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SPRING 2012

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Reenergizing Healthcare Policy:

Defining government's role in healthcare

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MANY THANKS TO

SAC, PubCo, *The Philadelphia Inquirer*, Andrew Coopersmith, Sana Mehkri, Michael Collins, Fareeha Safir, Peter Tarr, Kimberly Gallagher

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Reenergizing healthcare policy

Dear readers,

The relationship between government and healthcare is one that traverses many generations, nations, and cultures. In the U.S., as early as 1798 we see the creation of the Public Health Service. President John Adams signed a bill establishing the U.S. Marine Hospital Service and ensuring medical care for merchant seaman. The current healthcare sphere reveals the multifaceted role of government. The government plans and prepares for illness and emergency, finances and delivers healthcare, monitors spending and advances legislation. Disparities in access to health services and an abundance of debatable principles, begs the question: how can the government stimulate healthcare policy?

To help answer this question, SYNAPSE is publishing four unique and relevant articles in our Spring 2012 issue, hoping to make the theme of "Reenergizing Healthcare Policy" an item of community discourse. Each article touches upon the different roles of the government in bridging the gaps of medical access and establishing criteria for policy changes. One article discusses the causes of widespread and pressing national drug shortages, focusing on potentially crucial policy measures and economic instigators. We then take our focus off the Obama administration and the FDA to focus on a case study on disappointing healthcare privatization policies in India, analyzing the success of government sponsored healthcare delivery. We have an article on the Supreme Court's posturing toward the patentability of personalized medicine, and finally one article describes how the government prepares for the drop in medical access that occurs in the wake of a national disaster. These articles are meant to facilitate an active understanding of different governmental approaches to broad problems of poor healthcare distribution and national crises.

We hope you read this excellent collection of articles and make a personal investment in the issues we are presenting. As the fifth installment of SYNAPSE, we would like to sincerely thank each and every member of our team, without whom, this issue would never have been possible. Importantly, we would like to thank Nick Wilcox, Cary Kraft, Jaclyn Chen, Josh Sherman, Meera Ragavan and Elise Dihlmann-Malzer who founded not only an undergraduate publication, but also a lightening rod of community dialogue.

Rohaid Ali and Nuvid Bhuiyan
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ON OUR COVER

Dr. Lih Y. Lin and Fred Rieke of the University of Washington discovered a promising new approach to treating cancer and neurodegenerative disease using quantum dots, tiny light emitting semi conductors (pictured). Researchers cultured prostate cancer cells on quantum dot films and observed the effect of photo stimulation on their activity. Researchers were able to suppress and increase cancer cell activity at will, effectively regulating the cells. The photo above shows quantum dots from the So-Jung Park Group of the University of Pennsylvania. Much like the ones used in Dr.Lin's study, these quantum dots emit various wavelengths of light based on their size.

For more, read the article on pg. 21

public health

government and healthcare

research

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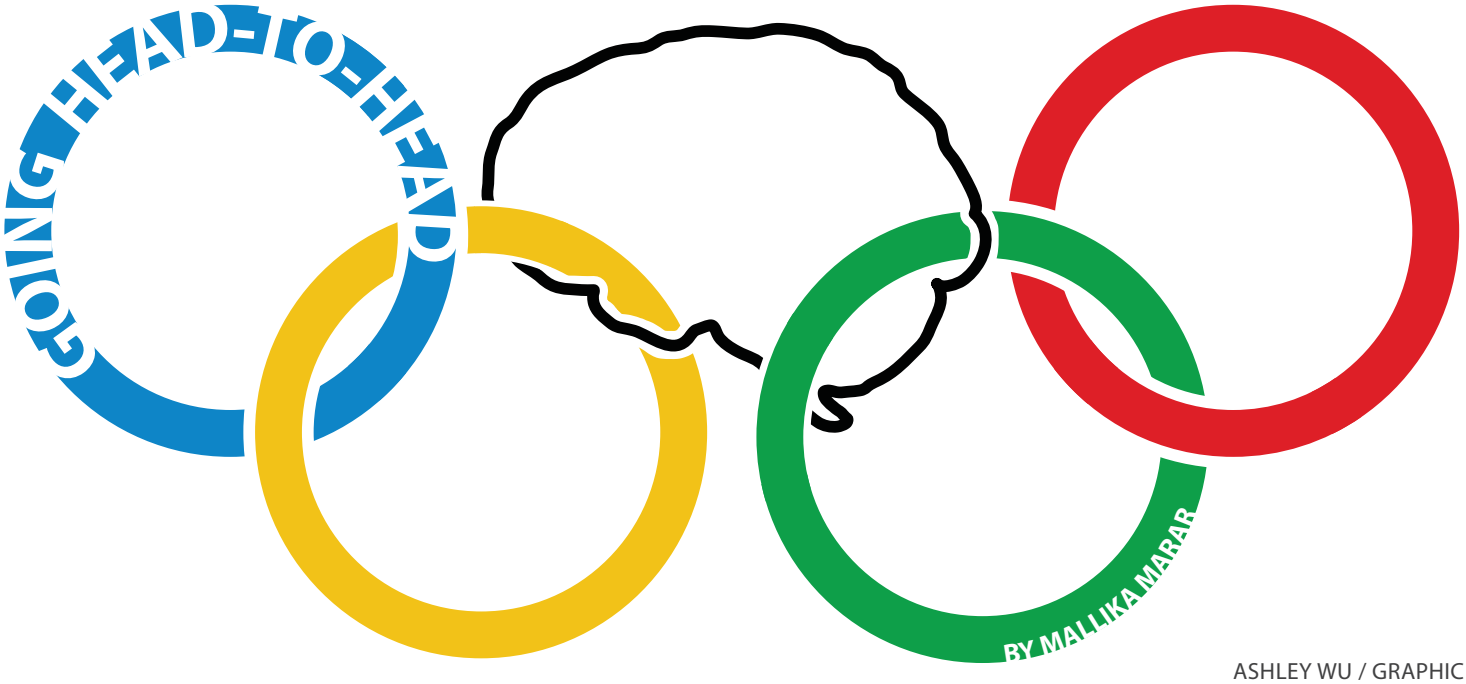


ASHLEY WU / GRAPHIC

Reasons for increasing awareness of traumatic brain injuries at the upcoming Olympic Games

The summer of 2012 represents to atheletes the greatest glory in all of sports—the Olympic Gold. Also focused intensely on the game-play will be athletic trainers, who often serve as the first line of response when athletes are injured. However, this role entails more than simply reacting when injuries occur; it is also a trainer's responsibility to actively watch for certain potentially devastating injuries that can easily go unnoticed, even by the athletes themselves: concussions.

Officials at the 2012 Olympic Games will be more vigilant than ever before about recognizing and treating concussions, as head injuries accounted for nearly one-tenth of all injuries sustained at the 2008 Beijing Summer Olympic Games.[1] A recent sports-injury consensus statement by the International Olympic Committee emphasizes new standards regarding concussions and indicates that health evaluations will henceforth take into consideration athletes' past concussion symptoms, astutely "appreciating the fact that many athletes will not recognize all the concussions they may have suffered in the past."[2]

Classified as mild traumatic brain injuries, concussions are particularly frightening injuries because their symptoms can be many, varied and unpredictable in their severity. In recent decades, increasing attention has been paid to concussions in athletics, although sports medicine professionals still have difficulty precisely defining them. Concussions have been broadly characterized as involving a blow to the head, causing some alteration in neurological or cognitive functioning and possibly resulting in a loss of consciousness.[3,4,5] However, it is not only the inconsistencies in definitions or diagnostic criteria that make the task of diagnosing concussions exceptionally problematic for athletic trainers; athletes demonstrate a notable tendency to under-report concussion symptoms or events of head trauma.[5]

Particularly with concussions that do not result in loss of consciousness, athletes may not realize that they have sustained a serious head injury. It is easy to imagine that, in the heat of game-play, athletes might disregard vague symptoms such as dizziness, difficulties with concentration or nausea. It may only be when such symptoms persist into the hours and days following an athletic exposure that an athlete, trainer or physician may identify an athlete as symptomatic of a head injury.

More worrisome, however, is a social stigma that may prevent athletes from reporting symptoms or the idea that a blow to the head is "just part of the game" for contact sports and is no cause for concern.[5] Indeed, a recent investigation on concussion incidence makes note of the fact that female athletes are typically more forthcoming about reporting injuries of all types than male athletes.[6] Likewise, there may exist a perception that concussions should be a concern primarily for intense athletic competition at the professional level; however, young athletes are in fact more susceptible

to concussions than older athletes and are similarly at risk for severe acute and long-term complications.[7,8,9]

Further adding to the complexity of concussion diagnosis are variability in risk factors among different sports and the method by which such an injury could be sustained—by contact with another athlete, contact with sporting equipment or contact with the playing surface. The implication is that risk for concussion exists among both contact and noncontact sports.[10] Perhaps surprisingly, even events such as road cycling and slalom canoeing saw concussion incidence in the 2008 Beijing Olympics.[1] Moreover, it is worth noting that athletes are not only at risk for injury while competing, but in practice situations as well, which are often less supervised by medically trained professionals. Roughly one-fourth of injuries sustained during the 2008 Beijing Olympics occured during training.[1]

Lack of effective diagnosis makes epidemiological investigation incredibly difficult and has led to the belief that incidences of sports-related concussions have been seriously underestimated in the past. Recent reports approximate between 1.6 to 3.8 million sports-related concussions occurring annually in the US alone, including those for which follow up medical care is not explicitly sought.[11] Not attaining immediate medical attention following a concussion is potentially lethal, as the primary hazard posed by concussions may not be the original head trauma itself: the chemical shifts that result from severe impact or jolting place the brain at heightened sensitivity to further stress or injury until it has fully recovered to its normal state. The relative ease by which concussions can be overlooked in athletic activity places athletes at an inordinate risk of continuing to compete when having sustained some trauma-induced alteration in mental status.[12]

Mild traumatic brain injuries present a wide and varied spectrum of risk for further complications. In the best scenarios, symptoms resolve quickly, allowing athletes to recover fully and complete a stepwise return-to-play protocol. However, for all athletes, concussions have the potential to result in long-term cognitive disturbances that could affect ability to perform daily activities.[11] Ultimately, each incident of concussion is unique to the athlete and the circumstances of injury, further making it an injury that no athlete should have to take a gamble on.

Without doubt, a heightened level of concussion awareness among all athletes, athletic trainers, coaches, and sporting officials alike is a crucial step towards limiting the danger posed by concussions. And though the task at hand appears daunting, the complexity of concussion risk factors and symptoms should not discourage investigators—understanding concussion patterns in a wide range of athletic activities will lead to a safer playing field for all athletes, whether they be competing for national pride at the 2012 Olympics or simply enjoying a game of pick-up basketball.

References

1 Junge, A., Engebretsen, L., Mountjoy, M.L., Alonso, J.M., Renström, P.A., Aubry, M.J., & Dvorak, J. (2009). Sports injuries during the Summer Olympic Games 2008. *American Journal of Sports Medicine, 37(11):2165-72.*

2 Ljungqvist, A., Jenoure, P., Engebretsen, L., Alonso, J.M., Bahr, R., Clough, A., et al. (2009). The International Olympic Committee (IOC) Consensus Statement on periodic health evaluation of elite athletes March 2009. *British Journal of Sports Medicine, 43(9):631-43.*

3 Kelly, J.P., Nichols, J.S., Filley, C.M., Lillehei, K.O., Rubinstein, D., & Kleinschmidt-DeMasters, B.K. (1991). Concussion in sports: guidelines for the prevention of catastrophic outcome. *Journal of the American Medical Association, 266, 2867-2869.*

4 Quality Standards Subcommittee, American Academy of Neurology. (1997) Practice parameter: the management of concussion in sports. *Neurology, 48(3), 581-585.*

5 Echemendia, R.J., & Julian, L.J. (2001). Mild traumatic brain injury in sports: neuropsychology's contribution to a developing field. *Neuropsychology Review, 11(2):69-88.*

6 Dick, R.W. (2009). Is there a gender difference in concussion incidence and outcomes? *British Journal of Sports Medicine, 43, 46-50.*

7 Buzzini, S.R., & Guskiewicz. K.M. (2006). Sport-related concussion in the young athlete. *Current Opinion in Pediatrics, 18(4), 376-382.*

