difficult to control than chemical weapons. Gas dissipates and loses its lethality as it travels further from the point of dissemination. Biological weapons continue to spread, can become more deadly and become worldwide threats in a short time.

Viruses are susceptible to control through vaccines. As such, the more scientist who have access to the potential evolution of viruses into killer strains, the more work that can be done to anticipate vaccine design and prepare potential countermeasures.

In short, attempts to control and/or contain scientific discovery don't work. The only thing that does work, is to allow scientific knowledge to disseminate so that responsible scientists can discover how to control the consequences of that knowledge.

Scientists have often said that knowledge is neither good nor bad. Chlorine was developed for a good purpose, as a byproduct of Germany's dye-making industry, and used as a military weapon. Atomic energy was developed as weaponry and later turned to peaceful

purposes. Recent events underscore the truth that scientific knowledge can be used either for destructive or constructive purposes. It is up to us how it is used.

Flu Prevention Saves Lives, Money[223]

The U.S. is now in the grip of a nationwide influenza surge that threatens the lives of thousands of people. City and state governments are declaring health emergencies and television personalities are getting vaccinated on live TV. But people so greatly misperceive the severity of flu that it became the punch line for a joke during Sunday night's Golden Globe award show. What many people in the audience and watching television failed to understand is that flu is not a laughing matter. More than 3,700 people have been hospitalized and at least twenty children have already died from flu-related causes since October 1, 2012, when the flu season officially began.

Thousands of people die in the U.S. of seasonal flu each year. Many more are hospitalized and require long recuperation times before they can return to fully active lives. Most of the tragic victims of flu are among the very old, young and sick. The cost of caring for them is staggering.

Influenza prevention and treatment is an area where there is an urgent need to spend money in order to save money and lives. As many as 49,000 people have died of seasonal flu-related causes in one year in the U.S. and many more elsewhere. Novel influenza strains that pop up unexpectedly can cause many more fatalities. In 2003, an extremely deadly strain of

[223] Steve Brozak, Henry Bassman, and Emad Samad, "Flu Prevention Saves Lives, Money," *ABCNews.com*, January 18, 2013, https://www.google.com/url?q=http://abcnews.go.com/Health/ColdandFlu/flu-outbreak-government-solution-problem/story?id%3D18242477&sa=D&ust=1461915775501000&usg=AFQjCNGxnAajf-UAxAw7m4iLCAzxEJEl9g.

H5N1 Avian Influenza began infecting people in Asia. The number of cases increased in 2004 and 2005, causing great concern among U.S. government agencies that the disease could spread to the U.S.

In response to the Avian Flu threat, Congress created the Biodefense Advanced Research and Development Authority (BARDA) in 2006, as part of the Pandemic and All Hazards Preparedness Act. Among BARDA's responsibilities are stockpiling vaccines and antiviral medicines in the case of a severe flu attack, advancing innovation to protect the U.S. against the flu, and insuring that the U.S. has a manufacturing infrastructure to make the country self-sufficient in combating a flu epidemic.

In 2006, BARDA began making long-term investments in biodefense- and pandemic-related vaccine production facilities and drugs. Those investments are now starting to bear fruit. Just three months ago, one of the largest pharmaceutical companies, Novartis, opened a new vaccine manufacturing plant in North Carolina that was begun in 2006 with $500 million from BARDA.

This new plant will increase the production speed of seasonal flu vaccines and enable faster response to flu emergencies. It uses the latest vaccine technology, which cultivates the virus used for flu vaccine in 1,250 gallon vats rather than thousands of fertilized eggs. In the event of a worldwide pandemic, our nation is guaranteed to have production capacity on our own shores through investments like this one with Novartis.

Vaccine manufacturing went out of vogue decades ago as a high-risk, low-reward endeavor. Without government involvement, large pharmaceutical companies like Novartis wouldn’t be able to justify to their stockholders the commitment of capital to build a new

vaccine facility, when other companies, like Merck, are moving vaccine production offshore to countries like China, where they can save several dollars per delivered vaccine dose.

The Novartis plant is not the first example of BARDA's efforts paying off. During the 2009/10 flu season, when the H1N1 Swine Flu struck suddenly and without warning in the U.S., a new vaccine was created, packaged and distributed in the previously unheard of time of six months, making it available during the second surge off that flu threat. Fortunately, the second surge was milder than the first and the vaccine was not as crucial as first thought. But the experience demonstrated that in an emergency, flu vaccine can now be developed and produced in time to meet an unforeseen threat.

The work to improve response to influenza continues in several government agencies. The National Institute of Allergy and Infectious Diseases (NIAID), which is a part of the National Institutes of Health, under the Department of Health and Human Services, has been leading an effort to develop new and better flu vaccines for more than eight years.

In 2005, when the pharmaceutical company, GlaxoSmithKline, wanted to produce a vaccine not yet approved for manufacture in the U.S., NIAID staff worked with the company to gain accelerated approval for Fluarix, the branded vaccine that is used widely in the U.S. today. In 2014, an additional component will be added to Fluarix vaccine, giving people immunity to four, rather than three flu subtypes.

The ultimate goal for vaccine research and development is a universal one-shot-for-life vaccine that protects most people against a wide range of flu variants. Previous funding from BARDA and NIAID has brought us closer to reaching that goal. Five vaccine candidates that confer broad immunity against flu have advanced to the first phase of human trials. These

candidates were developed by a group within NIAID that is working with the pharmaceutical manufacturer, MedImmune, under a Cooperative Research and Development Agreement.

Efforts such as these will help hold down healthcare costs. Seasonal flu imposes an $87.1 billion annual economic burden on the U.S., as estimated in a study by researchers at the CDC. Though the results of government/business cooperative efforts may not be reported on the nightly news, we as a nation, already reap the rewards of such investments that improve the quality of healthcare while reducing the economic impact of yearly flu.

But seasonal flu, as tragic and expensive as it can be, is only part of the challenge facing public health agencies. The steps that agencies like BARDA and other divisions within HHS take also protect us from the threat of a novel flu strain that could strike suddenly with devastating impact. The worst-case scenario is a 1918-like flu. In that year, there were 500,000 flu-related deaths in the U.S. and as many as fifty million people died worldwide. The potential for a repeat of a flu epidemic of such deadly proportions is the nightmare of many health professionals.

Even amongst the healthiest people, a common side-effect of an influenza infection is a secondary or opportunistic bacterial infection that develops when the body's resistance is lowered from fighting the flu. These infections can be equally or more life-threatening than the original virus. Since the late 1940s, antibiotics have been used to battle bacterial infections, but the bugs are developing immunity to the antibiotics at an alarmingly rapid rate.

BARDA has funded development of new antibiotics to meet the challenge of increased resistance to drugs currently in use. Last year, Congress incorporated the Generate Antibiotic Incentives Now (GAIN) Act into reauthorization legislation for the FDA. The purpose of this legislation is to extend the exclusivity time for new antibiotics and thereby encourage their

development. When these new antibiotics become available they will provide additional opportunities to reduce flu-related deaths.

The progress made in combating flu is an example of an activity where no news is the measure of success. Government agencies, scientists and companies are working together to achieve progress in an area that could present a great threat to our nation and its people. The absence of headlines means they are doing their job to protect us and the fact that someone can joke about a disease as severe as influenza on national television, demonstrates that what was once a greatly feared disease appears a lot less frightening to the general public, but only because government planning years ago made it possible.

Flu, The Ninja Disease

To many of us, influenza, or flu, is just a head cold on steroids. For young adults, a case of the flu may be a nuisance, keeping them in bed for a week to ten days, but for the very young, very old or those in poor health, the flu continues to be life-threatening. Like a ninja warrior, silently stalking its victims, each year close to 30,000 people die from flu in the U.S. and 200,000 are hospitalized. And every so often, as in 1918, a unique and unexpected variant of the flu bug appears that could become an international disaster.

Flu is not all bad. It is a disease that has been beneficial to the science of medicine because it has been the focus of research and development. Each year it returns, but we don’t know for sure how bad it will be. The danger of another 1918 epidemic is always lurking in the background.

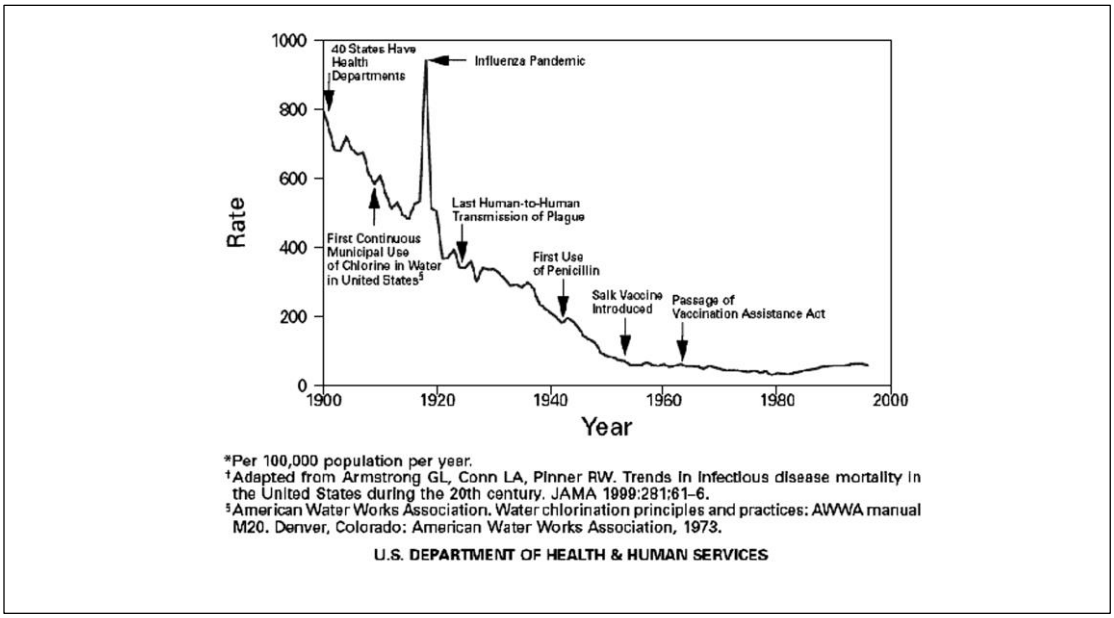


Figure 13. Influenza Pandemic. Available at HHS.gov.

The consequences of working to control flu have had many beneficial spinoffs. After the great flu epidemic of 1918, it took sixteen years of searching for scientists to isolate flu's cause, yielding much knowledge of the nature of viruses. Then five years later, in 1938, Jonas Salk, developed the first flu vaccine. The knowledge he gained in developing viral vaccines using eggs as a growth medium led to the creation of the first Polio vaccine in 1952.

From 1938 until 2004, little progress was made to advance flu vaccine technology, anti-viral therapy or methods for treating deadly opportunistic bacterial infections that often accompany a case of the flu. We knew for decades that the U.S. was vulnerable to a biologic military weapon, but did little to prepare to defend ourselves. But, after the 9/11 2001 attacks, our country decided something must be done.

In 2004, Congress voted for the Project Bioshield act, authorizing $5 billion for purchasing vaccines that would be used in the event of a bioterrorist attack. The Biomedical Advanced Research and Development Authority (BARDA) was established within the

Department of Health and Human Services (HHS) to carry out the requirements of the act. In 2006, Congress enacted and the President signed into law the Pandemic and All Hazards Preparedness Act. The act gave BARDA broad powers to work with the Centers for Disease Control and National Institute of Allergic and Infectious Diseases to prepare for and respond to natural disasters, like pandemic flu, as well as man-made medical disasters.

Flu is different from other biothreats in one way, the influenza virus mutates so often that the vaccine used this year is likely to be ineffective next year and sometimes unique and deadly flu strains appear without warning. The flu virus is constantly changing and evolving with new strains evolving in a process called antigenic shift. Within each strain there can be many sub-strains, each different enough that a vaccine which works on one may not work on another.

So that unexpected new strains can be thwarted, the government, through BARDA has now spent about $50 billion to purchase vaccines and create the ability to react to a flu threat within six months. In November, 2009, Novartis AG (NVS) opened the doors at its first U.S. plant to produce flu vaccines using cell cultures instead of egg-based methods in Holly Springs, VA. The government allocated $487 million of the $1 billion needed to build this 430,000-square-foot plant that is geared to supply 150 million doses of flu vaccine within six months of an influenza pandemic declaration.

One of flu's nasty characteristics is that it leaves people susceptible to opportunistic bacterial infections, especially pneumonia. Though we have yet to develop a cure for viral pneumonia, antibiotics have been effective against bacterial pneumonia. But many of the old stand-by antibiotics are losing their punch, so BARDA has provided funds for companies like

Cempra, Inc. (CEMP) and Tetraphase Pharmaceuticals, Inc. (TTPH) to develop new antibiotics that are effective against biothreats like influenza.

Flu reminds us that continuity of healthcare services is as crucial to our society as a continuous supply of water, electricity, telephone and Internet services. Loss of any one of these systems, healthcare included, causes chaos.