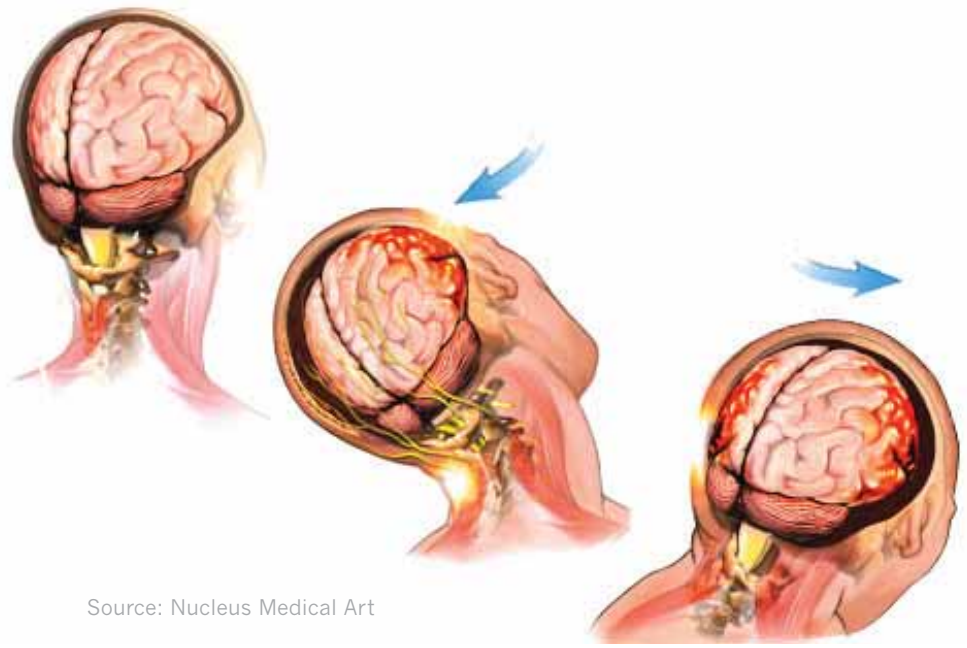
8 Patel, D.R., & Greydanus, D.E. (2002). Neurologic considerations for adolescent athletes. *Adolescent Medicine, 13(3), 569-578.*

9 Patel, D.R., Shivdasani, V., & Baker, R.J. (2005). Management of sport-related concussions in young athletes. *Sports Medicine, 35(8), 671-684.*

10 Marar, M., McIlvain, N.M., Fields, S.K., & Comstock, R.D. (2012). Epidemiology of concussions among United States high school athletes in 20 sports. *American Journal of Sports Medicine, (Epub ahead of print).*

11 Langlois, J.A., Rutland-Brown, W., & Wald, M.M. (2006). The epidemiology and impact of traumatic brain injury: a brief overview. *Journal of Head Trauma Rehabilitation, 21(5):375-8.*

12 "Concussion and Mild TBI." (2011, October 6). *CDC.gov.* Retrieved March 17, 2012, from http://www.cdc.gov/Concussion/.



Source: Nucleus Medical Art

A concussion occurs when a physical shock shakes the brain back and forth inside the skull. Even though many concussions are mild, they can leave lasting damage on the brain if it does not fully heal afterward.

Corporate Health: colalife

Adopting corporate strategies to improve global health delivery

BY SHABNAM ELAHI

Simon Berry started working in global development right after his college graduation, and travelled across the world helping local governments plan development programs. In the late 1980s his work as a technical cooperation officer for a British aid program took him to Mpika, a remote town in northeast Zambia. There, he saw much of what he had seen before; the lack of basic medical facilities, high child mortality, poor public health services –and Coca Cola. Berry noticed that even in the most remote parts of developing countries, he could purchase the popular American soda. And in these same regions, one in every five children under the age of five died due to the lack of basic health services. It was this observation that inspired Berry to spend the next twenty years advocating for ColaLife.

BERRY NOTICED THAT EVEN IN THE MOST REMOTE PARTS OF DEVELOPING COUNTRIES, HE COULD PURCHASE THE POPULAR AMERICAN SODA. AND IN THESE SAME REGIONS, ONE IN EVERY FIVE CHILDREN UNDER THE AGE OF FIVE DIED DUE TO THE LACK OF BASIC HEALTH SERVICES.

ColaLife is a nonprofit organization that utilizes the power of Coca-Cola's product distribution channels to disseminate Aidpods, small packages containing "social products" such as basic medical items including oral rehydration salts and zinc supplements. These aidpods are efficiently fitted into the empty spaces in a crate of Coke bottles, and their contents are shipped along with the bottles of soda. The program was initiated by Berry in 2008 and has recently started its first pilot plan in Zambia with hopes to expand to other regions of the developing world.[1]

Source: www.colalife.org

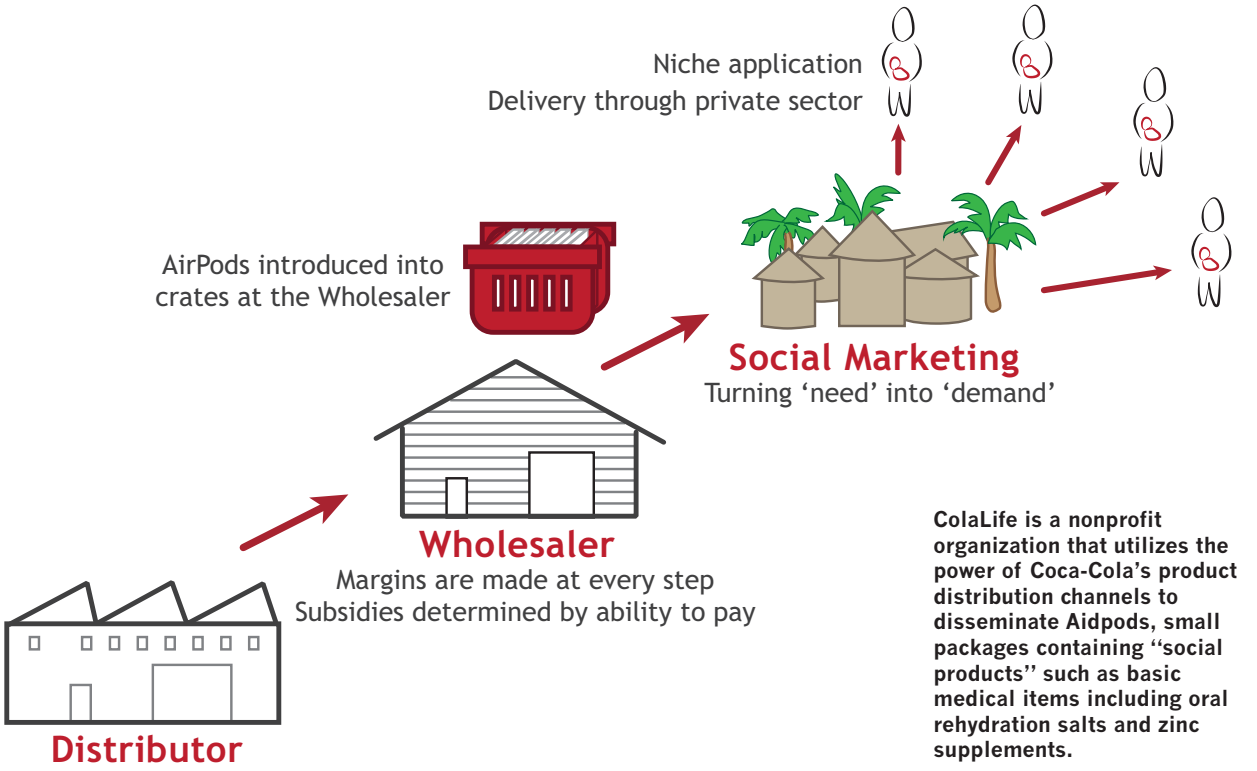
ColaLife aidpods fit efficiently in the spaces between Coke bottles and are shipped together.

ColaLife is just one example of how perspectives on global health are rapidly changing. In the past, much of global health has focused on increasing funding and promoting biomedical research. However, for the most part, there are treatments and advanced medical knowledge about the major health problems facing developing countries. For instance, many diarrheal illnesses can be easily treated with low-cost zinc tablets. Yet despite this, diarrhea is still the leading cause of child mortality in many developing countries and accounts for over 2 million child deaths each year. Secondly, funding in the global health sector has been increasing over the past few decades, and one example of this is the increase in the US's global support for HIV/AIDS prevention and treatment. In 1996, the US allocated $330 million to HIV/AIDS treatment and prevention in developing countries. By 2003, this number increased to $10 billion per year.[2]

Despite the availability of funding and basic medicines, every year there are 10 million deaths in developing countries caused by conditions that could have easily been treated. And this is mainly a consequence of inadequate healthcare delivery. We have reached what Ramchandani, a member of the ColaLife pilot project team, calls "a crossroads in public health. Much of the world's mortality can be prevented with existing solutions… So the problem is not so much about what's needed. It's more about how to effectively deliver what is needed to those who need it most."[3] The focus of global efforts should be in reducing the fundamental "implementation bottleneck", the gap between providers and populations in need. So, what can global health organizations learn from consumer corporations like Coca-Cola?

The first step in expanding delivery is creating a wider healthcare distribution network. Coca-Cola is able to distribute its products to the most remote regions of developing countries by adopting a Micro Distribution Center (MDC) model. The company employs regional independent small businesses, "microdistribution centers", who then hire local salesmen to distribute the product within their communities. Coca-Cola has set up over 3,000 microdistribution centers in Africa, which have employed approximately 15,000 local residents. Several global health organizations have been utilizing these existing distribution channels such as ColaLife,

the colalife process



ColaLife is a nonprofit organization that utilizes the power of Coca-Cola's product distribution channels to disseminate Aidpods, small packages containing "social products" such as basic medical items including oral rehydration salts and zinc supplements.

Source: www.colalife.org

ASHLEY WU / GRAPHIC

and Scaling Up Zinc in Bangladesh. Scaling Up Zinc is a governmental project that distributes zinc tablets through the food and beverage distribution channels of the country's major pharmaceutical company, ACME Laboratories Ltd. Meanwhile, other organizations have adopted this distribution model to create their own networks. For instance, in Ethiopia, many people live far away from any kind of health facility. In response, in 2003 the Ethiopian government set up the Ethiopian Health Extension Program. This program trained local health extension workers in areas such as family planning, immunization, and prenatal care, and stationed them in regions with limited access to health facilities. The increased access to health services has contributed to Ethiopia's 25% decline in child mortality from 2000 to 2008.[4]

While distributing these medical services, global health organizations can also take into consideration the private's market's real-time data collection methods. Like other consumer companies, Coca Cola uses its continuous stream of data to gain a greater understanding of the state of the company and how to move forward. Yet often in global health, the data is collected at the end of a project or program, once the funds have been spent and it is too late to make meaningful change. This has led some NGOs to utilize revolutionary smart phone technology to monitor patient data. For instance, it is quite common in many slum areas to experience cholera outbreaks of up to 1,000 cases. Community health workers at Tabitha Clinic, a clinic organized by the Carolina for Kibera Program in Naibora, Kenya, were able to use smart phone technology to detect a case of cholera in the local community. And because of this early detection, they were able to immediately treat the infected individual resulting in only 4 cases of cholera in the area. The collection of real-time data has the potential to create more avenues of preventive care.[5]

Yet adopting these corporate strategies will not resolve all the challenges facing global health delivery. Unlike large systematic corporations, global healthcare is extremely fragmented, and sometimes poorly coordinated as a single region may have multiple government providers as well as a plethora of NGOs. Also, the "delivery of care" is more than just providing the treatments, or getting the product to the consumer. Rather it requires trained physicians and workers to ensure the effective use of health services and provide adequate follow-ups treatments. Even though delivering and implementing adequate healthcare is far from simple, there are some real lessons that can be learned from corporations such as Coca-Cola.

References

1 Tedxwarwick - simon berry - colalife: An idea worth spreading [Web series episode]. In *Tedx*. TedxBerlin. Retrieved from http://tedxtalks.ted.com/video/TEDxWarwick-Simon-Berry-ColaLife

2 *Colalife*. (n.d.). Retrieved from http://www.colalife.org/

3 Marshall, A. (2012). A refreshing development.*Development Asia*, 48-52.

4 *The business summit*. (2012). (Master's thesis, Harvard University) Retrieved from http://www.hbs.edu/centennial/businesssummit/healthcare/redefining-global-health-care.html

5 Gates, M. "What nonprofits can learn from coca-cola" [Television series episode]. In *Tedx*. Tedx. Retrieved from http://www.ted.com/talks/melinda_french_gates_what_nonprofits_can_learn_from_coca_cola.html

The High Costs of Hydraulic Fracking: To Drill or Not To Drill

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A cost-benefit analysis of obtaining cheap natural gas and its effects on public and private sectors

BY LAUREN WILCOX

The Delaware River is the longest undammed river east of the Mississippi, meandering for roughly 400 miles through New York, Pennsylvania, New Jersey and Delaware to the Atlantic Ocean.[1] Supplying water to over 15 million people, the river is also home to some of the best fly-fishing in the country. As a living ecosystem rich in beauty, culture and community, the Delaware exists as one of the cleanest free-flowing rivers in the United States. However, the untapped clusters of land in the basin have attracted various energy companies to extract natural gas by the highly controversial means of hydraulic fracturing. Despite the economic benefits that stem from the hydraulic fracturing process, many have raised pressing concerns of contaminated water supplies, increased air pollution, elevated health risks, industrial disasters and animal deaths. Hydraulic fracturing typifies the a firm's sole responsibility to increase profits without bearing accountability for the consequences.