The one fundamental difference between healthcare and all other systems is lack of backup. If the Internet fails, we can use a cell phone to communicate with others. If electricity fails, a gas heater can keep us warm, or a home generator can give us power. If we lose access to healthcare, either at a hospital or our doctor's office, we have no alternative but to suffer.

The flu fight is one example of government agencies and businesses working together to minimize a known threat and prepare for the unknown. Under the direction of BARDA, working with both large and small companies, you and I, as well as hospital operators, individual physicians, vaccine developers and manufacturers, have all benefitted.

Rapid Onset

Since a virus cell cannot reproduce on its own, it must form a bond with an animal cell. When virus cells invade the human body, they attach themselves to the epithelial lining of the respiratory tract, which stretches from the throat down to the minute air sacs (alveoli) where fresh air infuses blood with O_2 and waste gases, like CO_2, are evacuated from the blood.

About ten hours after the first virus bond is formed, the human cell bursts open, releasing between 1,000 and 10,000 new virus cells. At even the lowest rate of multiplication (10^3 every ten hours) a single virus cell can become one million virus cells in less than three days. This explains the rapid onset of viral diseases.

Secondary Infection

While the virus is duplicating inside the respiratory system, it is releasing chemicals that inhibit the release of interferon, the first line of defense against viruses, making the infected person more susceptible to other infections like bacterial pneumonia.

Sore Throat, Inflammation, Fever and Aching Bones

By attaching to epithelial cells, using them to incubate virus cells and then causing them to explode, even mild viruses can strip the throat of epithelial cells, thus making it sore.

When an infection gets a toehold, the patient's white blood cells respond by releasing specialized proteins called "cytokines." There are many different types of cytokines and each is highly specialized. Some cytokines some attack invaders directly, some act as messengers to other cells such as the cytokines that stimulate the production of more white blood cells in bone marrow, which may cause aching bones. Some cytokines can affect the hypothalamus, deep inside the brain, driving up the body's temperature because some diseases do not tolerate high temperature.

Respiratory Congestion and Asphyxiation

When a killer flu attacks the body, the normal, measured and appropriate responses of the body can over-react. The healthier the immune system, the stronger the reaction can be. This over-reaction, called cytokine storm, can kill quickly and dramatically, especially among people in the twenty-five to thirty-four age group as was experienced in 1918.

In cytokine storm, the capillaries that supply blood to the alveoli expand, flooding the air-sacs with white blood cells, antibodies, other elements of the immune system and more

cytokines. More fluid pours into the lung. Pink glassy membranes called hyaline membranes line the alveoli. The fluid that coats alveoli to facilitate oxygen replenishment disappears. Then areas of the lung become tangled in cell debris, fibrin and collagen (blood clotting factors). Proteins fill the space between lung tissue cells. Eventually, portions of the lung become totally blocked, cease functioning and the patient can die.

The Nature of Flu

Flu viruses are constantly changing and evolving. This constant change is what makes it necessary to develop different seasonal flu vaccines every year. Flu viruses are categorized by how they attach to and detach from human cells within the respiratory tract. The enzymes used for attachment are the virus's Hemagglutinin (H) spikes and those used for release are Neuraminidase (N) enzymes. Each virus strain is identified by its H and N sequence. Hence, the currently threatening virus is H5N1 because it attaches to Hemagglutinin connector 5 and releases via Neuraminidase connector 1.

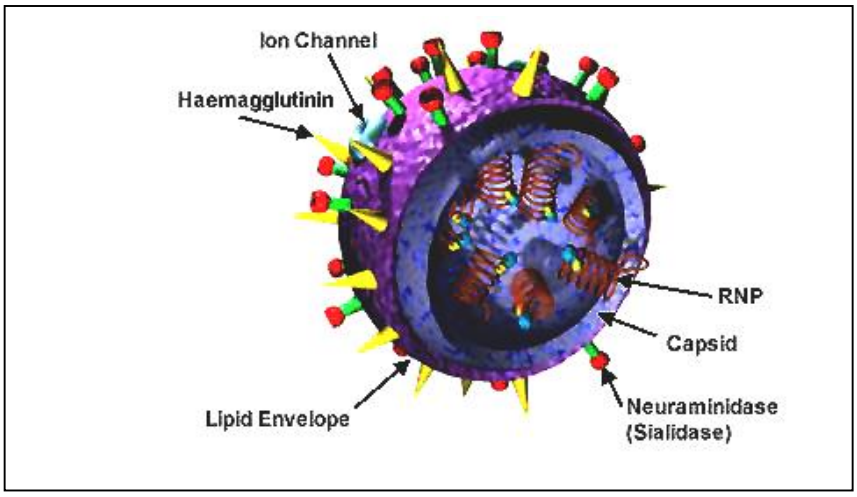


Figure 14. Source: U.S. Government

How Flu Tried to Steal the World Cup's Thunder[224]

At 4PM ET, the German soccer team will face Brazil in the World Cup semi-finals. The Germans might not have made it. Just a few days ago, the team could have been stopped, not by their opponent France, but by a virus that caused seven of the team's players to come down with flu-like symptoms.

After almost a century of investigation, more than a half-century of creating seasonal vaccines, and a decade of vital U.S. Government involvement through the Biomedical Advanced Research and Development Authority (BARDA) partnering, we are still learning how flu evolves and what the future of vaccines and anti-viral medicines might look like.

That was until Dr. Yoshiro Kawaoka, a name not well known outside the flu research community, grabbed headlines. He made a presentation about his research, revealing that he was able to manipulate the genetic code of the killer Swine Flu in his laboratories to make it even more lethal. Now many in the media have vilified him as a modern day Dr. Frankenstein, who engineered a zombie flu strain that could potentially kill up to a billion people if it escapes. And the villagers (on social media at least) are restless.

Dr. Kawaoka's lab at the University of Wisconsin's Influenza Research Institute (IRI) has been safely conducting important influenza research since it opened in 2008. Dr. Kawaoka, a professor of pathobiological sciences and an expert on influenza, has been one of IRI's most prolific scientists. In addition to explaining how he developed the ability to alter influenza viruses, he also reported that current viruses have all the elements necessary to

---

[224] Steve Brozak, "How Flu Tried to Steal the World Cup's Thunder," *Forbes.com*, July 8, 2014, https://www.google.com/url?q=http://www.forbes.com/sites/stephenbrozak/2014/07/08/how-flu-tried-to-steal-the-world-cups-thunder/%236ec20cd671a1&sa=D&ust=1461915775491000&usg=AFQjCNHk6WVodefgq42-i1WT7SiZ1DWv5g.

recreate the deadly 1918 influenza virus, which was responsible for killing as many as fifty million people worldwide.

Several articles about Dr. Kawaoka's work generated a great deal of misunderstanding. The truth is that Dr. Kawaoka's work provides a better understanding of how viruses change over time so their evolution can be anticipated, enabling vaccines to become available faster and better anti-viral drugs to be created.

The most effective way to treat influenza today is through a targeted vaccine that prevents people from catching a specific strain of flu. Each year, as the flu virus evolves and changes, the previous year's seasonal flu vaccine becomes ineffective. Sometimes a novel strain for which there is no vaccine appears. Manufacturers like Novartis AG, Glaxo SmithKline and Sanofi make enough targeted flu vaccines each year to meet most of the world's annual need for seasonal flu. With support from the U.S. government, the vaccine industry has made great progress in early identification of novel influenza viruses and accelerated production of vaccines to counter them.

For those people who didn't have access to a vaccine or came down with the flu anyway, drugs like Relenza (zanamivir) from Glaxo SmithKline plc and Tamiflu (osaltimivir), developed by Gilead Sciences with exclusive rights licensed to Roche Holding AG, are available. Our government stockpiles both of these drugs for distribution in the event of a major influenza emergency.

As good as our current defenses may be, our current flu-fighting tools have shortcomings. Vaccines take months to create and distribute once a unique influenza virus is identified. Anti-virals are only effective early in the course of flu and the flu virus eventually develops resistance to the drugs, rendering them useless.

But what if we could take just one vaccine and be protected for decades from any strain that emerges? Dr. Kawaoka is one of several researchers seeking a universal vaccine – one vaccine that will immunize a population from all flu variations for years to come. His research is being conducted with funding from the National Institute of Allergy and Infectious Disease (NIAID). The purpose of this government/academic partnership is to discover why some viruses are highly lethal to humans and to model how humans respond to these viral pathogens. To gain this better understanding of how viruses evolve, Dr. Kawaoka is stitching together gene-creating proteins to create new viruses.

Every year as billions of animals around the globe contract and spread viruses, the chance of a pandemic influenza emerging through evolution increases. Dr. Kawaoka's research is incredibly important, as it continues to unfold information that could lead to a vaccine system that will be able to anticipate and prevent the threat of an influenza virus.

Much has been overstated about Dr. Kawaoka's research; including the ease his work can be replicated. Some news articles and commenting scientists would have you believe Dr. Kawaoka's experiments could be re-created in a high school lab. But Dr. Kawaoka's research isn't the stuff of Science Fairs. It is highly complex science that requires access to sensitive equipment and commercial-grade strains of multiple influenza genomes. The project requires extraordinary clinical skill and scientific expertise, not easily replicated by laymen or rogue operators. It is assumed, however, that similar work is being conducted in the highly secure labs of other developed nations, and we must never forget that the evolution of influenza is ongoing as its components morph into continually changing forms in the world's largest open and uncontrolled lab -- planet earth itself.

CHAPTER SIX

VETERANS' MODEL

The Veterans Healthcare Administration (VHA) has been the most transparent in talking about its flaws such as the infrastructure, funding for VA hospitals and TRICARE coverage, all of which are often short of sufficient funds. Failures in veterans' healthcare have been related to understaffing, poor medical standards, and unattended mental health issues. Remediation steps are being created and implemented to add workability in this system.

The value of the VHA is that it not only cares for over 9 million people, but also it is a microcosm of the practices and problems of the national healthcare system, it is a test-bed for new medicines, protocols and administrative practices, it provides training for thousands of doctors and it can provide a template for greater transparency, accountability and penalties for malfeasance.

Our national healthcare system is in crisis. It has been this way for a while and the perception has only recently caught up with reality. The way the VHA recovered from its crisis could be an effective model for recovery of the larger system. Ten years ago, no one even thought about the VHA. RThe medical service was adequate. The system treated mostly WW2 and Vietnam vets, who were aging and becoming less vocal. The system's budget was a target of government thrift and that was not a problem since the veteran population was contracting and aging. Then in 2008, when numbers of troops coming home from wars in Afghanistan and Iraq were given five years of treatment by VHA, the demands on the system changed. Suddenly, there were thousands of new veterans, reservists and national guard members who needed to be served. The VHA was underfunded and understaffed to provide care to young, recently wounded or injured and often emotionally injured young veterans.

The VHA provides benefits beyond medical care for the veteran community. Military medicine is responsible for much of the advances in civilian medical practice. Anesthesia, blood transfusions, mass inoculation, vector control of communicable diseases, trauma surgery and physical therapy were all innovated, improved upon, or quickly adopted by military and VHA practitioners. The VHA is the only government body allowed to negotiate with pharmaceutical companies for the price of medicines. Thousands of fourth-year medical students and residents are trained in VHA facilities. Hundreds of clinical trials are conducted in VHA facilities.

In addition to these ancillary benefits, the VHA system must be considered as a test system for United States healthcare in general. Organization, accountability, and penalties for negligent performance can be administered on a system-wide basis to test potential solutions to healthcare problems in other realms.

Our 'New Normal' Wounded Healthcare System[225]

When wounded warriors are now sent to the Bethesda Naval Medical Center for treatment, whether missing a leg, an arm or having sustained a traumatic brain injury, they are introduced to a novel expression: "This is your new normal." It is explained to them that from now on they will have to accept a new way of life and their expectations must be changed to meet their new realities. These realities mean new sacrifices for them into their futures, with an even longer duration than the unparalleled conflict we are engaged in.

---

[225] Stephen Brozak and Henry Bassman, "Our 'New Normal' Wounded Healthcare System," *ABCNews.com*, August 22, 2011, https://www.google.com/url?q=http://abcnews.go.com/Health/saving-us-healthcare-system-research-development-funding-key/story?id%3D14343836&sa=D&ust=1461915775511000&usg=AFQjCNH7FSKxLLkpw1IqeVUn76KNvLPHNw.

There is only one exception that can be labeled a comparator in our nation's history. That exception is the wounded U.S. healthcare system, which is suffering from inherent disabilities that are beginning to preclude effective functioning and will only become worse in the future.

Without significant investment in new medical technology, our wounded healthcare system will become our "new normal" of diminished quality-of-life, shorter life expectancy, and diminished access to healthcare.

The way to restore both the wounded warrior and the healthcare system is through federally funded research and development of new technology. Given the rough patch the U.S. economy is facing—something not seen since the Great Depression—experts both conservative and progressive will ask: "What will be the payback on this investment be?" The answer has a proven track record of creating new high-paying jobs, new business opportunities for biotechnology, medical device, and pharmaceutical companies—this while adding a much needed positive contribution to our GDP and continued U.S. leadership in medical science and technology. So what is the problem?

Even the currently modest funding for healthcare research is now being threatened. To meet the current fiscal challenge, the director of the Office of Management and Budget sent a memorandum on Wednesday, Aug. 17, to all agency and department heads, asking them to submit two budgets for President Obama's consideration. One proposal would reflect a five percent budget reduction and the other would include a ten percent reduction for the 2013 fiscal year. The memorandum also says that submissions "should identify programs to 'double down' on because they provide the best opportunity to enhance economic growth." This last sentence we believe carries the only credible opportunity for many Americans to receive the

quality of medical care that they are hopeful of receiving. We believe healthcare research is one of those areas that has repeatedly proven its ability to enhance economic growth and its budget must actually be increased.

There are multiple examples of federally funded new healthcare initiatives leading to economic breakthroughs that have revolutionized daily life, put thousands of people to work and earned billions of dollars for Americans. Unfortunately, Wall Street has focused the healthcare industry on meeting today's earnings per share (EPS) demands instead of focusing on the challenges to create what is needed for tomorrow's healthcare requirements. This has resulted in neither the innovation that will be needed or even in meeting the future EPS demands. Large pharmaceutical companies are struggling to maintain their current operations by reducing or even eliminating research programs. Hospitals are increasingly financially challenged. Physicians and other healthcare professionals now work longer hours at compensation levels that bring into question the value of the many years they committed to their training.

The federal government is the only entity that has the resources to foster the technology that will achieve the breakthroughs to sustain high-quality medical care in the U.S., cut costs and sustain healthcare industries. The government already acts as the de-facto standards-setter for medical care through the Centers for Medicare and Medicaid Insurance, which decides the procedures and medicines that will be covered by health insurance and how much can be charged for each. But that is primarily a cost-cutting activity and there is an adage in business that you can't grow a business solely by cutting costs.

Compared to the potential benefit, the current investment in healthcare research is small and should be increased significantly. Research programs given the backing of agencies

that most Americans only know by their initials have become the backstop of medical innovation with new Commercial Pharma, Biotech, and Medical Companies as the outgrowths of this funding. For example, the anti-cholesterol medication, Lipitor, the biggest selling drug of all time, came into being because of National Institute of Health (NIH) federal funding that identified LDL receptors.

Between 2003 and 2010, U.S. sales of Lipitor were more than $47 billion. Lipitor, and other drugs, biologics and medical devices that were made possible by federal funding have improved the quality of life for millions, provided jobs for thousands and created tremendous economic benefit to the U.S.

Just to make obvious that this process is still vibrant, an example of breakthrough technology funded by the Defense Advanced research Projects Agency (DARPA) (the scientific military collaboration agency) can be used. DARPA invested for a legitimate military need in a mechanized back support system called the exoskeleton (more equipment carried caused back problems, both short and long term impacts for soldiers). A start-up company, spun out of an academic institution brought the concept to actual practice, filling a military need and creating a whole new market. What is potential healthcare application? The sixty-eight million people wheel chair bound worldwide which would dwarf any possible military usage.

President Obama has announced he will unveil a new jobs program early next month. Shovel-ready infrastructure projects will probably be part of the program and may be necessary short-term steps to alleviate immediate job shortages. Longer-term solutions also must be included in any economic stimulus and job development program. The steps taken will tell us what the "New Normal" will be in many ways.

No one debates whether future healthcare demographics will be unsustainable at current obligation levels even with a robust recovery. Given the return on investment from today's relatively modest government funding of healthcare research, increased funding to advance medical science is a crucial step toward economic recovery. Such a "double down" in research today has the hope of creating what we began this article by stating: new jobs, higher educational attainment, opportunities for economic growth, and improving the quality of medical care in the U.S. It could also finally offer all Americans a real hope in finally holding down or reducing medical costs overall.

A New American 11/11/11 Day: The Health Care Veterans Deserve[226]

On this Veterans Day, our military forces are engaged in continuing conflict that has lasted longer than any war in our nation's history. As a Marine Corps veteran, I have experienced men and women who served for decades, returning home to find the country's promise of medical care for them and their families being unfulfilled.

Medical care for military personnel, military retirees, some members of reserve units and their dependents is administered through a government-created health insurance system called TRICARE. It was established in 1966—originally under the name CHAMPUS, short for the Civilian Health and Medical Program of the Uniformed Services—to provide military families with healthcare from civilian practitioners. The program is managed under the

[226] Stephen Brozak, "A New American 11/11/11 Day: The Health Care Veterans Deserve," *ABCNerws.com*, November 11, 2011, https://www.google.com/url?q=http://abcnews.go.com/Health/doctors-failing-veterans-accepting-tricare-veteran/story?id%3D14926386&sa=D&ust=1461915775525000&usg=AFQjCNFiEr3F7NtusEvRqcUDVKa8BKg3XQ.

Assistant Secretary of Defense for Health Affairs Dr. Jonathan Woodson, who is a graduate of City College of New York and New York University Medical School.

The War against Terror has created a new generation of veterans who are eligible for healthcare under TRICARE. Unfortunately, that care is often unavailable. As a recalled Marine Reservist, I have personal experience with this dilemma. Immediately after 9/11, I was called to active duty in and around Ground Zero. When I would return home from time to time, to visit my newborn daughter, I would throw away my uniform because of the acrid smell and the potential for hazardous particles embedded in the fabric.

After my retirement from active duty, I resumed my civilian job as a Wall Street financial research analyst. My job is to evaluate all aspects of healthcare – new biotechnology products, new medical devices and healthcare services. When men and women with whom I served told me how difficult it is to find TRICARE coverage in New York City, I turned my analytical skills to quantifying TRICARE availability for active, reserve, or retired service members and their families within the New York City limits beginning at Ground Zero.

Using skills I learned at business school, I conducted a statistically valid survey of one-hundred primary care physicians in New York City. I asked their offices if they accepted TRICARE, Medicaid, or another major insurance plan. I repeated the survey with a different group of one-hundred primary care physicians ten months later to ensure consistent results.

Here is what I found: ninety-six percent of the called offices accepted some major insurance. Medicaid was accepted by forty percent and TRICARE accepted by only twenty-five percent of those surveyed. If you extrapolate the findings from these 200 practices to the possible 22,000 primary care practitioners with offices in NYC, these results suggest that you are almost twice as likely to receive medical care funded through Medicaid than TRICARE.

The fact that the majority of respondents were unfamiliar with TRICARE is even more disappointing.

This weekend there will be many events celebrating our men and women in uniform. Politicians and prominent citizens will be extolling the sacrifice and courage of our military. Others will be expressing their gratitude for our service. As a group, military people have special medical needs; some serve twenty years of arduous duty that can be as physically challenging as professional sports with much lower pay. Military people carry heavy loads of up to one-hundred pounds over difficult terrain for days, they are exposed to noise and concussion from artillery pieces, serve in cramped and noisy spaces aboard ships and experience collisions with the ground when they jump from airplanes and helicopters.

In my experience, our uniformed service members aren't asking for any special "deal" for their service. What they do expect is that we fulfill our pledge of medical care for them and their families. They are not looking for elite care. Very few will be looking for treatment by the proverbial "Park Avenue" practitioners.

The sad truth is that when TRICARE clients need medical treatment from the same people who woke up to the horrors of 9/11, they have to go "out of network" for treatment. As anyone who has had this experience knows, going "out of network" is a financial and emotional strain. First you must pay the practitioner for medical care, which is a burden for those with few financial resources, then you need to submit multiple complex documents, and in the end, you are uncertain of how much reimbursement will be allowed.

It is also true that New York City medical practitioners have little risk of being overrun by wounded warriors, even if all of them accepted the TRICARE plan. It would be a

fitting and symbolic thank you if more practitioners in and around Ground Zero were to accept TRICARE as a recognition of the service of the few for the many.

Commentary by both the advocates labeled the right and the left mean little if our veterans cannot identify with the people they defend. It is no small irony that our "first soldier," George Washington, faced the same decision even while the beginning of our country was in grave doubt. He made it clear by saying: "... it must be laid down as a primary position and the basis of our (democratic) system, that every citizen who enjoys the protection of a free government owes not only a proportion of his property, but even his personal service to the defense of it." On this 11/11/11 let's see if we as Americans can return to that primary position.

Veterans' Access to Mental Health Services Needs Fixing[227]

Much has been made about the lack of jobs for veterans, and in fact the unemployment rate for veterans of the Iraq and Afghanistan wars stands at ten percent, compared to 6.8 percent of the civilian population. But the insufficient attention given to veterans' health -- especially mental health -- is actually the greatest risk to returning service members.

There are approximately 2.6 million American service members who fought in Iraq or Afghanistan, and there have been 1.5 million new veterans since 2001. As a retired Marine, I have witnessed firsthand the hardships facing our returning men and women, and know the difficulties don't end when their tours are over.

---

[227] Ret. Lt. Col. Steve Brozak, "Veterans' Access to Mental Health Services Needs Fixing," *CNN.com*, November 11, 2013, https://www.google.com/url?q=http://money.cnn.com/2013/11/11/news/economy/veterans-mental-health/&sa=D&ust=1461915775525000&usg=AFQjCNFV2-l5CSjRQHcRVaVIXHxctTlu2g.

An estimated twenty percent of Afghanistan and Iraq veterans screen positive for PTSD or depression, and the mental health community is, at best, disjointed in dealing with this. Veteran's Affairs spent $6.2 billion -- up slightly from last year -- on inpatient, residential, and outpatient mental health programs, but veterans are still having difficulties being treated.

In fact, the VA recently released data showing that a third of veterans seeking mental health appointments wait longer than fourteen days. In cities like Orlando, Houston and Los Angeles' VA hospitals, the wait times are even higher. In Houston, for instance, veterans waited an average of twenty-eight days for an appointment. The initial step to seek treatment can be a hurdle in and of itself, and half of those with PTSD go untreated.

Many Americans are familiar with the concussion-related traumatic brain injuries (TBIs) suffered by NFL athletes. In fact, just last month the NFL agreed to pay $765 million to settle a lawsuit brought by 4,500 retired athletes claiming that the NFL worked to conceal the long-term impacts of concussions from players. What's been less publicized is the number of veterans who are also diagnosed with traumatic brain injuries.

There have been nearly 250,000 veterans with TBI since 9/11 according to the Congressional Research Service, and the number of diagnoses continues to increase. On top of that, the Defense Medical Surveillance System found that nearly 6,500 veterans suffered Severe or Penetrating TBI, which can impair cognitive function, motor function and sensation —making it hard for veterans to perform the most basic of daily functions.

TBI often leads to more medical complications as well: The Centers for Disease Control says forty-three percent of individuals hospitalized after a severe TBI will have a related disability within a year of the injury.

Physical and mental health issues represent a very real barrier for our nation's service men and women. Returning veterans already cope with the daunting task of re-assimilating into their civilian lives, with health and financial woes further complicating this transition. I have witnessed firsthand the physical, mental, and financial stresses facing veterans across the country.

Unfortunately, in many instances the pressure can prove to be too much, and veterans account for twenty percent of suicides, despite making up only ten percent of the U.S. population. Suicide rates among the veteran population are the highest they have been since the beginning of the Iraq and Afghanistan wars.

As a first step in supporting these veterans, those of us in civilian life can work to close the gap between providers of mental health services and the veterans who desperately need their help. An April GAO report surveyed civilian mental health care providers, finding that only thirty-nine percent were accepting new patients with veteran's TRICARE health insurance coverage. For many veterans, this is the only way they can afford mental health assistance, and yet in many regions of the country it can be nearly impossible to find someone who accepts their insurance. It is a significant -- and unnecessary -- barrier to veterans getting the help they need. On this Veteran's Day, we should start taking steps to bridge that barrier.

Does the GI Bill Even Work?[228]

Over the last twelve months, failures in the VA health care system have dominated reporting about the Veterans Administration.

---

[228] Ret. Lt. Col. Steve Brozak, "Does the GI Bill Even Work?," *CNN.com*, November 11, 2014, https://www.google.com/url?q=http://money.cnn.com/2014/11/11/news/economy/veterans-education-gi-bill/&sa=D&ust=1461915775529000&usg=AFQjCNHXp4AwQOjQUWdP03vD3NOmksq4LA.

But as tragic as these failures are, the Post-9/11 GI Bill has as big an impact on recently discharged veterans, and we have limited data about that program's efficacy.

Today, there are close to 950,000 pre- and post-9/11 veterans in education and job training programs at a cost of more than $10 billion a year. Over the next few years, one million men and women will leave military service and will be eligible for educational benefits under the Post-9/11 GI Bill, which provides for a significant part of tuition, fees and books and offers an allowance for living expenses.

By definition, these new veterans will constitute a nontraditional student body. Eighty-nine percent are under thirty-four years old, fifty-six percent are married and forty-five percent have children.

This generation of veteran students is much like the Greatest Generation that won World War II. In 1947, veterans accounted for forty-nine percent of college admissions. Under the original GI Bill, 7.8 million veterans participated in an education or training program.

Back then, universities responded to the challenges of those "nontraditional students" by changing admission standards, acknowledging real world skills like management and adapting curricula to different learning paces. That is not happening today.

Today, we are incapable of even controlling the cost of veteran student debt, let alone monitoring the quality of service being provided. In May, Sallie Mae, agreed to pay close to $96.6 million in restitution and civil penalties for illegal student loans. The loan servicer was accused of overcharging 60,000 active military members and then improperly seeking default judgments against the borrowers.