The United States possesses 2,543 trillion cubic feet of potential natural gas resources and consumes roughly 24.1 Tcf per year. The majority of gas is collected when the gas migrates naturally towards the Earth's surface from organic-rich sources into a highly permeable reservoir rock. However, hydraulic fracturing and horizontal drilling are newly developed extraction methods that allows gas companies to obtain the natural gas trapped in impermeable shale source rocks. This procedure has enabled the vast expansion of U.S natural gas reserves and allow gas-drilling corporations to provide commercial quantities at economically viable costs. Production of shale gas is expected to continue to increase, and studies predict that it will constitute 46% of total U.S natural gas supply in 2035, versus 14% in 2009.[2]

What makes the process of hydraulic fracturing potentially destructive? Firstly, a device called 'the derrick' drives deep beneath the earth's surface towards the shale containing natural gas where it can reach more than 5,000 feet in depth. The next step involves pumping roughly 1-7 million gallons of water mixed with sand under extremely high pressures that fracture the shale formation-soft sedimentary rock that can be split up into fragile parts.[3] The water is infused with up to 600 different chemicals, including known carcinogens

The Delaware River has attracted various energy companies to extract natural gas by the higherly controversial means of hydraulic fracking.

and biocides such as benzene, toluene, and xylene, which are not biodegradable. During the process, an estimated 30% to 70% of this "fracking fluid" remains in the ground. Although gas-drilling companies state that the contaminated water is stored safely and never reaches people's homes or drinking sources, environmentalists fear that the cement casing holding the water will fail sooner or later. In order to achieve cost effective operations, the wastewater often sits in the frack pond, which expedites the process of evaporation where it will later resurface as acid rain. In addition to the harmful environmental effects from the actual process, thousands of gallons of diesel fuel are required to run the drill rig, and as a result, the oil truck engines create ground level ozone of nitrogen oxides and volatile organic compounds.[4]

With the recent upsurge of media interest directed at the potential dangers of fracking, the American public is becoming increasingly aware of the tradeoffs resulting from obtaining cheap natural gas. Contaminated water supplies, increased air pollution, increased health risks, animal deaths, and industrial disasters are only some of the direct consequences generating scrutiny towards the practice. TEDX, founded by Dr. Theo Colborn, is a non-profit organization dedicated to disseminating scientific evidence on "the health and environmental problems caused by low-dose exposure to chemicals that interfere with development and function ." By chasing down trucks, combing through material safety data sheets, and collecting samples, Colborn has identified 596 different chemicals in 900 chemical products.[5] As high as 92% of the products used in the water for fracking had as many as 14 different health effects. Colborn discovered from sampling that from 68% to 86% of the volatile chemicals caused "irritation of the skin, eye sinuses, nose, throat, lungs, and the stomach," and could have detrimental effects on the brain and nervous system ranging from "headaches, blackouts, memory loss, confusion, exhaustion, and permanent neuropathies."[6] Furthermore, 35% to 55% of the chemicals were found to cause disorders that develop slowly such as "cardiovascular, kidney, immune system changes, and reproductive organ damage."[7]

In a recent study conducted by environmental chemist Robert Jackson of Duke University, drinking water samples from 68 wells in the Marcellus and Utica shale areas of Pennsylvania and New York were collected, establishing the first definite connection between fracking and groundwater pollution. The findings, published in *Proceedings of the National Academy of Sciences*, gave conclusive evidence that as the distance between fracking wells and drill sites decreased, methane concentrations increased to levels that were considered hazardous by the Department of the Interior. In subsequent samplings of more than 100 additional wells, the finding was confirmed, and led to an EPA report that declared fracking wastewater as "too radioactive to be handled safely by water treatment plants".

In addition to land and water contamination, immeasurable amounts of toxic volatile compounds, such as methane, benzene, toluene, ethylbenzene, and xylene, escape from the derrick to produce a ground level ozone.[8] This ozone not only causes irreversible damage to lungs, but it can also harm crops and farm animals up to 200 miles beyond the immediate region. In many cases, the drinking water turns brown from the extreme levels of methane and corrodes all objects with which it comes into contact. People also develop dizzying headaches, sores, and stomach ulcers from the chemicals in the water. Unfortunately, they often cannot afford to buy a new house on top of their current mortgage, and are forced to live in an unsellable house.[9]

DESPITE THE ECONOMIC BENEFITS THAT STEM FROM THE HYDRAULIC FRACTURING PROCESS, MANY HAVE RAISED PRESSING CONCERNS OF CONTAMINATED WATER SUPPLIES, INCREASED AIR POLLUTION, ELEVATED HEALTH RISKS, INDUSTRIAL DISASTERS, AND ANIMAL DEATHS. HYDRAULIC FRACTURING TYPIFIES THE A FIRM'S SOLE RESPONSIBILITY TO INCREASE PROFITS WITHOUT BEARING ACCOUNTABILITY FOR THE CONSEQUENCES.

Since 2001, energy corporations have donated $115 million to federal politicians in campaign contributions to sway their policies into favoring deregulation. In his second week in office, President George W. Bush appointed Vice President Richard Cheney as the Chairman of the National Energy Policy Development Group, whose mission was to develop a national energy policy designed to help the private sector. As the former CEO of Halliburton, one of the largest companies exercising hydraulic fracturing , he helped to pass the Bush/Cheney Energy Bill of 2005, which exempts hydraulic fracturing[7] from the Safe Drinking Water Act, the Clean Air Act the Clean Water Act, and the Superfund Law. The loophole exclusively authorizes oil and gas drillers to inject known hazardous materials, unchecked, directly into or adjacent to underground drinking water supplies.

Despite the plethora of environmental and health hazards that are direct outcomes of hydraulic fracturing, there are positive aspects of the practice related to the stimulation of the economy, U.S energy independence and the reduction in emission of greenhouse gases. At a time when the United States is facing a persistent high unemployment rate of roughly 9% as of October 2011, the gas drilling industry continues to sustain stable growth, generating hundreds of thousands of jobs throughout the country.[10] In addition, the increased production of domestic natural gas resources from shale deposits holds the promise of decreasing energy costs and dependency on imported fossil fuels. According to PFC Energy, a Washington-based consultancy, by 2020, shale sources will compromise roughly a third of total U.S oil and gas production, where it will be the top global oil and gas producer. This prediction has the potential to shift the power from the Organization of Petroleum Exporting Countries towards the Western hemisphere, where political unrest in Middle Eastern countries would have less influence on the prices of the energy commodities.[11]

The underlying problem overlooked by these companies is the extent to which the short-term profits may undermine the very existence of the industry in the future. Managers are

choosing to solve the problem through a means that seems to be both most profitable and least troublesome for the company in the short term. In this particular case, the decisions made by gas drilling companies and the government will have such detrimental long-term effects to both the environment and societal health that they cannot continue to blanket the problems. This is exemplified in the recent news where Texas-based Legacy Resources backed out of a $45 million deal to buy the field near Pavillion, Wyoming. Legacy Resources had agreed to buy the area wells, which produce around 13 million cubic feet of gas per day, until the EPA detected "cancer-causing benzene at fifty times the level safe for humans and other carcinogenic pollutants during its latest round of sampling."[12] The EPA advised residents in the vicinity to drink replacement water and to ventilate their homes when they showered or washed dishes. This withdrawal may indicate future complications for corporations trying to overturn aging gas fields.

Termed as "the great shale gas rush" by National Geographic, the rising popularity of hydraulic fracturing by gas drilling companies has seen little decrease in momentum. In the past ten months alone, sixteen hundred new wells have been drilled in Pennsylvania, and it is predicted that the number in the state will ultimately increase to more than one hundred thousand.[13] In the United States, shale-gas production has increased by a staggering factor of twelve in the past ten years. Although a moratorium has been placed on the Delaware River Basin, providing drinking water to roughly 15.6 million people, gas-drilling companies continue to have heavy influential power in lobbying the government to concede to their desires.[5]

In light of the recent attention directed at the fusion between competitive corporate advantage and social impact, certain media outlets have developed into activist organizations that promote public awareness of social issues. By targeting the most visible and successful companies, they are able to draw attention to issues like hydraulic fracturing that would otherwise be overlooked. However, energy companies have enough political and monetary power to quell the reservations made by media reports. Instead of investing more of their corporate resources on strategic and operational improvements, they have predominantly chosen to implement cosmetic responses with public relations and media campaigns, the centerpieces of which are often glossy CSR reports that showcase companies' social and environmental good deeds. In effect, perceiving social responsibility as building shared value rather than as "damage control or as a PR campaign," will require dramatically different frameworks in business settings, where social responsibility must play a larger, more influential role.

With increasing concern directed at the long-term environmental effects and health-related consequences of hydraulic fracturing, numerous solutions have been investigated by both the public and private sectors. One promising way to make fracking less toxic and more efficient has been proposed by the company GasFrac. Instead of pumping millions of gallons of water and fracturing fluid, GasFrac suggested that companies should use liquefied petroleum gas gel (LPG), propane gas compressed into liquid, to break up the shales. Recent studies demonstrated that this would simultaneously reduce the carbon footprint of the activity, whilst limiting harm to the land and water used. The advantages of LPG stem from the fact that it can be sucked back out as gas, leading to an almost 100% recovery rate instead of the estimated 50% percent recovery of fracking water. Freshwater tanks and waste pits would no longer be necessary, and the projects would require less transportation trucks, cutting carbon emissions. In the meantime, legislators are pressing for more supervision with stricter regulations that encourage companies to act responsibly. For instance, Pennsylvania has proposed doubling fines for safety violations at fracking sites, and New York has extended the moratorium on drilling in the state. Given the high stakes of such a controversial procedure, the study of potential impacts on drinking water to be published by the EPA at the end of 2012 will mark significant implications for the future of the gas-drilling industry.

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References

1. Remember the River. (n.d) retrieved 04/08/2012, from Delaware Riverkeeper Network Web Site: http://www.delawareriverkeeper.org/delaware-river/remember-delaware-river.asp
2. Natural Gas Year-in-Review. (12/09/2011). retrieved 04/08/2012, from U.S. Energy Information Administration Web Site: http://www.eia.gov/naturalgas/review/index.cfm
3. Arthur, J. Bruce Langhus, & David Alleman (2008). An Overview of Modern Shale Gas Development in the United States. retrieved 04/08/2012, from ALL Consulting Web Site: http://www.all-llc.com/publicdownloads/ALLShaleOverviewFINAL.pdf
4. Gasland. (n.d) retrieved 04/08/2012, from Gasland - A film by Josh Fox Web Site: http://www.gaslandthemovie.com/
5. (n.d) retrieved 04/08/2012, from The Endocrine Disruption Exchange Web Site: http://www.endocrinedisruption.com/home.php
6. Colborn, Theo (October 25, 2007). Written testimony of Theo Colborn, PhD, President of TEDX, Paonia, Colorado before the House Committee on Oversight and Government Reform, hearing on The Applicability of Federal Requirements to Protect Public Health and the Environment from Oil and Gas Development. retrieved 04/08/2012, from The Endocrine Disruption Exchange Web Site: http://s3.amazonaws.com/propublica/assets/natural_gas/colburn_testimony_071025.pdf
7. The Best Energy Bill Corporations Could Buy: Summary of Industry Giveaways in the 2005 Energy Bill . (n.d) retrieved 04/08/2012, from Public Citizen Web Site: http://www.citizen.org/cmep/article_redirect.cfm?ID=13980
8. Chemicals in National Gas Operations. (n.d) retrieved 04/08/2012, from The Endocrine Disruption Exchange Web Site: http://www.endocrinedisruption.com/chemicals.introduction.php
9. Bateman, Christopher (06/21/2012). A Colossal Fracking Mess. retrieved 04/08/2012, from Vanity Fair Web Site: http://www.vanityfair.com/business/features/2010/06/fracking-in-pennsylvania-201006
10. The United States Unemployment Rate. (n.d) retrieved 04/08/2012, from Trading Economics Web Site: http://www.tradingeconomics.com/united-states/unemployment-rate
11. Detrow, Scott (10/20/2011). A Guide to Dimock's Water Problems. retrieved 04/08/2012, from State Impact Web Site: http://www.tradingeconomics.com/united-states/unemployment-rate
12. Lustgarten, Abrahm (11/29/2011). Company Backs out of $45 Million Deal to Buy Troubled Wyoming Gas Field. retrieved 04/08/2012, from Pro Publica Web Site: http://www.propublica.org/article/company-backs-out-of-45-million-deal-to-buy-troubled-wyoming-gas-field
13. Kolbert, Elizabeth (12/05/2011). Burning Love. retrieved 04/08/2012, from The New Yorker Web Site: http://www.newyorker.com/talk/comment/2011/12/05/111205taco_talk_kolbert