As a retired Marine and a health care financial analyst, I know the lifelong impact of education. Much is at stake, for the nation and for individual veterans. Typical bachelor's

degree graduates earn $1.19 million over the course of their careers -- twice that of typical high school graduates.

We know there are problems with the veteran education programs. Very few veterans are admitted to prestigious universities. There is scant information on their graduation rates. There are few, if any, facts about the usefulness of a degree from a private for-profit school, though they are among the most popular for veterans. Most of all, few of our best universities are making the accommodations that are needed for today's nontraditional students to be accepted.

The available data is not encouraging, especially in the area of nonprofit colleges. Of more than 10,000 campuses, 8,500 have fewer than one-hundred veterans enrolled. Among prestigious universities, the numbers are even more disappointing. In 1947, Princeton University reported 2,500 veteran students. Last academic year, there were twenty-one.

There are some bright spots. Columbia University's School of General Studies (my alma mater) now constitutes the largest veterans program in all the Ivy Leagues combined. Currently it has more than 350 veterans enrolled, which account for almost twenty percent of the program's student body. The school acts on its belief that these students bring a wealth of life experience to the classroom and contribute in a unique way to the diversity and cultural richness of the university.

The Veterans Administration is now examining its own data to ensure that veterans -- and the government paying for their education -- are getting value for their investment. There are discussions to do a thorough review of graduation, retention, and transfer rates, which would provide valuable insight into the efficacy of the Post-9/11 GI Bill.

In my experience, veterans are not looking for a handout; they are looking for a hand up. Their time in the service already puts them several years behind their peers when searching for a job and entering a career. The GI Bill should give veterans the opportunity to catch up with their peers. We owe it to them to gather the data, make the necessary adjustments to the program and make sure the bill for our veterans' education is worth the paper it is printed on.

CONCLUSION

The preceding chapters detail the many flaws that presently plague a deeply fractured U.S. healthcare system that desperately needs reform to prevent its collapse. But, if there are so many issues and conditions that are too costly, over treated, or undertreated in America – is there any system we can identify that works? What we do know is that when the right care is delivered at the right time, the U.S. healthcare system delivers superior outcomes for patients. We also know that serendipity drives breakthroughs in the drug development process as much as the scientific method. The refashioning of the healthcare apparatus should be to drive positives outcomes consistently and with efficiency.

The question should be asked: Is there a system or model in which large volumes of patients with similar conditions, spread about in many different geographic areas, receive outcome-based care that can be reasonably budgeted and covered?

The answer is yes, there is. It lies in the most challenged and berated medical system in the world: America's Veterans Health Administration (VHA).

The VHA is much more than just a constellation of government backed clinics that serve our veterans' health needs. It is a powerful, multifaceted healthcare organization whose domain includes not only clinical care of our veterans, but which also has the legal ability to negotiate drug costs directly with manufacturers, unlike its sister programs Medicare and Medicaid. The VHA also has limited, but critical powers to sidestep government regulation in order to overcome challenges to servicing our veterans. It also interfaces with academia and other governmental organizations to partner on many R&D efforts on some of the most advanced and cutting edge technologies being worked

on today. These and other characteristics found at the organization have allowed the VHA to create a thriving ecosystem of healthcare programs.

If we explore some of the novel healthcare systems in place within the VHA ecosystem, we will find templates for the advancement of healthcare solutions for the rest of the United States. For example, numerous major medical studies show that the VHA, even with budget constraints, excels in treating patients with some of the costliest chronic conditions—such as diabetes—using evidence-based protocols and generally producing better outcomes. By testing programs that have produced the best medical outcomes with greatest efficiency in several sectors of the VHA and applying them nationally, we can improve the nation's overall healthcare system.

In a perfect example of the need for such an approach, all of this year's presidential primary candidates have inveighed against the skyrocketing cost of health care in America. Regrettably, they have had few specific suggestions on how to both provide care and finance it. However, Republicans and Democrats have all agreed on one point: We need to try to control the increasing costs of healthcare, especially for prescription medicines, by instituting direct negotiation with drug makers for prices in the Medicare Part D system.

In the 2003 Medicare Reform Act, drug makers successfully crafted legislation prohibiting the negotiation of prices with Centers for Medicare and Medicaid Services (CMS), but, try as they might, they could not extricate themselves from the framework that allows the Department of Veterans Affairs to negotiate for the drug prices for their membership.

While the VHA maintains the right to negotiate prices with companies, it does not make those amounts and prices public. As a model for negotiation that is already in place, the VHA's procurement process for drug purchasing is one of several successful VHA programs that can be proposed as potential solutions to the overall health care cost crisis.

Among the many benefits of negotiation, according to several published independent medical studies as well as VHA data reviews, the VHA has seen improved outcomes in its treatments of chronic diseases like diabetes, because patients have a better record of taking medication for diabetes when the cost is regulated and relatively small.

Newspapers are replete with tragic stories of seniors, and even middle-class, middle-income people, trading off their necessary medicines in order to pay for their housing or food. But the VHA has demonstrated increasing success in helping patients control diabetes and avoid crises, because of the accessibility of affordable prescription medicines and equipment.

Today, the medical costs alone for diabetes in America run about $167 billion according to the American Diabetes Association—and that includes emergency room visits for patients who have not adhered to their medical program and drugs. The VHA also has improved outcomes among patients with hypertension, again, according to the VHA and independent studies, in part because patients can afford their blood pressure medicine, and adhere to their regimen.

There are a number of other programs developed by the VHA treating chronic diseases, traumatic brain injury (TBI), early-onset dementia and other geriatric conditions. But the savings alone from adopting the VHA's proven success record with

negotiating drug prices directly with drug makers would likely be several billion dollars per year. The first step in saving America's healthcare system from collapse is making Medicare Part D drugs negotiable for the government.

It cannot be gainsaid that the VHA seems an unlikely model for repairing the American healthcare system, which is on the brink of imploding. But dozens of studies in the past two decades have shown the VHA provides exemplary, as well as cost-effective, healthcare.

The VHA has been under constant attack from ideologues who see it as "socialized medicine" that corporate and academic medical centers that seek to carve up the VHA services for themselves. However, the bulk of the criticism of the agency is that its bureaucracy deliberately and repeatedly impedes patients trying to qualify for VHA care; that it has too few doctors to meet patients' needs in a timely manner; and that specialists are not easily geographically accessible.

These aren't about the quality of medical treatment. They are about resources and logistics—and the political will—to make changes in them.

The regulations circumscribing veterans' access to care were demanded by a Congress that has become more and more financially restrictive with each session over the last two decades—Congress has balked at providing a budget that could absorb more patients and their families, and could restructure the VHA system of physical facilities to align with major shifts in population to the South and Southwest.

Meanwhile, a large body of scientific literature shows that the VHA provides medical care that is equal to or better than private and insurance-covered medical care. That proof includes studies mandated by Section 201 of the Veterans Access, Choice and

Accountability Act of 2014 (Public Law 113-146), which was passed by Congress in response to reports that veterans in Phoenix and around the country were dying while waiting for appointments for treatment. The studies show that the VHA continues to outperform the rest of the U.S. health sector on nearly every metric of quality.[229]

Positive studies about the quality of VHA care in several sectors began appearing in the early 2000s, suggesting that the VHA was decades ahead of the rest of the health care system in the meaningful use of electronic medical records, in the investment in disease prevention, and in the integration of patient care.

In 2003 a study in the *New England Journal of Medicine*[230] used eleven measures of quality to compare veterans' health facilities with fee-for-service Medicare. In all eleven measures, the quality of care in veterans' facilities proved to be "significantly better" than private-sector health care that was paid for by Medicare.

In 2007, the *British Medical Journal*[231] noted that while "long derided as a US example of failed Soviet-style central planning," the VHA "has recently emerged as a widely recognized leader in quality improvement and information technology. At present, the Veterans Health Administration offers more equitable care, of higher quality, at comparable or lower cost than private-sector alternatives."

And despite negative attention garnered in recent years, a systematic review of thirty-six studies comparing the quality of VHA and non-VHA care found that as of

---

[229] "Independent Assessment of the Health Care Delivery Systems and Management Processes of the Department of Veterans Affairs," *U.S. Department of Veterans Affairs* 1 (2015).

[230] A.K. Jha, J.B. Perlin, K.W. Kizer, and R.A. Dudley, "Effect of the Transformation of the Veterans Affairs Health Care System on the Quality of Care," *New England Journal of Medicine* 348 (2003): 2218–2227.

[231] Steffie Woolhandler and David U. Himmelstein. "Competition in a Publicly Funded Healthcare System," *BMJ* 335 (2007): 1126-1129.

2009, "almost all demonstrated that the VHA performed better than non-VHA comparison groups."[232]

What of physician familiarity with VHA? About sixty-five percent of doctors and surgeons practicing in the United States have received all or part of their residency training in VH of the Office of Academic Affiliations.[233] The VHA has partnered with medical schools to conduct practical training for medical interns and residents at VHA hospitals, and many VHA doctors hold joint appointments on the faculties of medical schools.

In addition, doctors employed by the VHA have been engaged in important medical research, which resulted in FDA approval for novel medical devices and new drugs (VHA-experienced researchers have even been recognized by three Nobel prizes in medicine.[234]

Author Philip Longman, a scholar at the New America Foundation, has chronicled the VHA's improvements in his book, now in its third edition, called "Best Care Anywhere: Why VA Care Is Better than Yours."[235]

The VHA has always been at the forefront in the treatment of the physical wounds of war, including spinal injuries, paralysis, loss of limbs and traumatic brain injury.

---

[232] S. Asch, P. Glassman, S. Matula, A. Trivedi, I. Miake-Lye, and P. Shekelle,"Comparison of Quality of Care in VA and Non-VA Settings: A Systematic Review," *VA-ESP Project* 05-226 (2010), http://www.hsrd.research.va.gov/publications/esp/quality.pdf.

[233] "Mission of the Office of Academic Affiliations," *Va.Gov*., 2016, http://www.va.gov/oaa/oaa_mission.asp.

[234] "Timeline of Accomplishments," *Research.Va.Gov*., 2016, http://www.research.va.gov/about/history.cfm.

[235] Longman, Phillip, *Best Care Anywhere: Why VA Health Care Is Better Than Yours*, 3rd ed. (Berrett-Koehler, 2010).

It has excelled in its innovative approaches to treatment of post-traumatic stress disorder (PTSD) resulting in improved outcomes for patients suffering from the psychological impact of war. VHA mental health doctors know that anti-depressants have limited efficacy unless there is a non-pharmaceutical reinforcement system, and the VHA has increased the patients' visits to counselors and psychiatrists, and emphasized the need for engagement with its community.

Finally, the VHA is in the forefront of treating a number of chronic diseases that are common in the American public such as cardiovascular conditions and diabetes. The total estimated cost of diagnosed diabetes in 2012 was $245 billion, including $176 billion in direct medical costs and $69 billion in reduced productivity.[236]

But the VHA has been in the forefront of developing protocols that keep patients adhering to their medication schedules, to their checkups, and to some extent, to their diets.

Can the VHA system serve as a model for changes in American healthcare and be replicated? Yes, with political and popular will. VHA innovations have been largely provider-driven. The VHA and its facilities have functioned in many respects as a giant research lab where new ideas—proposed by doctors and nurses, not just financial administrators—are given a chance to grow.

The VHA faltered badly in the post-Vietnam era, but many improvements were made during the Clinton administration under the directorship of Dr. Kenneth Kizer.

Dr. Kizer's philosophy was that the VHA has an incentive as an institution to invest in prevention, effective disease management, and other measures that maximize

[236] "Economic Costs of Diabetes in the U.S. in 2012," *Diabetes Care* 36, no. 4 (2013): 1033-1046.

long-term well-being. Dr. Kizer used those built-in incentives to develop what he called an "integrated system."

Dr. Kizer transformed the VHA into what Washington health care policy academics call an "accountable care organization," or ACO, by developing approaches to coordinate care among specialists, so that patients are treated as whole persons rather than as collections of body parts.

The VHA was roughly twenty years ahead of the rest of the U.S. in its use of what we today call electronic medical records and telemedicine. During the 1990s, many VHA doctors were experimenting with using their personal computers to improve the practice of medicine. VHA health administrators adopted many of the experiments. The result was its VistA software designed by doctors, for doctors. However, during the Bush administration, with the push to privatize many government functions, the VHA's coordinated IT record system was outsourced to Cerner, a large corporate software company.

There have been widely publicized problems at VHA facilities—as in major hospitals and medical centers. But some of those crises were in fact due to outsourcing and poor quality control of VHA vendors.

For example, between 2002 and 2008, the Philadelphia VA medical center outsourced its prostate cancer unit to a team from the University of Pennsylvania. Investigators later found that of the 114 patients who went through the treatment, ninety-two received either too much or not enough radiation to the prostate, and in some cases the physician missed the prostate altogether.