Not quite what the doctor ordered: America's drug shortage crisis

Across the country, shortages of necessary medications are compromising care and imposing daunting obstacles for hospitals, providers, and patients alike

BY ANAND GOPAL

When 16 year-old Abigale Hamlin was diagnosed with acute myelogenous leukemia (AML) in the spring of 2011, doctors had little doubt that the teenager would endure a grueling road to recovery. At the time, however, no one could have imagined that Abigale's fight against cancer would be made even more trying by the shortage of drugs central to her treatment. After learning that the preferred chemotherapeutic for Abigale's condition could no longer be procured, doctors at Seattle Children's Hospital had little choice but to switch her to an alternative drug for her second round of therapy. The effects were nothing short of disastrous. Abigale would spend the subsequent weeks in a hospital room, suffering the unforgiving side effects of an inferior therapeutic substitute.[1,2]

That something like this should happen in a nation known for cutting-edge care and novel advances in treatments may come as a shock to many and yet, Abigale Hamlin's story is far from unique. On the other side of the country, in Virginia, the recent shortage of methotrexate, a powerful drug used in the treatment of blood and bone cancers, left 10 year-old Alyssa Divers and her family wondering whether she would receive the drug so crucially needed in her battle against osteosarcoma.[3] For the countless number of patients who have been affected by supply shortfalls of critical medications, the story is strikingly similar and yet equally tragic.

A GROWING EPIDEMIC

Across the country, shortages of necessary medications are compromising care and imposing truly daunting obstacles for hospitals, providers, and patients alike. According to a 2011 survey by the American Hospital Association, drug rationing, treatment delays and an increased risk of medical errors are but some of the negative consequences that supply shortages pose.[4] While drug shortages are certainly not a new phenomenon in the healthcare sector, their increasing incidence since 2007 has given rise to growing concern. The scope and scale of recent trends has cast light on a mounting problem affecting the U.S. healthcare system. In 2011, a staggering 267 drug shortages were reported, a number more than quadruple the 58 drug shortages reported in 2004.[2,5] This figure is expected only to increase in coming years.[2] Even more alarming however is the disproportionate share of cancer drugs appearing on the list.[5] According to a report from the IMS Institute for Healthcare Informatics, of the 168 drugs in shortage as of October 2011, a total of 28 (16%) were oncologics.[5] Other therapeutic classes affected include antibiotics, surgical anesthetics and certain nutritional therapies.[2,5]

Although current shortage trends are a general cause for apprehension, the concentration of shortages affecting the oncology space is particularly worrisome. For one thing, chemotherapeutics are drugs of medical necessity, as timely administration of therapy is critical for patient survival. Delayed treatment or failure to treat altogether can be tantamount to a death sentence for individuals with aggressive, yet treatable forms of disease. Moreover, most oncology drugs are generally non-substitutable. Many types of cancers, including Abigale Hamlin's leukemia, can be treated safely and effectively with only a very specific regimen of drugs. Substitution can spell for devastating side effects. The painful mouth sores that Abigale Hamlin developed from her alternative therapy forced doctors to place her on powerful pain medications and left her unable to eat or sleep for days on end.[1,2] For Alyssa Divers, the poor efficacy of her chemotherapeutic substitutes made her situation all the more dire.[3] Recent shortages of these crucial therapies have sparked a growing crisis in the oncology space, as doctors and hospitals scramble to ensure the best care for their patients under increasingly thorny circumstances.

Recent shortages of sterile injectable drugs threaten patient safety and quality of care across the United States. Although a number of factors are no doubt at play, the problem appears fundamentally economic. Recent efforts have dampened the impact of drug shortfalls, but truly effective legislative solutions remain to be seen.

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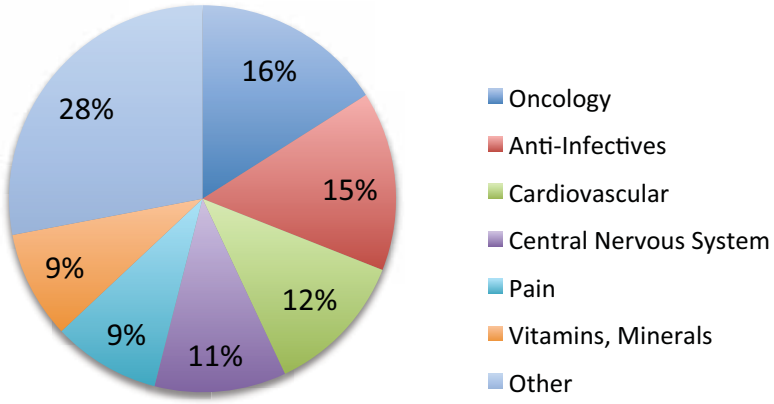
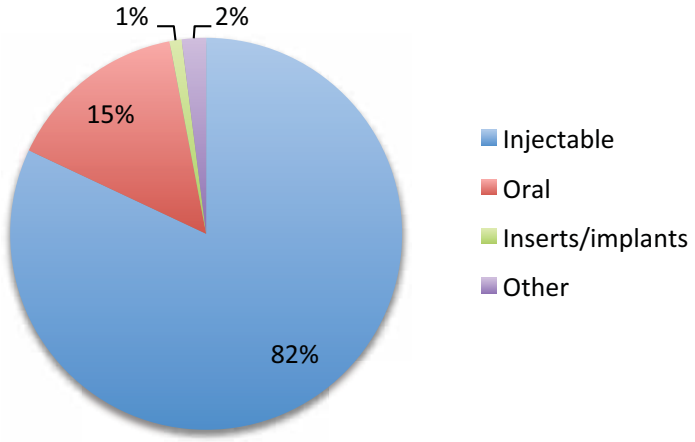




Anticancer drugs are among the therapeutic classes most affected by recent shortages. The vast majority of drugs in shortage are sterile injectables. These are compounds that must be administered to the body via an injection or IV infusion.

Source: IMS Institute for Healthcare Informatics

DIAGNOSING THE DISORDER: WHAT'S TO BLAME?

In light of the current crisis, recent attention has been directed toward understanding the causal drivers of these drug shortfalls. Raw material shortages, quality-control issues, production difficulties and FDA bureaucracy have all been cited as contributory players.[2,3,6] While a number of factors are no doubt at play, academics point to a problem that is highly systemic and in large part economic.[2,3,6-8] To understand why, consider first the very nature of the oncology drugs currently in shortage. The majority are generic sterile injectables, for which the profit margins are typically slim and the production process highly capital intensive.[2,6] The manufacturing process of these drugs is an inherently complicated and expensive affair compared to the production of small molecule entities, or pills.[3] Fixed costs for the manufacture of sterile injectables are typically high.[7] In addition, stringent regulatory requirements exist to ensure the safety and quality of these drugs.[3] Given their relatively low profitability and intensive quality-centric production process, generic injectables are not as "financially attractive" for drug manufacturers in comparison to other generics whose costs can be more easily recouped.[2] Pharmaceutical companies have little reason to invest heavily in these drugs when they can reallocate resources and limited production capacity toward more lucrative therapeutics. As such, supply tends to be relatively concentrated among a few firms within this market. The IMS reported in 2011 that a remarkable 82% of drugs in shortage were some form of injectable drug.[5]

Recent shortages of crucial therapies have sparked a growing crisis in the oncology space, as doctors and hospitals scramble to ensure the best care for their patients under increasingly thorny circumstances.

The profit disincentive for drug manufacturers in the injectables market has been further exacerbated by government price controls via the Medicare reimbursement channel.[9] Unlike with most drugs, patients cannot simply purchase chemotherapeutics from local pharmacies the way that they may purchase an allergy or blood pressure medication. Instead, oncologists must buy the drug from the manufacturer—usually by way of a group purchasing organization (GPO) that leverages buying power to secure the lowest possible prices from drug makers.[8] Within this scheme, insurers directly reimburse oncologists for not only the service provided, but also for the cost of the drug administered.[10] Prior to the passage of the Medicare Modernization Act of 2003, reimbursement for these drugs was based on average wholesale prices (AWP), figures that were typically exaggerated, difficult to validate and historically lucrative for providers and drug companies alike.[10]

The 2003 legislation put an end to that arrangement, known as "buy and bill", by restricting Medicare provider reimbursements to no more than 106% of the national average sales price (ASP) paid to manufacturers in the preceding quarter for a particular drug.[2,6,10] Intended to temper unsustainable growth in drug prices and medical care spending for the government as a payer, this policy essentially increased price stickiness by limiting price rises to 6-month intervals, and, moreover, to just 6 percent increments at a time.[2,6,10] In an article published in the *New England Journal of Medicine* last December, Harvard professor and clinical oncologist Bruce Chabner wrote that the 2003 legislative restrictions "affect price and reimbursement for all purchasers and providers, result in little profit for the manufacturer and the provider in the U.S. market, and greatly limit the ability of generic-drug manufacturers to increase their prices."[11] With Medicare as the largest single payer for inpatient and outpatient services, there is little doubt that its ASP pricing scheme has been a major contributor to the recent shortage trends.[7]

The ultimate result of such price controls has been a less-than-stable supply chain for drugs in the sterile injectables market. The policy, for one, has had the unintended consequence of barring manufacturers from adjusting prices to reflect changes in production costs.[12] Besides limiting profitability in this respect, the legislation discourages drug makers from investing in manufacturing upgrades, capacity expansions and improved quality measures.[2,7,9] Under current ASP pricing, suppliers have little incentive to invest in production processes that carry only slight and often unreliable returns on investment. With aging production lines and increasingly stringent FDA regulation for sterile injectables, firms are very often faced with tough choices: invest further in the production of a potentially lifesaving but unprofitable drug, or devote these resources towards products with greater profit potential.

That companies are apt to choose the latter has resulted in a supply chain vulnerable to random shocks and, furthermore, ill-equipped to respond appropriately. On one level, the disincentive to upgrade facilities and to enhance quality control practices under ASP pricing makes supply disruptions more likely. Potential safety or quality concerns in the manufacturing process may force firms to close down facilities and halt production altogether. On another level, price controls seriously dampen market incentives for manufacturers to appropriately respond to such disruptions in supply.[7] Without controls on price, a shortage of a drug would result in price increases, which would, in turn, induce market entry and encourage current suppliers to ramp up production.[10] By preventing prices from rising, however, Medicare ASP effectively handicaps a supply-side response that would otherwise quickly act to mitigate the disruption.

AN UNCERTAIN PROGNOSIS: TOWARDS A REMEDY

The undeniable trends in drug shortages, brought to public attention by such stories as Abigale's and Alyssa's, have prompted an earnest search for solutions to curb the escalating problem. In October of 2011, President Obama issued an Executive Order in an effort to reduce the future incidence of prescription drug shortages.[2,3] The order directed the FDA to broaden its reporting of potential shortages and to expedite regulatory reviews of new manufacturing sites, suppliers and manufacturing changes to better prevent and respond to supply shortfalls.[2,3] In response, the Food and Drug Administration (FDA) adopted a rule in January 2012 requiring manufacturers of certain medically-necessary therapies to provide 6-month advance notification to the FDA prior to discontinuing or temporarily halting production.[2] The rationale behind such measures has been the belief that early warning will enable the FDA to work with suppliers to address manufacturing problems, in addition to providing hospitals and providers with a sufficient buffer so as not to be blind-sided by sudden supply shortfalls.[2] More recently, the FDA has allowed import of shortage drugs, such as methotrexate, from foreign countries to eliminate the immediate danger facing patients.[3]

While current efforts can certainly help to mitigate the impact and severity of prescription drug shortages, they do little to address the underlying systemic drivers of the problem. As long as government price controls prevent manufacturers from being assured of a reasonable rate of return on investment, the supply for these drugs will continue to remain unstable. Interestingly, the US is unique in its shortage problem as far as industrialized nations go, a fact that stems largely from the lower profit margins that these drugs fetch in this country.[3] In many European countries, generics are typically reimbursed at a rate higher than are branded drugs.[3]

To truly eliminate the shortage problem, effective policy measures must directly attack the root economic instigators, namely low reimbursements and price controls. Proposals under current consideration including revamping the Medicare payment system for injectable drugs in addition to other measures that would increase the profits seen by manufacturers. The effects of increased prices on healthcare expenditures would be negligible, and the benefits more than justifiable.[10]

> In 2011, a staggering 267 drug shortages were reported...a number more than quadruple that reported in 2004.