Under the Obama administration, the VHA leadership again picked up the Ken

Kizer philosophy of integration, trying to avoid the mistakes and omissions that fragment today's healthcare. The VHA began providing each of its patients with a "home" team of health care professionals—including a specific primary care physician, nurse, social worker, pharmacist, and health technician—who managed and coordinated the patient's care in a continuous relationship. The VHA's heavy emphasis on primary care has the same problem facing the American health care system as a whole – an acute shortage of primary care physicians.

The VHA has also integrated mental health professionals and substance abuse specialists into its medical home teams. This practice is virtually unknown outside of the VHA because insurers, including Medicare and Medicaid managed care organizations, will not pay for it. But the innovation has been crucial in treating the VHA's patient population, twenty-five percent of whom suffer from chronic mental illness and sixteen percent of whom struggle with addiction. With rising trends in mental health problems in the general population, now may be a very appropriate time to implement a similar version of the holistic VHA program to the national system.

Further, the VHA matches or excels over the private sector in its use of evidence-based therapies for mental illness. A 2014 study of how often appropriate drugs are prescribed to mentally ill patients[237] found that "[i]n every case, VHA performance was superior to that of the private sector by more than thirty percent."

[237] Katherine E. Watkins, M.D., M.S.H.S., Brad Smith, Ph.D., Ayse Akincigil, Ph.D., Melony E. Sorbero, Ph.D., Susan Paddock, Ph.D., Abigail Woodroffe, Ph.D., Cecilia Huang, Ph.D., Stephen Crystal, Ph.D., and Harold Alan Pincus, M.D, "The Quality of Medication Treatment for Mental Disorders in the Department of Veterans Affairs and in Private-Sector Plans," *Psychiatryonline.org*, 2015, http://dx.doi.org/10.1176/appi.ps.201400537.

The VHA's reliance on evidence-based mental health treatments has saved hundreds if not thousands of lives. Between 2000 and 2010, rates of suicide increased by forty percent among veterans who didn't use the VHA, but declined by twenty percent among those who did.

Looking at sectors where VHA has excelled can help us test and improve our health system, for the following reasons:

1) The VHA, unlike Medicare, can and does negotiate prices with drug and medical device makers. This gives the VHA an advantage in cost control, particularly for expensive medicines like anti-anemia drugs Procrit® and Epogen® used for kidney dialysis patients. The government has no template available in addressing Medicare Part D costs, except the VHA's track record in purchasing and dispensing drugs.

2) The VHA excels at preventive medicine for chronic disease and cancer, according to medical studies.

3) The VHA conducts research both solely and in partnership with major medical and academic centers looking at new treatments and taking new looks at outcomes in older treatments. Among current trials, the VHA is studying whether older age should rule out knee replacement; whether a commonly used back pain medication is really effective; and in its state of the art medical device research division, the VHA's "Gait Lab" is building an evidence base to help physicians determine which kind of bionic limb to prescribe. And as an example of next generation medicine, the VHA and Yale University are partnering in a project using a collagen scaffold to deliver stem cells to help heal diabetic ulcers.

4) Finally, the VHA is on the cutting edge of research and treatment for disorders of Central Nervous System (CNS). That includes TBI as well as PTSD.

The VHA cares for a geriatric population that suffers from many CNS disorders. Just as importantly, the VHA understands how to look at CNS disorders that present at a much younger age—patients whose physical condition mimics many of the conditions of old age. For example, the VHA application of geriatric care protocol helps patients who suffered TBI and have developed early onset dementia, or Alzheimer's or Parkinson's diseases.

The VHA's integrated system has been crucial in treating such patients— for instance, the integrated approach helps doctors and nurse practitioners distinguish between symptoms of dementia and those of a urinary tract infection or dehydration.

And last, we have no collective system for safeguarding the health of low-income people. The closest system we have for dealing with the marginalized in the population is the VHA. The VHA has shown it can succeed in producing better outcomes for chronic diseases among such populations.

In conclusion, Americans in general are sicker than they have ever been, but are not getting better. We need to modernize our healthcare system now, because in a decade the current ad hoc system will be unsustainable. If we do not plan for a coherent future strategy, we will be courting disaster.

We have roughly a decade to find reasonable solutions; otherwise solutions will be foisted on us. We need to recognize the VHA's era of exemplifying what the best way to implement healthcare by addressing and then adopting the VHA's many practices we can see about American healthcare rising to the needs of its citizens instead of collapsing.

APPENDICES

Appendix A

Long Shadow of the Stem-Cell Ruling[238]

Two months on from the court decision that briefly suspended US federal funding for human embryonic stem-cell research, uncertainty still stalks the field. Here a lawyer, an ethicist and a team of bankers warn that the effects of this saga will be felt for years to come.

THE BANKERS · John M. Nolan, Emad U. Samad, Suy Anne R. Martins, and Stephen G. Brozak are at WBB Securities, Clark, New Jersey.

The recent litigation in the District of Columbia Circuit attempting to suspend the public funding of hESC research in the United States also threatens privately-funded research. It has created an atmosphere of grave uncertainty among Wall Street investors. They now shy away from hESC products, alarmed by the increased risk that stems from protean federal policy and the ambiguous regulatory requirements.

The United States is at a crossroads. Never before has there been such a paucity of funding for the commercialization of a technology with such huge therapeutic potential. To date, we estimate that a total of less than US$250 million has been directly committed to meaningful enterprises engaged in translating the hESC research into viable therapeutic candidates for human disease.

Without the immediate adoption of a clear federal policy, backed by substantial funding for basic research and product development, we believe that the market for hESC technologies in the United States will be irreparably harmed. The country will lose its position as a leading developer of regenerative medical therapeutics despite the fact that as many as sixty percent of Americans now approve of the creation of hESC lines for research and therapeutic use.[239]

Researchers and companies are already turning to other nations to advance basic hESC science and product development.[240] The United Kingdom, for example, has made hESC research a national priority with funding commitments in excess of £350 million ($556 million) and economic incentives that have already lured many top researchers to the

[238] John M. Nolan, Emad U. Samad, Suy Anne R. Martins, and Stephen G. Brozak, "Long Shadow of the Stem-Cell Ruling," *Nature* 467, no. 7319 (2010): 1031-33.

[239] "Gallup Stem Cell Research Poll," Go.nature.com/y5kxvi.

[240] D. Sipp, *Regen Medical* 4 (2009): 911-18.

country. Government-sponsored programmes, such as the UK Stem Cell Initiative (SCI), have encouraged collaborations between public and private institutions, in some instancemandating academia to seek out partners in industry for projects to qualify for government funding.[241]

By comparison, only $42 million of the National Institute of Health's (NIH's) roughly $30-billion budget in the 2007 financial year was allocated to hESC research. Even after President Barack Obama lifted the Bush-era cell-line restrictions, federal funding levels increased to a projected $123 million in 2010, far less than the allocations for many conditions such as nutritional education, alcoholism, substance abuse and gene therapy. Compared to the $424.8 million allocated to the Human Genome Project in 2000 ($335.9 million by the NIH and $88.9 million by the Department of Energy) and the roughly $2.6 billion that was allocated to the project throughout the 1990s, current funding levels for hESC are simply not sufficient to bring a concept from inception to commercialization, nor have they been adequate to entice private industry into the market.

The United States must act now to rectify the missed opportunities of the past decade and to protect its future scientific, medical and commercial interests. It can begin by revising the 1996 Dickey–Wicker Amendment to permit future and continued use of embryonic cell lines.

We also recommend that the US government makes a financial commitment as large as that dedicated to the Human Genome Project and increase yearly NIH appropriations for hESC research to at least $500 million. Otherwise, as research continues, European pharmaceutical companies will continue to build a strong intellectual-property position that they will use to protect their investments and generate perpetual development and revenue cycles through licensing the rights to their science and technology to strategic partners.

Some US companies have built substantial hESC intellectual-property portfolios. But their science and commercialization pipelines are not maturing at the same pace as those of their European or Asian counterparts. Thanks to scant national coherence and significant regulatory risk, the US capital markets have failed to provide financing in sufficient sums to spur serious product development. As a result, hESC science and technology is now concentrated in the hands of a few undervalued US companies.

Over the past two years growing numbers of pharmaceutical companies from emerging economies have vied for entry into Western pharmaceutical markets by manufacturing generic drugs. China, for example, is poised to become the world's third-largest pharmaceutical market next year and will contribute the same in annual sales in 2013 — more than $40 billion — as the US market. Meanwhile American and European pharmaceutical companies have become desperate to sustain eroding revenue as proprietary patents for blockbuster drugs expire, allowing more generic competition.

---

[241] *UK Stem Cell Initiative: Report and recommendations*, UK Stem Cell Initiative (UKSCI), 2005.

To corner the market that may hold the next medical revolution, an Asian pharmaceutical company could easily decide to acquire US companies that have advanced technologies but very low market valuations. If foreign pharmaceutical companies focused resources, they could proceed with product development at a pace that the US pharmaceutical industry would be unable to match. Such a move would signify a shift in the balance of power of the health-care market and set US stem cell science back a generation.

Appendix B

The Antibiotic Bubble — A Quest for Continued Antibiotic Effectiveness[242]

The world is facing a new "bubble", but this one is medical rather than financial. The bubble will burst when antibiotics are no longer able to fight common and rare infections. The antibiotic wonder drugs of the last half-century are becoming ineffective.

Illnesses we now treat with a week's worth of pills are becoming deadly, and new antibiotics to treat infections caused by evolving bacteria may not be available in time to avoid a bursting antibiotic bubble.

Antibiotics represent a huge proportion of the drugs we consume today. More than seven million pounds of antibiotics are sold in the U.S.each year, but the healing power of these wonder drugs is threatened by the same diseases they cure. Unlike other bubbles, when antibiotics fail, millions will become sick and die.

Deadly hospital infections attack one in 20 patients in the U.S. each year, and of the 1.7 million people who acquire infections while in hospitals, 99,000 die from them, costing the medical system as much as an additional $33 billion. According to the Infectious Disease Society of America, just one organism, methicillin resistant Staphylococcus aureus, better known as MRSA, kills more Americans every year than the combined total of emphysema, HIV/AIDS, Parkinson's disease, and homicide.

Though most persistent infections occur in older or health-challenged patients, young and healthy people are also susceptible. NFL tight end Rob Gronkowski broke his forearm, had it repaired and then broke it again, requiring further treatment. During his treatments, he acquired a persistent infection. Thus far, he has had three surgical visits to treat his arm and it is likely he will need a fourth surgery to treat the persistent infection.

New antibiotics are just not coming on-line fast enough to combat bacterial resistance. Only nine new antibiotics have been approved by the FDA since 1998, of which only two incorporated novel mechanisms of action. In a recent survey of the development programs of the largest drug companies, only five new antibiotics were under development and none of them had novel mechanisms of action, meaning they could treat infections in a new way.

Antibiotics don't fit into the business model of the pill-a-day blockbuster drugs that big pharmaceutical companies chase after. Instead, large pharmaceutical companies have focused their drug development priorities on treating diseases like high cholesterol, hypertension, mood disorders, dementia and arthritis.

---

[242] Steve Brozak, "The Antibiotic Bubble—A Quest for Continued Antibiotic Effectiveness," *Forbes.com*, May 7, 2013, http://www.forbes.com/sites/stephenbrozak/2013/05/07/the-antibiotic-bubble-a-quest-for-continued-antibiotic-effectiveness/#7b03ca227953.

Last year Congress incorporated elements of a bill to encourage development of new antibiotics within its funding for the Food and Drug Administration (FDA). The new law extends the period of exclusivity for newly developed antibiotics, thus making what used to be pharmaceutical loss-leaders into potential money-makers and encouraging smaller, development-stage companies to fill the gap between drug-resistant bacteria and antibiotics that are losing potency. And it seems to be working. Jeffrey Stein, PhD, the CEO of the antimicrobial company, Trius Therapeutics, said he is greatly encouraged by FDA extending exclusivity for antibiotics, thus "giving small companies like his the opportunity to develop fast-acting drugs that can treat MRSA, and reduce both the frequency and duration of hospital visits, while saving significant sums of money."

The urgency of antibiotic development is enhanced by the emergence of new and deadly bacteria strains, usually called CRE, a term that includes bacteria like some strains of KPC or NDM that are antibiotic resistant. These deadly strains cause death in approximately half of the patients diagnosed with them. In spite of government and hospital efforts to control these deadly bugs, 200 healthcare facilities treated patients with CRE infections in the first half of 2012.

CRE infections, and others, such as Clostridium difficile, are caused by an imbalance in the natural population of millions of bacteria that live within us. Dr. Prabhavathi Fernandes, PhD, CEO of Cempra Pharmaceuticals, another antibiotic development company, identified the challenge of new antibiotic development as "being able to create targeted medicines that attack specific strains of bacteria, leaving the beneficial bacteria that live within us unharmed." By focusing development on such targeted pathogens, we will be able to cure disease without creating other problems.

Meeting the threat of both common and rare infections that continue to develop resistance over time is a race between drug development and bacterial evolution. Developing a new drug can take eight to ten years of clinical trials following extensive preclinical testing. The financial challenge is as significant as the scientific challenge. The cost of bringing a new drug to market is huge, estimated to be anywhere from $800 million to one billion dollars and smaller pharmaceutical companies must compete for capital with glamorous new stock offerings.

While Tetraphase Pharmaceuticals, Inc., a company that is developing novel antibiotics for serious and life-threatening multidrug-resistant infections had to lower its offer price to complete its recent initial public offer, Apple, Inc. was able to raise $17 billion of non-dilutive financing at highly favorable rates. The irony is that Apple's products, as compelling and useful as they have become, cannot directly save the millions of lives a new antibiotic could.

Government agencies like the Biomedical Advanced Research and Development Authority are attempting to fill gaps that are left by the drug industry and the shortcomings of financial markets. They are supporting the advance of scientific and pharmaceutical drug development to protect us against potential health threats, whether from bacterial infections or viral sources like influenza. Other agencies, such as the National Institute of Allergy and Infectious Diseases (NIAID), understand the desperate need for new antibiotics. The NIAID has a

considerable research program dedicated to fighting antibiotic resistant bacteria and the agency awards grants to deserving companies that focus on the identification of new antimicrobials to fight threatening superbugs.

In a speech last summer, Dr.Margaret Chan, head of the United Nations World Health Organization, threatened that the world faces a post-antibiotic era. Chillingly, she foretells that we would experience "in effect, an end to modern medicine as we know it. Things as common as strep throat or a child's scratched knee could once again kill. Some sophisticated interventions, like hip replacements, organ transplants, cancer chemotherapy, and care of preterm infants, would become far more difficult or even too dangerous to undertake."

Companies that are directing their efforts toward combating bacterial infections are the cavalry of the modern medical era, riding to our rescue from pathogens that cause deadly and debilitating diseases. Without their help, we would be defenseless against common bugs that have morphed into medical monsters and threaten the well-being of ourselves, our neighbors and our children.

BIBLIOGRAPHY

"12.00-Mental Disorders-Adult." *Social Security Administration [US]*. https://www.ssa.gov/disability/professionals/bluebook/12.00-MentalDisorders - Adult.htm (n.d).

"2014 Top 10 Health Technology Hazards." *Health Devices*, Emergency Care Research Institute (ECRI) (2013). www.ecri.org.

Aaronson, S., P. Sears, F. Ruvuna, M. Bunker. "A Five Year Observational Study of Patients with Treatment Resistant Depression Treated with VNS Therapy® or Treatment as Usual: Comparative Response/Remission Rates, Duration of Response, and Quality of Life." *American Society of Clinical Psychopharmacology*, 2014.

"Abilify Prices and Abilify Coupons." *Goodrx*. <http://www.goodrx.com/ abilify> (accessed June 25, 2015).

Ackerly, DC., AM. Valverde, LW. Diener, KL. Dossary, and KA. Schulman. "Fueling Innovation in Medical Devices (and Beyond): Venture Capital in Health Care." *Health Affairs* 28, no. 1 (2009): 68-75.

After the Election. WBB. Securities, 2006.

Angst, J., F. Angst, R. Gerber-Werder, and A. Gamma. "Suicide in 406 Mood-Disorder Patients with and without Long-Term Medication: A 40 to 44 Years' Follow-Up." *Archives of Suicide Research* 9 (2005): 279–399.

Arrowsmith, J. "A Decade of Change." *National Reviews Drug Discovery* 11 (2012): 17-18.

Asch, S, P. Glassman, S. Matula, A. Trivedi, I. Miake-Lye, and P. Shekelle. "Comparison of Quality of Care in VA and Non-VA Settings: A Systematic Review." VA-ESP Project, 05-226 (2010). http://www.hsrd.research.va.gov/publications/esp/quality.pdf.

Aumeran, C., L. Poincloux, B. Souweine, F. Robin, H. Laurichesse, O. Baud, et al. "Multidrug-Resistant Klebsiella pneumoniae Outbreak after Endoscopic Retrograde Cholangiopancreatography. *Endoscopy* 42 (2010): 895-899.

Baker, KH., MP. Chaput, CR. Clavet, GW. Varney, TM. To, and CD. Lytle. "Evaluation of Endoscope Sheaths as Viral Barriers." *Laryngoscope* 109 (1999): 636-639.

Banerjee, S., B. Shen, DB. Nelson, DR. Lichtenstein, TH. Baron, et al. "Infection Control During GI Endoscopy." *ASGE Standards of Practice Committee, Gastrointestinal Endoscopy* 67 (2008): 781-790.

Berry, SM., B. Broglio, M. Bunker, A. Jayewardene, B. Olin, AJ. Rush. "A Patient-Level Meta-Analysis of Studies Evaluating Vagus Nerve Stimulation Therapy for Treatment-Resistant Depression." *Journal of Medical Devices: Evidence and Research* 6 (2013): 17–35.

Best Places to Work. "Best Places to Work in the Federal Government." *Best Places to Work,* http://www.bestplacestowork.org/BPTW/rankings/agency.php?code=HE36&q=scores_subcomponent.

Blair-West, GW., CH. Cantor, GW. Mellsop, and M. Eyeson-Annan. "Lifetime Suicide Risk in Major Depression: Sex and Age Determinants." *Journal of Affective Disorders* 55 (1999): 171–178.

Bommarito, M. "A Multi-Site Field Study Evaluating the Effectiveness of Manual Cleaning of Flexible Endoscopes with an ATP Detection System." *APIC 2013 Annual Conference.* June 9, 2013.

Booth, BL. "Beyond the Biotech IPO: A Brave New World." *Nature Biotechnology* 27, no. 8 (2009): 705-709.

Boyce, JM. and D. Pittet. "Guideline for Hand Hygiene in Health Care Settings. Recommendations of the Healthcare Infection Control Practice Advisory and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force." *Infection Control and Hospital Epidemiology* 23 (2002): S3-40.

Brozak, Stephen. "A New American 11/11/11 Day: The Health Care Veterans Deserve." *ABCNerws.com,* November 11, 2011. https://www.google.com/url?q=http://abcnews.go.com/Health/doctors-failing-veterans-accepting-tricare-veteran/story?id%3D14926386&sa=D&ust=1461915775525000&usg=AFQjCNFiEr3F7NtusEvRqcUDVKa8BKg3XQ.

Brozak, Stephen G. "The Three Things Ken Burns Gets Wrong About Cancer." *Bloomberg.com,* April 3, 2015. http://www.bloomberg.com/news/articles/2015-04-03/the-three-things-ken-burns-gets-wrong-about-cancer.

Brozak, Steve. "Big Pharma Learned the Wrong Marketing Lesson." *Forbes.com,* May 25, 2013. http://www.forbes.com/sites/stephenbrozak/2013/05/25/big-pharma-learned-the-wrong-marketing-lesson/#7cf1c346c452.

—. "Does the GI Bill Even Work?" *CNN.com,* November 11, 2014. https://www.google.com/url?q=http://money.cnn.com/2014/11/11/news/economy/veterans-education-gi-bill/&sa=D&ust=1461915775529000&usg=AFQjCNHXp4AwQOjQUWdP03vD3NOmksq4LA.

—. “Ebola Has Landed.” *Forbes.com*, August 5, 2014. https://www.google.com/url?q=http://www.forbes.com/sites/stephenbrozak/2014/08/05/ebola-has-landed/%2324e050d65c2b&sa=D&ust=1461915775494000&usg=AFQjCNEAHwS5JlZGzThPlubfOhimi9S1Ww.

—. “Greece is on the Verge of a Health Catastrophe.” *Forbes.com*, July 15, 2015. http://www.forbes.com/sites/stephenbrozak/2015/07/15/greece-medical-collapse/#6ec1dd8d12b1.

—. “Harvard Professors Balk as Obamacare Comes to Cambridge.” *Forbes.com*, July 9, 2015. https://www.google.com/url?q=http://www.forbes.com/sites/stephenbrozak/2015/01/09/harvard-professors-balk-as-obamacare-comes-to-cambridge/%23579f1dda61c2&sa=D&ust=1461915775557000&usg=AFQjCNF7rR88VDYRSPus1QhuweSJGi-krA.

—. “How Flu Tried to Steal the World Cup’s Thunder.” *Forbes.com*, July 8, 2014. https://www.google.com/url?q=http://www.forbes.com/sites/stephenbrozak/2014/07/08/how-flu-tried-to-steal-the-world-cups-thunder/%236ec20cd671a1&sa=D&ust=1461915775491000&usg=AFQjCNHk6WVodefgq42-i1WT7SiZ1DWv5g.

—. “I'm Shocked, Shocked to Find That Pharma Is Paying Doctors!” *Forbes.com*, October 1, 2014. http://www.forbes.com/sites/stephenbrozak/2014/10/01/i-am-shocked-shocked-to-find-that-pharma-is-paying-doctors/#94738f15a87e.

—. *Influenza Outbreak Raising the Stakes*. Clark: WBB Securities, LLC, 2009.

—. “Obama's New Healthcare Proposal: A Precise Vision or a Political Football.” *Forbes.com*, February 3, 2015. https://www.google.com/url?q=http://www.forbes.com/sites/stephenbrozak/2015/02/03/obamas-new-healthcare-proposal-a-precise-vision-or-a-political-football/%23336958385b5b&sa=D&ust=1461915775555000&usg=AFQjCNFx_KtTF9DNP3Gcauf4PSJ8-EzDig.

—. “Retrophin, Gilead, And Our Healthcare Values.” *Forbes.com*, September 12, 2014. http://www.forbes.com/sites/stephenbrozak/2014/09/12/retrophin-gilead-and-our-healthcare-values/#69d47264fca4.

—. “Roche and InterMune Beckon Pharma's Summer of Discontent.” *Forbes.com*, August 24, 2014. http://www.forbes.com/sites/stephenbrozak/2014/08/25/roche-and-intermune-beckon-pharmas-summer-of-discontent/#40f276fc256d.

—. “The Antibiotic Bubble — A Quest for Continued Antibiotic Effectiveness.” *Forbes.com*, May 7, 2013. http://www.forbes.com/sites/stephenbrozak/2013/05/07/the-antibiotic-bubble-a-quest-for-continued-antibiotic-effectiveness/#7b03ca227953.

—. “The 5 Things You Should Know When Your Healthcare Claim Is "Denied. *Forbes.om*, October 26, 2013. http://www.forbes.com/sites/stephenbrozak/2013/10/26/the-5-things-you-should-know-when-your-healthcare-claim-is-denied/#79922a344ba7.

—. *The Last Straw (A Report on the Threat of an Influenza Pandemic)*. Clark: WBB Securities, 2009.

—. “Veterans' Access to Mental Health Services Needs Fixing.” *CNN.com*, November 11, 2013. https://www.google.com/url?q=http://money.cnn.com/2013/11/11/news/economy/veterans-mental-health/&sa=D&ust=1461915775525000&usg=AFQjCNFV2-l5CSjRQHcRVaVIXHxctTlu2g.

—. “Winners and Losers of the Greek Financial Crisis.” *ABCNews.com*, May 12, 2010. http://abcnews.go.com/Business/winners-losers-greek-financial-crisis/story?id=10619137.

Brozak, Stephen and Henry Bassman. “Fukushima -- A Nuclear Threat to Japan, the U.S. and the World.” *ABCNews.com*, April 6, 2011. http://abcnews.go.com/Health/fukushima-leak-threat-japan-us-world/story?id=13303513.

—. “Fukushima and Nuclear Power: Playing with Fire.” *ABCNews.com*, April 25, 2011. http://abcnews.go.com/Health/fukushima-nuclear power-energy-lessons-japans-tragedy/story?id=13439654&page=3.

—. “Fukushima Joins Titanic, Katrina as Iconic Word for Disaster.” *ABCNews.com*, March 16, 2011. http://abcnews.go.com/Health/japans-fukushima-prepare-disaster/story?id=13143270.

—. “Our 'New Normal' Wounded Healthcare System.” *ABCNews.com*, August 22, 2011. https://www.google.com/url?q=http://abcnews.go.com/Health/saving-us-healthcare-system-research-development-funding-key/story?id%3D14343836&sa=D&ust=1461915775511000&usg=AFQjCNH7FSKxLLkpw1IqeVUn76KNvLPHNw.

Brozak, Stephen and Larry Jindra, M.D. “A Fall for Stem Cells.” *ABCNews.com*, August 27, 2010. http://abcnews.go.com/Health/Wellness/stem-cell-injunction-impact-research-industry/story?id=11491225.

—. "Nuclear Medicine Meltdown Threatens Heart and Cancer Patients Shortage of Isotope Technetium-99 Has Big Implications for Patients." *ABCNews.com*, June 15, 2009. http://www.wbbsec.com/attachments/142_Nuclear%20Medicine%2006-15-09.pdf.

—. "The Facts Versus the Truth About Swine Flu." *ABCNews.com*, September 3, 2009. https://www.google.com/url?q=http://abcnews.go.com/Health/SwineFlu/swine-flu-test-us-health-care-delivery-system/story?id%3D8475278&sa=D&ust=1461915775492000&usg=AFQjCNEtQCRNccojmiXMGTOKOD2jGpFV_Q.

Brozak, Stephen G., Lawrence F. Jindra, M.D., and Daniel Mallin, Ph.D. *Influenza Outbreak A Call to Action. Clark:* WBB Securities, LLC, 2009. http://www.wbbsec.com/attachments/119_WBB%20Swine%20Flu%20050409.pdf.