Unfortunately, the current problem is only expected to worsen before it improves. Meaningful legislation is nowhere in the immediate future. Even with the passage of an effective solution package, augmenting production capacity and fixing up aged facilities will take time, easily on the scale of several years.[2] Until then, shortages will continue to be a recurring feature of the sterile injectables market. For cancer patients such as Abigale Hamlin and Alyssa Divers, the imminent danger seems to be passing, as the FDA and policymakers take on more proactive roles to stem shortage effects on multiple dimensions. Pending a definitive solution to the underlying problem, however, the future in this space remains uncertain at best.

References

1 National Patient Advocate Foundation: Diane and Abigale Hamlin's Statement at the FDA Public Hearing on Drug Shortages: Food and Drug Administration, FDA Public Hearing on Drug Shortages (2011). Retrieved from http://www.npaf.org/diane-and-abigail-hamlins-statement-fda-public-hearing-drug-shortages.

2 Wilson, D. (2012). Deepening Drug Shortages. *Health Affairs, 31*(2), 263-266.

3 Park, A. (2012, March 19, 2012). Inside America's Drug Shortage. *Time Magazine,* Retrieved from http://healthland.time.com/2012/03/19/where-have-all-our-drugs-gone/.

4 American Hospital Association. (2011). *AHA survey on Drug Shortages.* American Hospital Association. Retrieved from www.aha.org/content/11/drugshortagesurvey.pdf.

5 IMS Institute for Healthcare Informatics. (2011). *Drug shortages: A closer look at products, suppliers, and volume*IMS. Retrieved from http://www.imshealth.com/deployedfiles/ims/Global/Content/Insights/IMS%20Institute%20for%20Healthcare%20Informatics/Static%20Files/IHII_Drug_Shortage_Report.pdf.

6 Gatesman, M. L., & Smith, T. J. (2011). The shortage of essential chemotherapy drugs in the United States. *New England Journal of Medicine, 365*(18), 1653-1655.

7 McElligott, S. (2012). Personal Communication.

8 Haninger, K., Jessup, A., & Koehler, K. (2011). *Economic analysis of the causes of drug shortages* (ASPE Issue Brief. U.S. Department of Health and Human Services.

9 Federgruen, A. (2012, March 2, 2012). The drug shortage debacle--and how to fix it. *The Wall Street Journal,* pp. A13.

10 Emanuel, E. (2011). Shortchanging cancer patients. *The New York Times, August, 6, 2011.*

11 Chabner, B. A. (2011). Drug shortages—a critical challenge for the generic-drug market. *New England Journal of Medicine, 365*(23), 2147-2149.

12 Gottlieb, S. (2011). The Causes of Drug Shortages and Proposals for Repairing these Markets (Statement before the Committee on Oversight and Government Reform Subcommittee on Healthcare on 30 November 2011).

The Privatization of Healthcare in Hyderabad: A Case Study

A look into the effects of rapid privatization of healthcare in India

BY BRIDGET ELLSWORTH

An ongoing ethical debate in the healthcare field has been whether quality healthcare is a right or a luxury. Different countries have answered this question in different ways through their policies on the provision of healthcare to low-income citizens. Many countries have healthcare systems that guarantee citizens receive a certain level of care regardless of income. The key to providing healthcare to low-income citizens in a private sector system is regulation by the government. If regulation is non-existent and the private sector has no incentive to treat low-income patients, these patients will not receive proper healthcare and the government will have decided that healthcare is not a right but a luxury. This is essentially what occurred in India through the rapid privatization of healthcare without regulation by the Indian government.

In the 1980s and 90s, India experienced a rampant rise in private sector healthcare catalyzed both directly and indirectly by the Indian government. This had major implications for the poor's access to healthcare because only about 5% of total health expenditure in India is reimbursable through insurance[1], and without reimbursement the poor cannot take advantage of private sector healthcare. The privatization of healthcare spread rapidly throughout India, but nowhere was it more pronounced than in the state of Andhra Pradesh and in particular the city of Hyderabad. Private hospitals accounted for 58% of hospital births in Andhra Pradesh in 1992-93, and this number jumped to 75% in 1995-96. Comparatively, the national growth rate of private hospital births grew only from 43% to 52% in the same years. The private sector accounted for 88.5% of outpatient services in Andhra Pradesh in 1995-96[2]. This privatization of healthcare adversely impacted the poor by reducing the quality and the amount of services offered by government hospitals.

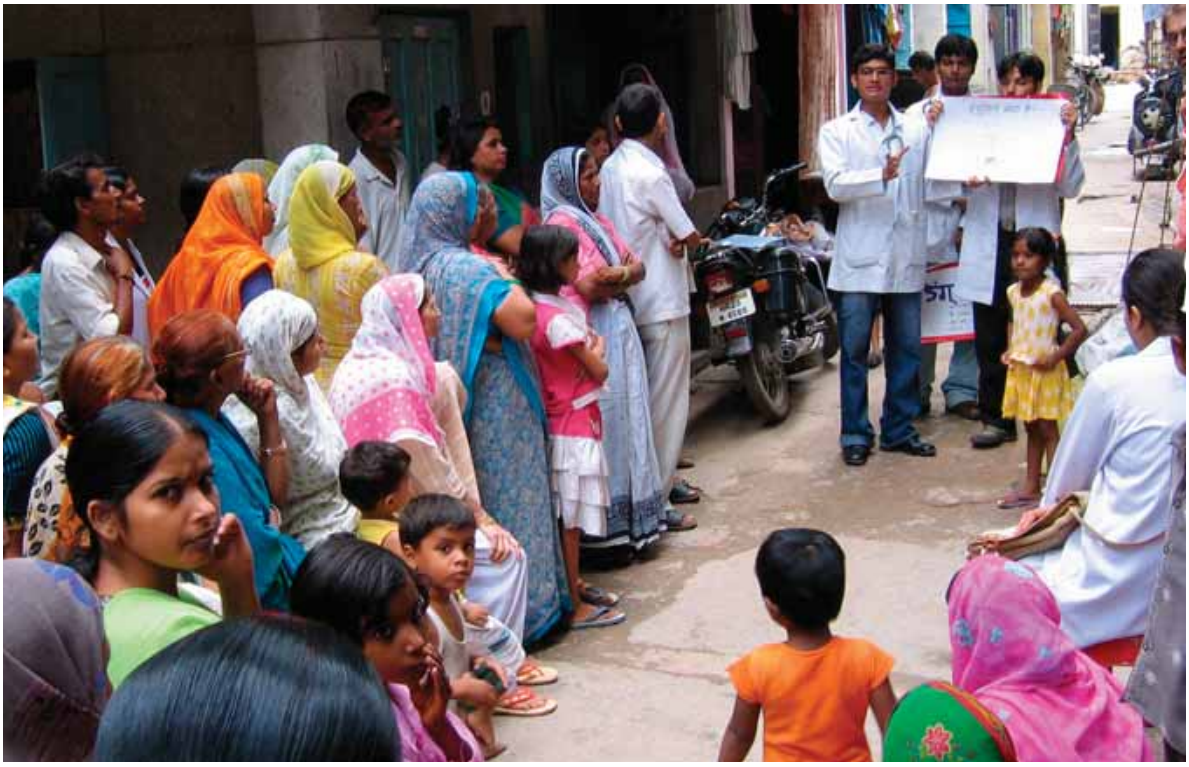
> The problems were readily apparent when the poor were unable to attain proper healthcare in both government and corporate hospitals.

The 1982 Indian Government's Health Policy document stated the need for the privatization of healthcare[3]. In passing this document, the government recognized its inability to achieve its healthcare goals on its own as the population continued to rise and invited the already present private sector to grow rapidly. The government did not want to and could not afford to allocate more of its resources to healthcare and decided to help private sector hospitals grow as a way to increase the number of total beds and provide complementary care in addition to the care provided at existing government hospitals. The idea behind this partnership between private and public sector healthcare was that the government could provide free services to the poor in higher quality, private hospitals while the hospitals could focus on care without having to worry about investing in buildings and other infrastructure[4]. Yet the government did not place any controls on the private sector and did not adequately define its role, allowing the private sector to take advantage of government resources without being held accountable.

The government offered several direct concessions to the private sector for the establishment of large corporate hospitals: it reduced import duties on high technology medical equipment, recognized medical care as an industry making it eligible for public loans, and offered subsidized land and total duty exemption for private hospitals willing to treat 40% of patients free of charge[3]. Simultaneously, the government indirectly fed the growth of the private sector by reducing the number of services offered in government hospitals and neglecting the quality of those services[2]. Due to the low allocation of resources to the public health sector, government hospitals often provided low-quality, overcrowded services in urban areas which caused a huge increase in demand from the urban middle class for private hospitals[2].

The government gave these concessions to corporations like Apollo Hospitals Enterprises, Ltd, a chain of hospitals based in Hyderabad. Apollo Hospital, established in 1989, is the largest corporate hospital in Hyderabad with about 300 beds (today there are 350) on 33 acres of land which was subsidized by the state of Andhra Pradesh[3]. The hospital was given this land on the condition that they reserve an extra 15% of beds for the poor[2]. In 1995, the government of Andhra Pradesh appointed a committee to investigate whether corporate hospitals were in reality treating a percentage of patients free of charge as they had agreed upon when accepting government concessions. In short, the committee found that the corporate hospitals, including Apollo Hospital, were not. This suggests that when left unregulated, corporate hospitals take advantage of government resources at the expense of leaving the poor without proper healthcare.

Apollo Hospital is laid out like a five star hotel serving mostly middle and upper class patients. Interviews have been conducted to examine the experiences of low-income patients who visit Apollo Hospital: one such patient had been suffering from kidney stones for three years and came to Apollo because she heard that they would be able to remove the stones without surgery. The patient's husband had a monthly income of just Rs. 800; however, she and her husband had spent Rs. 10,000 at Apollo on tests alone thus far, and have pawned all her jewelry and taken out loans to make up the difference. When asked about this, she and her husband said



There are many problems associated with the expansion of private healthcare in Hyderabad due to the lack of regulation by the government. These problems have revealed themselves in the inability of the poor to attain proper healthcare in both government and corporate hospitals because of the lack of quality in government hospitals and the lack of access to corporate hospitals.
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"Our hope is that at least by paying the money we will get the best. We can always make money but we cannot get life."[3] This situation is not uncommon; in fact, approximately a quarter of hospitalized Indians fall below the poverty line as a result of their hospital stay[5]. This demonstrates that although Apollo is supposed to treat low-income patients free of charge, in reality, it and other corporate hospitals in Hyderabad are charging the same rate for everyone regardless of ability to pay and placing huge amounts of financial burden on low-income families[6].

Ultimately, the government's plan in 1982 of having extra private hospitals in order to complement existing public ones failed because private hospitals were not punished for denying care to low-income patients[7]. With no incentive to provide care for the poor, private hospitals became more corporate in nature and less concerned with their responsibilities to treat low-income patients, leading to very limited access to healthcare for the poor. Simultaneously, government hospitals, working with a lower budget, offered fewer, lower-quality services than private hospitals.

The decline in quality of government hospitals is also due to the fact that most government specialists eventually move to working in the private sector because they can make more money. They start off in government teaching hospitals in order to gain experience and then move to corporate hospitals where they can earn more and have better working conditions[2]. The government invests in the training of these doctors but then provides no incentives for them to remain in the public sector. This is detrimental to the poor because the care they receive in government hospitals is often from recent medical school graduates who are still learning and do not provide the quality of care that private physicians with more experience do.

In essence, the government's role in the expansion of the private healthcare sector caused the degradation of government hospitals because private hospitals utilize government resources, which could have been used to further invest in government hospitals, while not upholding their responsibility to treat low-income patients free of charge. There are many problems associated with the expansion of private healthcare in Hyderabad due to the lack of regulation by the government. These problems have revealed themselves in the inability of the poor to attain proper healthcare in both government and corporate hospitals because of the lack of quality in government hospitals and the lack of access to corporate hospitals. In this article I have closely examined Hyderabad and Apollo Hospital in particular, but this is just one example of the private sector taking advantage of government resources and in turn leaving the most destitute without proper healthcare. There are five other corporate hospitals similar to Apollo Hospital in Hyderabad alone and many more throughout India. If private hospitals continue to remain unregulated, the poor will continue to suffer. Healthcare is not an industry that should be solely about profit maximization.

The key to providing healthcare to low-income citizens in a private sector system is regulation by the government.

References

1 Bhat, R., & Jain, N. (2006). Analysis of public and private healthcare expenditures. *Economic and Political Weekly*, 41(1), 57-68.
2 Narayana, K. V. (2003). Changing healthcare system. *Economic and Political Weekly*, 38(12/13), 1230-1241.
3 Baru, R. V. (1998). *Private healthcare in India: Social characteristics and trends*. New Delhi: Sage Publications.
4 Raman, A. V., & Björkman, J. W. (2009). *Public-private partnerships in healthcare in India: Lessons for developing countries*. London: Routledge.
5 Peters, D.H., et al. (2002). *Better health systems for India's poor: Findings, analysis, and options*. Washington D.C.: World Bank.
6 Ahuja, R. & De, I. (2004). Health insurance for the poor: Need to strengthen healthcare provision. *Economic and Political Weekly*, 39(41), 4501-4503.
7 Qadeer, I., & Reddy, S. (2006). Medical care in the shadow of public private partnership. *Social Scientist*, 34(9/10), 4-20.

Prometheus v. Mayo

The Battle for the Future of Personalized Medicine

BY ANDREW HONG

Legal and moral implications of patenting a method that tailors a drug to an individual

A NEW FRONTIER

On June 26th 2000, in the same White House room where Merriwether Lewis and William Clark presented Thomas Jefferson with a map of the Louisiana Purchase,[1] two researchers unveiled a very different map to Bill Clinton, one that detailed the very core of who we are on a molecular level. Francis Collins, director of the NIH's Human Genome Research Institute, and Craig Venter, founder of Celera Genomics, met with the president to announce that the human genome's three billion base pairs of DNA had been mapped, an accomplishment Clinton called "the most wondrous map ever produced by humankind."[2] The culmination of nearly 13 years of scientific collaboration across private and public sectors, the landmark finding, Clinton proclaimed, will "revolutionize the diagnosis, prevention and treatment of most, if not all, human diseases." The central question following the completion of the Human Genome Project is how we will apply our newly gained knowledge to design more efficient treatments. Herein lies the question that will ultimately determine the future of biotechnology and healthcare as a whole. How can we use this information to individualize dosages and make personalized medicine a reality? How can we reach a tomorrow where the prescription you fill at CVS has not just your name on the bottle, but on the pill itself? These are the questions that inspire scientists and invigorate doctors. However, this new arena of personalized medicine raises important questions for scientific patents. Namely, can a firm patent a method that tailors a drug for an individual?

THE PATH OF PROMETHEUS (LEGAL BACKGROUND)

This is the central issue in the Supreme Court battle *Prometheus v. Mayo* that will ultimately affect the future of biotech patents and genetic research. It is a case about the patentability of a personalized treatment method built from gene sequencing. There are a few ground rules to set up the case. The Supreme Court leans heavily on prior verdicts in deciding such cases. For example, in *Bilski v. Kappos*, the Supreme Court ruled that the primary focus in method patent cases is whether or not the patent's claims cover abstract processes. Abstract processes are unpatentable, but specific applications of processes are patentable.[3] It's the difference between "this can be done" and "this is how it is done." On December 7th 2011, the Supreme Court heard opposing arguments in *Prometheus v. Mayo*.[4] The contention hinges on whether or not a claim that covers correlations between blood tests and patient health is patentable. But a case does not merely waltz on up to the Supreme Court level. This is the culminating step in a legal journey that began four years ago in a California district court. Along the way, each side has gathered allies, with large-scale drug makers Roche and Abbot backing Prometheus, and the American Medical Association supporting Mayo.[5]

In 2008, Prometheus Laboratories, a California firm, patented a way to optimize certain drug treatments for individuals. They had discovered how to tailor the specific dosage for a certain class of immunosuppressants, namely thiopurine drugs used to treat Crohn's disease. Crohn's disease is a gastrointestinal autoimmune disorder where your body goes overboard and attacks its own cells, causing inflamation in the gastrointestinal tract. When a patient takes a thiopurine drug, his body suppresses the inflammation by decreasing the activity of T-Lymphocytes that lead to inflammation.[9] The patient's body metabolizes the drug and releases the resulting metabolites (6-thioguanine nucleotides and 6 thio-GTPases) into the bloodstream,[5] where its levels can be measured. By analyzing each individual's metabolite levels, Prometheus

How can we reach a tomorrow where the prescription you fill at CVS has not just your name on the bottle, but on the pill itself?

discovered the exact benchmarks for drug dosage calibration on a personal level. Because of this streamlined thiopurine dosage, doctors could more efficiently administer an optimal dose based on the metabolite range. And as any reasonable scientists would do upon a discovery, they celebrated and filed for a patent in 1998. The patent covers the process of administering a specific thiopurine drug targeting a gastrointestinal disorder, measuring that drug's level in a patient's body, and then adjusting the dosage of the drug. Prometheus sells a blood test containing this method of analyzing metabolite levels based on its patients' metabolite levels to hospitals and clinics. In 2004, the Mayo Clinic developed a test using the same method; however, they recommended a different level of metabolites. Consequently, Prometheus sued them.

A COURT BATTLE

As a testament to the speed of the American court system, it took until March of 2008, four years afterwards, for a California district court to hear the case. They invalidated Prometheus's patents, ruling that the claimed methods were not patentable subject matter under Section 101 of the Patent Act. Section 101 reads "whoever invents or discovers any new and useful process… or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title."[6] After the loss in district court, Prometheus appealed, and the case went to the Federal Circuit Court of Appeals in September 2009. The Federal Circuit ruled that the methods Prometheus claimed in its patent satisfied the machine-or-transformation test, which is used to test a patent under Section 101. The machine-or-transformation test is so named because a method is patentable only if it is tied to a particular machine or if it transforms an article into a different state or thing. In this case, the question was whether the method satisfied the transformation branch of the test. The Federal Circuit Court of Appeals, reversing the ruling from the California district court, declared that it did. The Federal Circuit's reasoning was that the method described by the patent resulted in sufficient tangible transformations, or chemical and physical changes in the human body, to make it patentable.

Mayo's lawyers say that Prometheus simply patented an observation of the body's basic natural relationships, namely the relationship between metabolite levels and patient health. Furthermore, Mayo claims that if Prometheus's patent had provided competitors room to develop different, more accurate metabolite levels, it may have passed the test of patentability. Mayo leans on Justice Stevens' 1978 declaration that "Abstract ideas are not patentable subject matter. A patent could not be issued on the law of gravity, or the multiplication tables…"[7] Mayo argues that the Prometheus patent refers to existing methods and fails to offer anything new, except for the metabolite reference levels or benchmarks between 230 pmol per $8x10^8$ red blood cells and 400 pmol per $8x10^8$ blood cells.[4] Mayo argues that nobody should enjoy exclusive rights to tests that merely observe the human body's natural response to treatments. The argument boils down to the notion that discovering a scientific principle or relationship should be rewarded in the scientific community, with the likes of a Nobel Prize, not in the legal community with a patent.[8]

Hans Sauer, a lawyer at the Biotechnology Industry Organization, explains, "These patents protect innovations that allow companies to develop the right drugs for the right patients." Patents are a component of long-term stability in a volatile sector, and Prometheus argues that if Mayo wins, investor confidence in personalized medicine will be destroyed. Prometheus also argues that there is a "determining step" in their method that makes it patentable, i.e. isolating the genes from a blood sample and sequencing them. Prometheus argues that if the drugs themselves can be patented, why can't they patent unique ways to use them?

At its core, Prometheus vs. Mayo is a battle over the patentability of methods of formulating personalized medicine. We can all agree that personalized medicine holds promise for the future of healthcare. But in our quest for it, why are we letting issues of patentability distract us from the actual discoveries? The quest to deliver on the promises of the Human Genome Project is central to the future of modern healthcare. Patentability is crucial as an incentive for discovery and provides stability in an otherwise volatile field. But when questions of patentability begin to interfere with scientific progress, we are obligated to take a step back and reassess the situation. If private researchers were racing to patent discoveries in the process of sequencing the Human Genome Project, the cavorting of lawyers might have delayed and complicated the process to such a degree that we never would have emerged successfully. Will this tangle of legal battles be the downfall of personalized medicine? One would hope that a return to pure research comes back to the forefront.

PATENTABLE OR NOT?

CASE	CLAIM	PATENTABLE?
Diamond v. Diehr	The execution of a physical process, such as operation of a rubber-molding press, by a computer is patentable	Yes
Bilski	A method for managing consumption risk cost of a certain commodity by a provider through the described process	No
Gottschalk v. Benson	A process that converts signals from binary coded decimal form into binary	No
Neilson Case	A design for an apparatus that improves air flow to fires	Yes

Source: *Wall Street Journal* June 8, 2011

Ultimately, it should not be judges in robes deciding the future of personalized medicine, but scientists in white lab coats working at lab benches rather than on the steps of the Supreme Court. The battle for personalized medicine should be fought with rubber gloves and pipettes, not suits and gavels. How heavy a hand should law play in the realm of science?

References

1. Brandon, K (2010, March, 31). 10 Years on, 'The Genome Revolution Is Only Just Beginning.' retrieved February 15 2012, from Wired.com Web Site: http://www.wired.com/wiredscience/2010/03/genome-at-10/
2. Kristen, P (2000, June, 26). Human Genome: Because They Could.. retrieved February 15 2012, from Wired.com Web Site: http://www.wired.com/science/discoveries/news/2000/06/37206
3. Conley, J (2009, September, 24). Prometheus Returns to the Supreme Court, Medical Method Patent Speculation Intensifies. retrieved February 21 2012, from Genomics Law Report Web Site: http://www.genomicslawreport.com/index.php/2011/06/22/prometheus-returns-to-the-supreme-court-medical-method-patent-speculation-intensifies/
4. Anderson, J (2011, December, 8). Summary of Mayo v. Prometheus Oral Argument. retrieved February 14 2012, from Patentlyo.com Web Site: http://www.patentlyo.com/patent/2011/12/summary-of-mayo-v-prometheus-oral-argument.html
5. (2011, December 10). Biotech Patents: Taking it Personally. The Economist
6. Neurath M (2010). Thiopurines in IBD. Gastroenterology and Hepatology. 6(7), 435-436.
7. 35 USC § 101 – Inventions Patentable. Law.cornell.edu. Retrieved February 12, 2012, from http://www.law.cornell.edu/uscode/text/35/101
8. Lee, T (2011). Medical Mind Control. Slate, . retrieved Feburary 14, 2012, from http://www.slate.com/articles/technology/technocracy/2011/12/mayo_v_prometheus_and_the_fight_over_medical_patents.html
9. Fisher, D (2011, December 2). Mayo Clinic Case Asks If A Doctor's Method Can Be Patented.Forbes.

Note: This article was written before the March 20th 2012 Supreme Court decision on Prometheus v. Mayo, which unanimously ruled against the validity of Prometheus's patents.

Preparing for the unexpected: From H1N1 to natural disaster

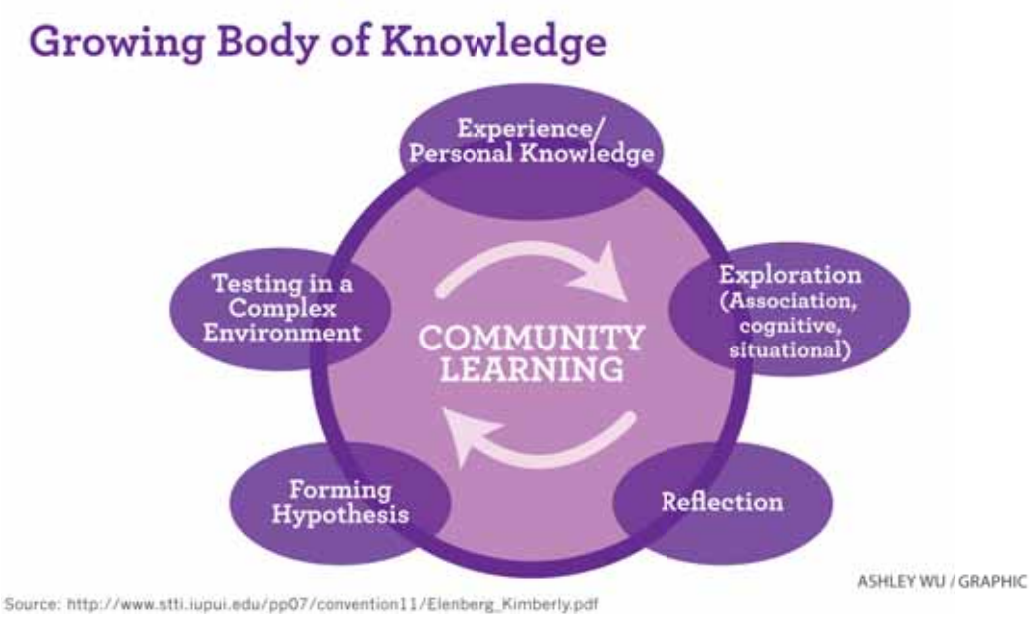
How the U.S. government utilizes service-oriented training to prepare for national emergencies

BY ROHAID ALI

Not even two months had passed before the Obama Presidency encountered a significant challenge in the form of a potential national emergency. Several cases of the H1N1 strain of the Influenza A virus, or "swine flu," were appearing in southern California. As the spread of H1N1 became apparent, Kathleen Sebelius, the newly appointed head of the Department of Health and Human Services (HHS), and her team began to mobilize response efforts to contain the spread of this pathogenic viral strain. In spite of their efforts, the H1N1 virus evolved to a national-level outbreak, causing the death of almost 12,000 individuals and the hospitalization of nearly 265,000 people[1].