Brozak, Stephen, Salman Punekar, M.D., and Emad Samad. "Patient Beware: When Stem Cells Harm A Case for Accelerating Regenerative Medicine." *ABCNews.com*, April 2, 2012, http://abcnews.go.com/Health/patient-beware-stem-cells-harm/story?id=16042857

Brozak, Steve and Anne Marie Noronha. "Stopping Ebola: Mali Matters; Maine and Manhattan Don't." *Bloomberg.com*, October 30, 2014. https://www.google.com/url?q=http://www.bloomberg.com/news/articles/2014-10-30/stopping-ebola-mali-matters-maine-and-manhattan-dont&sa=D&ust=1461915775490000&usg=AFQjCNGuvlPnnzTy1unlCZ0Sfkz0LR7_gA.

—. "Why the Ebola Crisis Won't End Without Military Intervention." *Bloomberg.com*, September 16, 2014. https://www.google.com/url?q=http://www.bloomberg.com/news/articles/2014-09-16/why-the-ebola-crisis-wont-end-without-military-intervention&sa=D&ust=1461915775502000&usg=AFQjCNFubQSVQhHDLD6acEc8yK5Bl0nl3A.

Brozak, Steve and Henry Bassman. "Meningitis Outbreak: Restoring Confidence in the Drug Industry." *ABCNews.com*, October 16, 2012. http://abcnews.go.com/Health/Wellness/meningitis-outbreak-restoring-confidence-drug-industry/story?id=17484794.

Brozak, Steve, Henry Bassman, and Emad Samad. "Flu Prevention Saves Lives, Money." *ABCNews.com*, January 18, 2013. https://www.google.com/url?q=http://abcnews.go.com/Health/ColdandFlu/flu-outbreak-government-solution-problem/story?id%3D18242477&sa=D&ust=1461915775501000&usg=AFQjCNGxnAajf-UAxAw7m4iLCAzxEJEl9g.

Bureau of Economic Analysis, U.S. *Department of Commerce*. http://www.bea.gov/bea/dn1.htm.

Butler, M., M. Blaskovich, and M. Cooper, M. "Antibiotics in the Clinical Pipeline in 2013." *The Journal of Antibiotics*, 66, no. 10 (.2013): 571-591.

Carter, KC. and BR. Carter. *Childbed Fever: A Scientific Biography of Ignaz Semmelweis*. Transaction Publishers, 2005.

Cêtre, JC., MC. Nicolle, H. Salord, M. Pérol, S. Tigaud, G. David, et al. "Outbreaks of Contaminated Broncho-alveolar Lavage Related to Intrinsically Defective Bronchoscopes." *Journal of Hospital Infection* 61 (2005): 39-45.

"Characteristics of Elderly Home Health Care Users." *National Center for Health Statistics, CDC*. http://www.cdc.gov/nchs/products/pubs/pubd/ad/301-310/ad309.htm.

"Choice Framework for Local Policy and Procedures 01-06—Decontamination of Flexible Endoscopes: Operational Management." *U.K. Department of Health* (2013). www. gov.uk/government/uploads/system/uploads/attachment_data/file/192522/ Decontamination_of_flexible_endoscopes.pdf.

Clemens, J. and JD. Gottlieb. *In the Shadow of a Giant: Medicare's Influence on Private Physician Payments* (Cambridge, MA, 2013).

Corne, P., S. Godreuil, H. Jean-Pierre, O. Jonquet, J. Campos, and E. Jumas-Bilak. "Unusual Implication of Biopsy Forceps in Outbreaks of Pseudomonas aeruginosa Infections and Pseudo-Infections Related to Bronchoscopy." *Journal of Hospital Infection* 61 (2005): 20-26.

"Cost to Develop and Win Marketing Approval for a New Drug Is $2.6 Billion." *Tufts Center for the Study of Drug Development*, November 18, 2014. http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study.

"Departmental Appeals Board. Decision that the NCD Record is Complete and Adequate to Support the Validity of NCD 160.18(C)." *Vagus Nerve Stimulation* (2014).

DeVenCI website, T*he Defense Venture Catalyst Initiative*. http://devenci.dtic.mil/aboutus.htm (accessed November 8, 2010).

DeVol, R., P. Wong, A. Bedroussian, et al. *Bipharmaceutical Industry Contributions to State and U.S. Economies* (Santa Monica: Milken Institute; 2004).

Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Arlington, VA: American Psychiatric Publishing, 2013.

Dilanian K. "Cutting Bioterrorism Funds a 'Self-Inflicted Wound,' Obama is Told." *Los Angeles Times,* July 14, 2010.

Donaldson, S., LH. Goldstein, S. Landau, V. Raymont, and S. Frangou. "Bipolar Disorder Project: The Effect of Medication, Family History, and Duration of Illness on IQ and Memory in Bipolar I Disorder." *Journal of Clinical Psychiatry* 64 (2003): 86– 93.

"Draft Guidance on Allocating and Targeting Pandemic Influenza Vaccine." http://www.pandemicflu.gov/vaccine/prioritization.html.

Drummond, M., B. O'Brien, GL. Stoddart, and GW. Torrance. *Methods for the Economic Evaluation of Health Care Programmes,* 2nd ed. (Oxford University Press, 1997).

"Economic Costs of Diabetes in the U.S. In 2012." *Diabetes Care,* 36 no. 4 (2013): 1033-1046.

Fava, M. and KG. Davidson. "Definition and Epidemiology of Treatment-Resistant Depression." *Psychiatric Clinics of North America* 19 (1996): 179–200.

FDA. "Information on Adverse Event Reports and Heparin." *U.S. Food and Drug Administration*. http://www.fda.gov/Cder/drug/infopage/heparin/adverse_events.htm (accessed June 16, 2008).

FDA. "FDA Issues Safety Alert on Avandia." *U.S. Food and Drug Administration*, May 21, 2007. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108917.htm.

FDA. "News and Announcements." *U.S. Food and Drug Administration*. http://www.fda.gov/bbs/topics/news/2008/new01856.html.

FDA. "News and Announcements." *U.S. Food and Drug Administration*, April 12, 2007. http://www.fda.gov/NewsEvents/Speeches/ucm051751.htm.

Feldman, RL. "Medicare Patient Experience with Vagus Nerve Stimulation for Treatment-Resistant Depression." *Journal of Medical Economics* 16 (2013): 62–74.

"First Smallpox Vaccine for Special Populations Delivered Under Project BioShield" (news release). *U.S. Department of Health and Human Services*. http://www.hhs.gov/news/press/2010pres/07/20100714c.html (accessed November 5, 2010).

Forsman, R. "Why is the Laboratory an Afterthought for Managed Care Organization?" *Clinical Chemistry* 42, no. 5 (1996): 813-816.

French, GL. "Dirty, Deluded, and Dangerous." *BMJ* 345 (2012): e8330.

"From the Centers for Disease Control (CDC). Nosocomial Infection and Pseudoinfection from Contaminated Endoscopes and Bronchoscopes—Wisconsin and Missouri." *JAMA* 266 (1991): 2197-2198.

"Gallup Stem Cell Research Poll." Go.nature.com/y5kxvi.

GAO Highlights. "Fundamental Restructuring Is Needed to Address Fragmentation and Overlap." http://www.gao.gov/new.items/d04588t.pdf (accessed March 30, 2004).

Garrett, Thomas. "Pandemic Economics: The 1918 Influenza and Its Modern-Day Implications." *Federal Reserve Bank of St. Louis Review*, March/April 2008.

Global Markets for Infectious Disease Treatments. BCC Research, May 2013..

Gonzalez-Candelas, F., S. Guiral, R. Carbo, A. Valero, H. Vanaclocha, F. González, et al. "Patient-to-Patient Transmission of Hepatitis C Virus (HCV) during Colonoscopy Diagnosis." *Virology Journal* 7 (2010): 217.

"Grassley Says FDA Problems Need Sunshine, Calls on Commissioner to Reverse Chill Factor." *United States Senate Committee on Finance*, March 12, 2007. http://www.finance.senate.gov/ranking-members-news/grassley-says-fda-problems-need-sunshine-calls-on-commissioner-to-reverse-chill-factor.

Greenwood, JC. "Biotechnology: Delivering on the Promise." *Science Translational Medicine* 2, no. 13 (2010): 13.

Guide to Biotechnology 2007 (Washington, DC: BIO, 2007).

Gupta, D., A. Srirajakalidindi, and H. Wang. "Reduced Turnover Times Make Flexible Optical Reusable Scope with EndoSheath® Technology Significantly Cost-Effective." *Journal of Biomedical Research* 26 (2012): 241-247.

Hall, KM. "Court Rules Against Tenn. Vet in Colonoscopy Case." *Associated Press*, June 1, 2012. http://bigstory.ap.org/article/court-rules-against-tenn-vet-colonoscopy-case.

"Healthcare Inspection: Follow-up Colonoscope Reprocessing at VA Medical Facilities." *Department of Veterans Affairs Office of Inspector General*. www.va.gov/ oig/54/reports/VAOIG-09-02848-218.pdf (accessed September 17, 2009).

"Hendra Virus." *Australian Veterinary Association*. http://www.ava.com.au/hendra-virus (accessed 2015).

Hervé, R., and CW. Keevil. "Current Limitations about the Cleaning of Luminal Endoscopes." *Journal of Hospital Infection* 83 (2013): 22-9.

Hoffmire, Claire A., Ph.D., Janet E. Kemp, R.N., Ph.D., and Robert M. Bossarte, Ph.D. "Changes in Suicide Mortality for Veterans and Nonveterans by Gender and History of VHA Service Use, 2000–2010." Psychiatryonline.org, May 01, 2015. http://dx.doi.org/10.1176/appi.ps.201400031.

"Hospital Codes." *Cyberonics Inc.* http://us.livanova.cyberonics.com/static/ pdfs/Hospital-Coding-Sheet.pdf (accessed June 15, 2015).

"Imitrex Generic: An Introduction." *Migraine.com*. http://migraine.com/migraine-treatment/imitrex/generic/.

"Independent Assessment of the Health Care Delivery Systems and Management Processes of the Department of Veterans Affairs." *U.S. Department of Veterans Affairs*, 1 (2015).

"Interim Pre-Pandemic Planning Guidance: Community Strategy for Pandemic Influenza Mitigation in the United States." *CDC, Division of Health and Human Services*, February 2007.

"Interim State Population Projections." *U.S. Census Bureau Population Division*, 2005.

International Economic Accounts annual tables 2001 and 2007. http://www.bea.gov/international/bp_web/simple.cfm?anon=71&table_id=20&area_id=1.

International Trade Administration. "U.S. Imports for Consumption and Domestic Exports tables." *International Trade Administration*. http://www.trade.gov/td/ocg/imp311.htm, http://www.trade.gov/td/ocg/exp311.htm.

Jha, A. K., J.B. Perlin, K.W. Kizer, K. W. and R.A. Dudley. "Effect of the Transformation of the Veterans Affairs Health Care System on the Quality of Care." *New England Journal of Medicine* 348 (2003): 2218–2227.

Jones, Vernon Dale. *Downsizing the Federal Government*. Armonk: M.E. Sharpe, 1998.

Kirsch, I., BJ. Deacon, TB. Huedo-Medina, A. Scoboria, TJ. Moore, and BT. Johnson. "Initial Severity and Antidepressant Benefits: A Meta-Analysis of Data Submitted to the Food and Drug Administration." *PLoS Med* 5 (2008): e45.

Klausner, A. "Biotech Venture Capital—It's Not Too Late to be Early," *Nature Biotechnology* 23, no. 4 (2005): 417-418.

Klausner, R. "Translational Science: A View from a Biotechnology Investor." *Science Translational Medicine* 2, no. 34 (2010): 34.

Kleiner, Perkins, Caufield, & Byers website, *KPCB*, http://www.kpcb.com/portfolio/portfolio.php?lifescience (accessed November 8, 2010).

Krebs, A. "Evaluation of Practice Efficiency with a Novel Sheathed Flexible Cystoscope: A Randomized Controlled Trial." *Urology* 70 (2007): 883-887.

Krebs, A., JF. Borin, IY. Kim, DJ. Jackson, EM. McDougall, and RV. Clayman. "Evaluation of Practice Efficiency with a Novel Sheathed Flexible Cystoscope: A Randomized Controlled Trial." *Urology* 70 (2007): 883-887.

Larson, JL., L. Lambert, RL. Stricof, J. Driscoll, MA. McGarry, R. Ridzon, et al. "Potential Nosocomial Exposure to Mycobacterium Tuberculosis from a Bronchoscope." *Infectious Control and Hospital Epidemiology* 24 (2003): 825-30.

Lawrentschuk, N. and M. Chamberlain. "Sterile Disposable Sheath System for Flexible Cystoscopes." *Urology* 66 (2005): 1310-1313.

Lee DP. and MD. Dibner. "The Rise of Venture Capital and Biotechnology in the US and Europe." *Nature Biotechnology* 23, no. 6 (2005): 672-676.

Lerner, J., F. Hardymon, A. Laeamon, and K. Book. *In-Q-Tel* (Boston: Harvard Business School, 2005).