The nature of this outbreak invited a question that frequently occurs after a national emergency: How can the U.S. government best prepare itself for such an event? One option is to increase outlays for in-classroom training for response workers built off of lessons learned from previous federal disasters. However, while in-classroom training is crucial for communicating new information, it often has difficulties in assessing how response teams will succeed in a real environment. For example, the confusion surrounding vaccination protocols during the H1N1 outbreak demonstrates how response plans learned in the classroom may meet unexpected challenges in the real world. Therefore, to augment this approach, HHS and others are increasingly exploring another educational model to help enhance federal preparedness to national emergencies, called service-oriented training.

As the name suggests, service-oriented training allows professionals to practice and improve their skills while simultaneously benefiting recipients. This form of training is a common practice among a variety of fields. For example, a medical



ASHLEY WU / GRAPHIC

Source: http://www.stti.iupui.edu/pp07/convention11/Elenberg_Kimberly.pdf

TIMELINE OF 2009 AMERICAN FLU PANDEMIC

MAR 2009	First cases of H1N1 appear in California
APR 2009	Kathleen Sebelius is sworn in as Secretary of the Department of Health and Human Services
MAY 2009	H1N1 is present in all 50 states
OCT 2009	President Obama declares a national emergency
JAN 2010	Disease has almost ended
FEB 2010	CDC says 11,690 people have died due to the disease to date
LATE 2011 TO APRIL 2012	An ongoing debate persists on the publishing of research over a more virulent cousin of H1N1, called H5N1

student providing patient care in a rural community or a law student doing *pro bono* consulting are both undergoing this type of training - improving their professional skillsets while also helping their patients and clients. Instances of federal emergency response professionals performing service-oriented training may be less common, but a collection of cases does exist.

One such training exercise occurred in the summer of 2011 when a free medical assistance program in south Texas doubled as a center for a simulated swine flu outbreak. When federal officials heard about this Texas-led program, they wanted to join. The Department of HHS in Washington, D.C. deployed over 100 federal emergency response workers—including doctors, epidemiologists, nurses, and scientists—to implement this service-oriented training. The program was located near the Mexican border and called "Operation Lone Star," and was a blessing to the patients. Indeed, those who showed up early enough were served regardless of insurance or legal status. The individuals who were treated were in addition to the over 100,000 patients served since Operation Lone Star's launch in 2000. Additionally, because the 2011 Operation Lone Star had attached to it a simulated swine flu outbreak, the deployment crew from HHS also uniquely benefited. Working alongside local health officials and members of the Texas Rangers, these HHS professionals experienced training for a real national threat.

The HHS has also found usage for service-oriented training in preparation for emergencies outside of an H1N1 outbreak. During the same summer as Operation Lone Star's swine flu simulation, HHS deployed another team to Paducah, KY, a town that lies along the New Madrid seismic zone. The New Madrid fault extends across five Midwestern states, and has been considered a national security concern. In a report funded by FEMA in 2009, it was found that if an earthquake were to occur throughout the fault, there might be a 7.2 reading on the Richter scale which would result in the death of 3,200 individuals.[2] Therefore, some missions for the training in Kentucky consisted of HHS workers creating evacuation plans for local hospitals, identifying secure shelters for the disabled, and simulating a federal medical station in an air dome, a location that was chosen because it could withstand the aftershocks of a potential earthquake.

These two training exercises represent one model being utilized by the federal government to prepare for potential national emergencies, but service-oriented training is not the only answer for disaster preparation. Didactic education still dominates, and with current advances in technology, in-classroom training will become increasingly fruitful for disaster preparation in the future. However, service-oriented training is a unique solution because it confers both a short-term and long-term advantage. The immediate benefit is to the community members to whom federal workers give service, but it most importantly has beneficial long-term effects. This is especially true when the bond formed between the federal government and a community cuts through the darkness of a chaotic, national emergency by representing the very real difference between the loss and savior of human life.

References

1 The 2009 H1N1 Pandemic: Summary Highlights, April 2009 – April 2010. Centers for Disease Control and Prevention http://www.cdc.gov/h1n1flu/cdcresponse.htm

2 Elnashai, A., et. al. (2009) "Impact of the New Madrid Seismic Zone." University of Illinois. http://www.ideals.illinois.edu/bitstream/handle/2142/14810/ImpactofNewMadridSeismicZoneEarthquakeso%20theCentral%20USAVol1.pdf

Epigenetics of Healthy Aging:
The Curious Case of Glutathione

STAGES OF STUDY

PHASE 1

Compare the effects of three antioxidant supplements on the aging of Drosophila melanogaster. Glutathione, Resveratrol, and Ginkgo biloba were administered in the diet of groups of Drosophila, and their life spans were compared with the control group.

PHASE 2

Test the optimal dosages of the three supplements. The dosages were increased to 3x and 6x of the equivalent dose prescribed by bio-pharmaceutical companies, for the three groups of Drosophila, and their life spans were compared with the control group.

PHASE 3

Explore the biochemical pathway of the above effects by measuring the levels of the enzyme Glutamate-Cysteine-Ligase (GCL) that is involved in Glutathione biosynthesis, and controls the levels of Glutathione. Western Blot tests conducted to determine GCL levels. Glutathione Assays completed to estimate the resultant in vivo antioxidant synthesis.

BY TESS MICHAELS

In *The Curious Case of Benjamin Button*, F. Scott Fitzgerald narrates of the vicissitudes of a young child born with the physical condition of a 70-year-old, who grew younger with time. The satire on aging published in 1922 poked scientists to look at the differences in when and how people age. Yet, aging remains the trickiest biological riddle of our times, and perhaps one with the most universal appeal.

Globally, there are about two billion people over 40 years of age who could benefit from medical advancements on healthy aging. There is little agreement among scientists on how or why people age beyond the recognition that aging involves the complex interaction of cellular dynamics, genetics, environment, and behavior. Some scientists believe that slowing down aging can add more years to our lives than curing cancer, heart disease, stroke and diabetes combined. Yet, theNational Institutes of Health allocates less that 2% of its research funding to aging.

As the research on the process of aging advances, scientists gain a further understanding of the mechanisms of aging and potential treatments that promote longer, healthier lives. Research on aging continues to draw upon the free radical theory[1] first proposed by Denham Harman in 1956. According to this theory, the basis of aging is the accumulation of oxidative damage caused by highly reactive free radicals. This perspective has led to the recognition of antioxidants and vitamins as ways to protect cells from free radicals.

Another theory, the genetic theory of aging, suggests that genes exert a significant control over human lifespan. According to this theory, DNA damage accumulation is the primary cause of physiological decline[2]. DNA damage may trigger cellular signaling pathways that result in faster depletion of antioxidants such as Glutathione, which in turn contributes to accelerated aging[3]. This research stream has suggested therapies to mitigate the deterioration of DNA by switching on and off certain genes. This explains diseases such as Progeria that result in premature aging and death. Epigenetics, the study of genome modifications through environmental effects without changing the underlying DNA sequence, offers a new paradigm on the biology of aging with multiple avenues for intervention. Specific epigenetic modifications such as those that increase antioxidants *in vivo* can have a direct functional outcome in aging depending on genetic, and environmental factors.[4]

Glutathione is the most abundant antioxidant in human body. It plays a crucial role in free radical scavenging, providing a reservoir for cysteine, and modulating DNA synthesis and immune functions[5]. Changes in glutathione levels have now been reported in the onset and progression of nearly all major human diseases. Blood glutathione levels are much higher in the youth and they reduce with age. The elderly with twenty percent higher glutathione levels have a one-third less rate of arthritis, hypertension, heart disease and neurodegenerative disorders. Without glutathione, the immune system would be greatly compromised and left with little defense against toxins and disease. This growing recognition has generated considerable interest in identifying therapies aimed at modulating glutathione levels to ameliorate disease risk or progression. Although such therapies have significant obstacles to overcome, they offer significant promise for many human diseases.[6]

Glutamate-Cysteine-Ligase catalytic unit (GCLc), the rate-limiting enzyme, plays an important role in glutathione biosynthesis. One line of research focuses on the GCLc-Glutathione pathway to aging and how certain antioxidants such as Ginkgo biloba, primarily marketed for improving memory in the past, can switch on and over-express the GCLc gene and thus increase the amount of glutathione. Some researchers had brought out the bio-chemical processes that result in increased Glutathione production. Researchers at SMU Biology Lab in Dallas have used transgenic flies with Glutamate-Cysteine-Ligase catalytic subunits (GCLc) to explore the Glutathione pathway[7].

This author conducted a multi-year research project that evaluated the epigenetic effects of Glutathione on longevity. The major impediment of using glutathione as a dietary supplement is that it is not well absorbed into the body because it does not pass through the cell membrane efficiently and is degraded by stomach acids. Alternate avenues of increasing glutathione levels in the body were explored. Since both Resveratrol and Ginkgo biloba extract helps the body get rid of cell-destroying free radicals and force the blood vessels to relax, the project compared the effects of these compounds on aging relative to glutathione.

The three-phased study explored the epigenetic pathways of longevity integrating the genetic theory and the free radical theories of aging. The study addressed an important bio-medical question: Can longevity be epigenetically modulated by dietary modification? Specifically, can *Drosophila melanogaster*

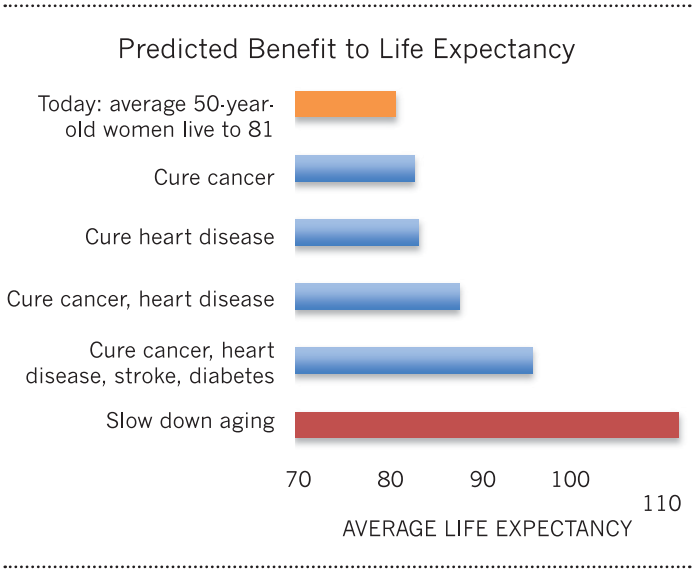
be therapeutically supplemented to enhance de novo Glutathione synthesis through overexpression of the GCLc gene and in turn extend their lifespan?

In the first phase, yellow-white male *Drosophila melanogaster* were given three different antioxidant supplements and compared to the control were found to live longer; 11% for Glutathione, 39% for Resveratrol and 42% for Ginkgo biloba. In the second stage of the study, optimal dosages and toxicity were tested for the three supplements testing single, triple and six times dosages. All the supplements except Resveratrol, when administered at the six times level, were toxic. Glutathione and Ginkgo biloba both decreased lifespan dramatically by 30%. The +48% to -30% variation in the average lifespan brings out the importance of 'optimal dosage' for dietary supplements. All results were found to be statistically significant at the 99% confidence level.

In the third phase GCLc enzyme levels and Glutathione levels were quantified. Western Blot tests and Glutathione Fluorimetric assays were performed at the SMU Biology Lab in Dallas. The Western Blots for Ginkgo biloba, Resveratrol and Glutathione-supplemented *Drosophila* showed that all three supplements increased the GCLc enzyme. Ginkgo biloba had the most significant increase supporting the hypothesis that the over-expression of the GCLc enzyme led to the production of Glutathione. Resveratrol had the least effect on GCLc implying other pathways (such as Sirtuin) for Glutathione synthesis. The Glutathione Fluorimetric assay showed that the Glutathione levels increased significantly and more than doubled with optimal doses of supplements and decreased dramatically with the highest doses indicating negative feedback and toxicity.