Leski, T., R. Ansumana, C. Taitt, J. Lamin, U. Bangura, J. Lahai, et al. "Use of the FilmArray System for Detection of Zaire ebolavirus in a Small Hospital in Bo, Sierra Leone." *Journal of Clinical Microbiology* 53, no. 7 (2015): 2368-2370.

London, AJ. and JB. Kadane. "Placebos that Harm: Sham Surgery Controls in Clinical Trials." *Statistical Methods in Medical Research* 11 (2002): 413–427.

Longman, Phillip. *Best Care Anywhere: Why VA Health Care Is Better Than Yours*. 3rd ed. Berrett-Koehler, 2010.

Lowry, F. "Long-Term VNS Safe, Effective for Resistant Depression." *Medscape Med News*, 2014.

Luo, Z., AJ. Cowell, YJ. Musuda, SP. Novak, and EO. Johnson EO. "Course of Major Depressive Disorder and Labor Market Outcome Disruption." *Journal of Mental Health Policy and Economics* 13 (2010): 135–149.

Macklin, R. "The Ethical Problems with Sham Surgery in Clinical Research." *New England Journal of Medicine* 341 (1999): 992–996.

Meyer, Jared, Anne Marie Noronha, and Steve Brozak. "How Mental Health Is Shortchanged by Lack of Reimbursement for Vagus Nerve Stimulation." *Brain Stimulation* 9, no. 2 (December 30, 2015). http://www.wbbsec.com/wp-content/uploads/2016/03/12.30.15-Brain-Stimulation-Journal-VNS-Reimbursement.pdf DOI: http://dx.doi.org/doi: 10.1016/j.brs.2015.12.002.

"Mission of The Office of Academic Affiliations." Va.Gov, 2016. http://www.va.gov/oaa/oaa_mission.asp.

Mitchell, P. "Venture Capital Shifts Strategies, Startups Suffer." *Nature Biotechnology* 27, no. 2 (2009): 103-104.

Molecular Diagnostics: Major World Markets. Kalorama Information, 2007.

Mundy, A. "Fight Breaks out Between Vaccine Firms." *Wall Street Journal*, June 28, 2010.

"National Survey to Evaluate the NIH SBIR Program." *National Institutes of Health Office of Extramural Research*, January 2009. http://grants.nih.gov/grants/funding/sbir_2008surveyreport.pdf.

Nature 443 (October 26, 2006): 894-895.

Nolan, John M., Emad U. Samad, Suy Anne R. Martins, and Stephen G. Brozak. "Long Shadow of the Stem-Cell Ruling." *Nature* 467, no. 7319 (2010): 1031-33.

Noronha, Anne Marie and Steve Brozak. "A 21st Century Nosocomial Issue with Endoscopes." *British Medical Journal* (2014): 348: g2047.

"Notes from the Field: New Delhi metallo-ß-lactamase–producing Escherichia coli Associated with Endoscopic Retrograde Cholangiopancreatography." *Centers for Disease Control and Prevention (CDC)*. 3 www.cdc.gov/mmwr/preview/mmwrhtml/ mm6251a4.htm (accessed January 3, 2014).

"Nursing Home Statistics." *AHCA*. www.efmoody.com/longterm/nursingstatistics.html.

"Pandemic Flu and the Potential for U.S. Economic Recession." *Trust for America's Health*, March 2007. http://healthyamericans.org/reports/flurecession/FluRecession.pdf.

Peery,AF., ES. Dellon, J. Lund, SD. Crockett, CE. McGowan, WJ. Bulsiewicz, et al. "Burden of Gastrointestinal Disease in the United States." *Gastroenterology* (2012).

"Pharmaceutical Research and Manufacturers of America." *Pharmaceutical Industry Profile 2008*, March 2008.

Phurrough, S., M. Salive, B. Lofton, and J. Schafer, "Decision Memo for Vagus Nerve Stimulation for Treatment of Resistant Depression (TRD)." (CAG-00313R) 2007.

Platzer, M. "Patient Capital: How Venture Capital Investment Drives Revolutionary Medical Innovation," *National Venture Capital Association*, http://www.nvca.org/index.php?option¼com_content&view¼article&id¼268:patient-capital- how-venture-capital-investment-drives-revolutionary-medical- innovation&catid¼40:research (accessed November 5, 2010).

Posternak, MA. and M. Zimmerman. "Dual Reuptake Inhibitors Incur Lower Rates of Tachyphylaxis than Selective Serotonin Reuptake Inhibitors: A Retrospective Study." *Journal of Clinical Psychiatry* 66 (2005): 705–707.

"Preparing for the Next Pandemic." *New England Journal of Medicine*, 352, no. 18 (May 5, 2005).

"Press Release: EMEA Statement on Recent Publication on Cardiac Safety of Rosiglitazone (Avandia, Avandamet, Avaglim)." *European Medicines Agency*, May 23, 2007. http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500013467.pdf.

Projan,SJ. "Why is Big Pharma Getting Out of Antibacterial Drug Discovery?" *Current Opinion in Microbiology* 6, no. 5 (2003): 427-430.

"Public Health Emergency Medical Countermeasures Enterprise Review." *U.S. Department of Health and Human Services*. http://www.phe.gov/Preparedness/mcm/enterprisereview/Pages/default.aspx (accessed November 5, 2010).

Routh, CH. and MD. Loud. "On the Causes of the Endemic Puerperal Fever of Vienna." *Lancet*, 1848, no. 2: 642-643.

Rush, AJ., LB. Marangell, HA. Sackeim, MS. George, SK. Brannan, SM. Davis, et al.. "Vagus Nerve Stimulation for Treatment-Resistant Depression: A Randomized, Controlled Acute Phase Trial." *Biological Psychiatry* 58 (2005): 347–354.

Russell, PK. "Project BioShield: What It is, Why It is Needed, and Its Accomplishments So Far." *Clinical Infectious Diseases* Suppl 1 (2007): S68-S72.

Ryan, K. "Patients at Chanute Hospital Possibly Exposed to Hepatitis, HIV." *Wichita Eagle*, July 16, 2013. www.kansas.com/2013/07/16/2890467/patients-at-chanute-hospital-possibly. html.

Sabnis, RB., A. Bhattu, and M. Vijaykumar."Sterilization of Endoscopic Instruments." *Current Opinion in Urology* 24 (2014): 195-202.

Schachter, SC. and D. *Vagus Nerve Stimulation*. London: Martin Dunitz, 2001.

Seoane-Vazquez, E., R. Rodriguez-Monguio, J. Visaria, and A. Carlson. "Exogenous Endoscopy-Related Infections, Pseudo-Infections, and Toxic Reactions: Clinical and Economic Burden." *Current Medical Research and Opinion* 22 (2006): 21.

Sipp, D. Regen Medical 4 (2009): 911-18.

Smiley, D. "Vet Who Contracted Hep C Wins Malpractice Suit Against VA Hospital" *Miami Herald*, November 21, 2012. www.miamiherald.com/2012/11/21/3108483/vet-who- contracted hep-c-wins.html.

Sobel, Robert. "Essays, Papers & Addresses: Coolidge and American Business." *Calvin Coolidge Presidential Foundation, Inc.*, 1988. https://coolidgefoundation.org/resources/essays-papers-addresses-35/.

Solomon, DA., AC. Leon, TI. Mueller, W. Coryell, J. Teres, and MA. Posternak. "Tachyphylaxis in Unipolar Major Depressive Disorder." *Journal of Clinical Psychiatry* 66 (2005): 283–290.

Srinivasan, A., LL. Wolfenden, X. Song, K. Mackie, TL. Hartsell, HD. Jones, et al. "An outbreak of Pseudomonas aeruginosa Infections Associated with Flexible Bronchoscopes." *New England Journal of Medicine* 348 (2003): 221-227.

"Standards of Infection Control in Reprocessing of Flexible Gastrointestinal Endoscopes." *Society of Gastroenterology Nurses and Associates, Inc.* sgna_stand_of_infection_control_0712_FINAL.pdf (accessed 2012).

Statistical Abstract of the United States. http://www.census.gov/prod/2001pubs/statab/sec03.pdf.

Stein, J. "Innovative Antibacterial Drugs: Nothing Ventured, Nothing Gained." *Expert Opinion on Investigational Drugs* 14, no. 2 (2005): 107-109.

Summary Health Statistics for U.S. Adults: National Health Interview Survey, 2003. http://www.cdc.gov/nchs/data/series/sr_10/sr10_225.pdf.

"Ten Leading Causes of Death and Injury." *Centers for Disease Control and Prevention*. http://www.cdc.gov/injury/wisqars/ leadingcauses.html (accessed June 15, 2015).

The MetLife Market Survey of Nursing Home & Home Care Costs, September 2004.

The National Association for Proton Therapy. http://www.proton-therapy.org/howit.htm.

"The World Factbook." *Central Intelligence Agency*. https://www.cia.gov/library/ publications/the-world-factbook/ (accessed June 15, 2015).

"Timeline of Accomplishments." Research.VA.Gov, 2016. http://www.research.va.gov/about/history.cfm.

Tosh, PK., M. Disbot, JM. Duffy, ML. Boom, G. Heseltine, A. Srinivasan, et al. "Outbreak of Pseudomonas aeruginosa Surgical Site Infections after Arthroscopic Procedures." *Infectious Control and Hospital Epidemiology* 32 (2011): 1179-86.

UK Stem Cell Initiative: Report and recommendations. UK Stem Cell Initiative (UKSCI), 2005.

"VA Continues Notification process for Veterans Affected by Reprocessing Issues." *U.S. Department of Veterans Affairs*, April 3, 2009. www1.va.gov/opa/pressrel/ pressrelease.cfm?id=1661.

"Vaccines Market by Technology (Live Attenuated, Toxoid, Conjugate, Subunit, Synthetic, Dendritic Cell, Inactivated), Type (Preventive, Therapeutic), End User (Pediatrics, Adults), Disease Indication (Infectious Disease, Cancer, Allergy) - Forecasts to 2019." *MarketsandMarkets*, January 2015.

"VC Investments Q4 '09-Money Tree-National Data." *Price-Waterhouse Coopers/National Venture Capital Association*.

"Venture Capitalists' Predictions for 2010" (press release). *National Venture Capital Association*, December 2009.

"VNS Therapy System." *United States Food and Drug Administration.* http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm078532 .htm> (accessed July 30, 2014).

Waraich, P., EM. Goldner, JM. Somers, and L. Hsu. "Prevalence and Incidence Studies of Mood Disorders: A Systematic Review of the Literature." *Canadian Journal of Psychiatry* 49 (2004): 124–38.

Warnell, RL. and N. Elahi "Introduction of Vagus Nerve Stimulation into a Maintenance Electroconvulsive Therapy Regimen." *Journal of ECT* 23 (2007): 114–119.

Watkins, Katherine E., M.D., M.S.H.S., Brad Smith, Ph.D., Ayse Akincigil, Ph.D., Melony E. Sorbero, Ph.D., Susan Paddock, Ph.D., Abigail Woodroffe, Ph.D., Cecilia Huang, Ph.D., Stephen Crystal, Ph.D., and Harold Alan Pincus, M.D. "The Quality of Medication Treatment for Mental Disorders in the Department of Veterans Affairs and in Private-Sector Plans." Psychiatryonline.org, November 16, 2015. http://dx.doi.org/10.1176/appi.ps.201400537.

"Welcome to VNS Therapy.com for Health Care Professionals." *Cyberonics*. <http://dynamic.cyberonics.com/depression/hcp/ForSurgeons/implanted.aspx> (accessed May 30, 2014).

Wheeler, C. and S. Berkley. "Initial Lessons from Public-Private Partnerships in Drug and Vaccine Development." *Bull World Health Organ* 79, no. 8 (2001): 728-734.

Winter SC., A. Thirwell, and P. Jervis. "Flexible Nasendoscope with a Disposable-Sheath System Versus Standard Nasendoscopy: A Prospective, Randomized Trial." *Clinical Otolaryngology and Allied Sciences* 27 (2002): 81-83.

Woolhandler, Steffie and David U. Himmelstein. "Competition in a Publicly Funded Healthcare System." *BMJ, 335* (2007:1126-1129).

World Health Organization Web site. www.who.int/csr/disease/influenza/pandemic/en/.

World Industry Outlook: Healthcare and Pharmaceuticals. The Economist Intelligence Unit, May 2014.

THANK YOU

For their help with and contributions to this dissertation, I would like to thank:

Anne Marie Noronha, MS
Alicia Mundy
Lynn Bosshard
Heer Patel
Henry Bassman
and Tara Jenner, MMH

With special thanks to:

Philip Scibilia, DMH
and Emad Samad

VITA

Full name: Stephen Gilbert-Paul Brozak

Place and date of birth: New York, NY

Parents Name: Stephen Brozak II
Mother: Paula DeJean

Educational Institutions:

School	Place	Degree	Date
Secondary:			
Walt Whitman High School	S. Huntington, NY	HS Diploma	June 1976
Collegiate:			
Columbia University	New York, NY	BA (East Asian Studies)	October 1982
Graduate:			
Columbia University	New York, NY	Master of Business Administration	October 1994
Drew University	Madison, NJ	Doctorate of Medical Humanities	May 2016