The findings support the emerging view that dietary supplementation can induce epigenetic changes and promote healthy aging.[8] Glutathione is a potent molecular target for novel therapies for diseases of aging such as Diabetes, Parkinson's & Alzheimer's. Therapeutic interventions based on GCLc-Glutathione pathway could potentially delay diseases of aging. A deeper understanding of similar biological pathways of aging would benefit prevention and treatment of many major diseases.

The true genius of Scott Fitzgerald is in reversing the riddle of aging. Can people grow younger with time? The curious case of epigenetic supplements that induce glutathione synthesis offers another glimmer of hope.



Some experts estimate that slowing down aging can add more years to our lives than curing all the major diseases associated with aging.

Source: University of Michigan, Miller (2003)

References

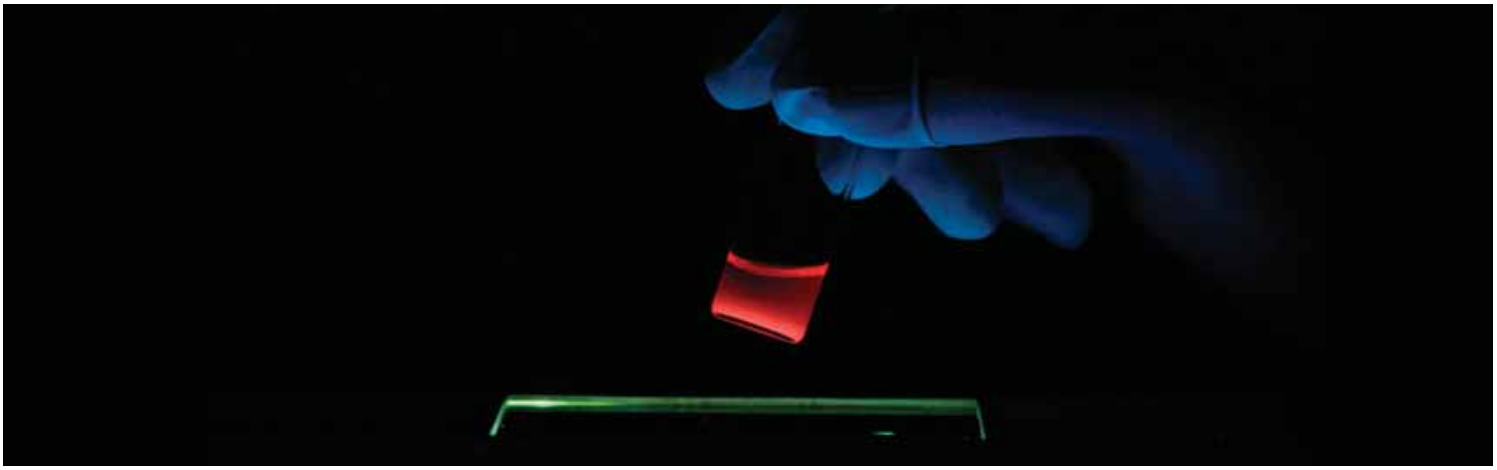
1 Harman, D (1956) *Journal of Gerontology* 11 (3): 298–300.
2 Gensler, HL; Bernstein, H. (1981) Quarterly Review of Biology, 56, 279-303.
3 Shelly L. (2009) Molecular Aspects of Medicine 30 42–59.
4 Calvanese V, Lara E, Kahn A, Fraga MF. (2009) Ageing Research Reviews. Oct;8(4): 268-76.
5 Meister, A., Anderson, M.E., (1983) Glutathione. Annual Review of Biochemistry 52, 711-760.
6 Nazzareno B. et al. (2009) *Biological Chemistry* March; 390(3): 191–214.
7 Orr, W., Luchak, J. et al. (2005) Journal of Biological Chemistry 280: 37331-37338.
8 Gregory B. (2010) *Experimental Gerontology* March; 45(3): 173–179

Quantum Dots: A New Approach to Disease Treatment

BY PRANEET MYLAVARAPU

Controlling the brain with tiny light-emitting semi-conductors a billionth of a meter across may sound like something straight out of science fiction, but the science of quantum dots (q-dots) has recently been used to tackle many neurodegenerative diseases. Currently, scientists place electrodes on the scalp or within the brain to electrically stimulate neurons, but this method is often very inaccurate, stimulating thousands or even millions of neurons of different cell types, making it difficult to study the mechanics of cellular communication that drives many disease pathways.

Recent research in targeted cellular activation has yielded a promising method of controlling precise neural activity with optical stimulation. Optogenetics hacks the brain, in a sense, using its own natural rhodopsin (a light sensitive pigment) activated G-protein coupled receptors (GPCRs) to stimulate neurons.[1] In the retina, the brain has natural rhodopsin-activated GPCRs that open ion channels upon photo stimulation, causing the propagation of action potentials. By adapting this photosensitive neuronal mechanism to other regions of the brain, scientists can precisely control cellular activity, choosing when and to what extent certain cells are stimulated. However, the problem with this technique is that light sensitive probes and promoters must be genetically inserted into specific populations of neurons. In addition to genetically altering populations of neurons, sources of optical stimulation (fiber optics or other solid-state light sources) must be implanted within the brain to emit remote flashes of light. Although work at the University of California San Diego and Stanford University has proven the success of Optogenetics, the



The smallest q-dots emit high-energy blue light while the largest emit low-energy red light.

Source: University of California, San Diego

extensive genetic and invasive requirements have limited the implementation of this approach in humans.

An alternative proposed by Lih Y. Lin and Fred Rieke, researchers at the University of Washington, uses q-dots.[2] Because of their specificity and control, these tiny semi-conducting crystals a billionth of a meter across carry immense potential. By confining electrons in all three dimensions, q-dots exhibit properties of both semiconductors and discrete molecules. Every molecule has a certain electronic configuration determined by its quantum state and steric symmetry, resulting in the formation of bonding and antibonding orbitals. According to molecular orbital theory, the strength of a chemical bond is roughly defined by the difference in the number of electrons occupying bonding and antibonding orbitals. Electrons fill these orbitals to minimize their energies, filling lower energy (bonding) orbitals first. Once all of the electrons in a molecule are placed in their respective orbitals, some unoccupied orbitals remain. The space between the highest occupied molecular orbital (HOMO, or valence band) and lowest unoccupied molecular orbital (LUMO, or conductance band) is known as the band gap. The amazing nature of q-dots is that each dot is itself a semiconductor with a particular band gap (defined by the size of the dot). As the size of the crystal increases, energy levels become more closely spaced, reducing the band gap and therefore requiring less energy for an electron to be transferred between the valence and conductance bands. The smallest q-dots emit high-energy blue light while the largest emit low-energy red light.[3] Thus, when excited, the electron makes this transfer across the band gap and emits a precise wavelength of light (corresponding to the band gap energy). Because of this specificity and control, q-dots have possible applications in many fields from solid state quantum computation, in-vitro imaging, and LEDs to efficient photovoltaic solar technology.

Q-dots have been a part of biomedical science for nearly two decades but are only recently being used as substitutes for conventional dyes.[4] Due to their bright fluorescence and great stability, q-dots are replacing rigid organic dyes as flexible markers and are increasingly desired in research and medicine. Furthering their potential in medicine, Lin and Rieke extended the role of q-dots to targeted stimulation of cells.[2] By culturing prostate cancer cells on q-dot films so that cell membranes bordered the surface of the dots, researchers observed the effects of photo stimulation on certain cell lines. Upon exposing the cells to flashes of various wavelengths of light, electrons within the q-dots were excited and generated electric fields, which then caused the surrounding cancer cells to spike in activity. Researchers were able to suppress and increase cancer cell activity at will, effectively regulating the cells. After initial success in controlling the activity of cancer cells, Lin's group expanded their study to cortical neurons and found similar results. Many neurodegenerative disorders including Parkinson's, Alzheimer's and Huntington's all result in imbalances of localized neuronal activity, and regulating targeted populations of neurons can greatly alleviate adverse effects.

This promising new technique for manipulating specific types of neurons can be adapted in many ways, from restoring function to retinas damaged by neuronal atrophy due to disease to aiding in the understanding of normal patterns of neural circuits by altering their behavior and monitoring the effects. Though immensely promising, the application of q-dots in neuroscience has been limited by their toxicity to humans. Q-dots dissolve upon exposure to UV radiation, releasing harmful cadmium ions into the surrounding area. Recent attempts to minimize their toxicity has led to the development of an amphiphilic coating, a film with both hydrophobic and hydrophilic properties. The water repulsive side attaches to the surface of the q-dot, leaving the hydrophilic side exposed. The exposed side attracts water and allows the molecules to dissolve. This resultant combination has been found to be essentially non-toxic and does not affect the dots' light-emitting nature, paving the way to in-vivo research on q-dot based cellular activation.

Although the day we see convenient and accessible applications of these microscopic semiconductors in healthcare may be in the distant future, quantum dots are directly revolutionizing the way we approach cancer and neurodegenerative diseases.

References

1. Deisseroth, K (2010, October 20). Optogenetics: Controlling the Brain with Light. Scientific American, , 48-55.
2. Optical Society of America (2012, February 8). Flipping a light switch in the cell: Quantum dots used for targeted neural activation. ScienceDaily. Retrieved March 8, 2012, from http://www.sciencedaily.com /releases/2012/02/120208132721.htm
3 DOE/Lawrence Berkeley National Laboratory (2012, January 30). Bright lights of purity: Why pure quantum dots and nanorods shine brighter. ScienceDaily. Retrieved April 8, 2012, from http://www.sciencedaily.com /releases/2012/01/120130172400.htm
4 University of Twente (2011, October 26). Quantum dots cast light on biomedical processes. ScienceDaily. Retrieved March 8, 2012, from http://www.sciencedaily.com / releases/2011/10/111026091008.htm

Neurostimulation for the 21st century

Deep Brain Stimulation for Treatment Resistant Depression may fill the void left by pharmaceutical treatments

BY ANDY TEKRIWAL

THE EMPTY MEDICINE CABINET

With weapons like antibiotics and vaccines, many of man's greatest killers have been conquered. Regarding the mental demons with which many struggle, we come up very short. Of the array of mental disorders commonly portrayed in popular culture, you are probably most familiar with depression. Depression has a lifetime prevalence rate of 16.5% in adults in the United States.[1] General terms like "depression" and "anxiety" are used by the public to describe conditions for which physicians have an entire book: the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM).[2] When reading the DSM, the fifth edition of which is expected in 2013, it becomes clear how difficult it is to properly diagnose mental illness. For the most part, physicians cannot use objective measures like blood tests or imaging technology to diagnose patients suffering from mental illness. As a result, diagnosis is challenging and it is not uncommon for people seeking psychiatric care to be labeled with not one but several concurrent mental disorders, an occurrence known as comorbidity, as most conditions share several symptoms and often have identical treatments.

Psychiatric evaluations and questionnaires, like the Hamilton Rating Scale for Depression (HAM-D), attempt to quantify depressive behavior by asking patients to rate how they feel about various aspects of their life and health. Once a patient receives an admittedly subjective diagnosis based on DSM criteria and questionnaire results, the most popular treatment for Major Depressive Disorder (MDD), the DSM term for depression, is pharmacological intervention. Monoamine oxidase inhibitors, tricyclics, and neurotransmitter reuptake inhibitors, like selective serotonin reuptake inhibitors (SSRI's, such as Prozac), represent the majority of these drugs. Strikingly, 30-40% of those who undergo treatment for depression will not see improvements in their condition.[3,4] On a population level that means about 5% of Americans will struggle with "treatment resistant depression". Keeping in mind that Major Depressive Disorder or a comorbid disorder is present in 90% of the 34,000 people a year that commit suicide, these treatment resistant patients are in life threatening danger.[5,6]

When pharmacological and cognitive behavioral treatments fail to treat depression, patients are left with few options. It has been well over twenty years since Prozac (fluoxetine) was released and since then pharmaceutical and drug discovery companies have fallen short of creating a more effective class of antidepressant drugs. Researchers have recently even turned to ketamine, a veterinary anesthetic turned club drug, to try to find new classes of drugs that can help depressed patients - even though ketamine carries a risk for dependency similar to that of amphetamines.[7] For the most part however, companies like AstraZanaca and GlaxoSmithKline are shutting down their drug discovery programs for depression, schizophrenia, bipolar disorder, and related disorders.[8,9] Public outcries for novel treatments of these conditions have only increased as a result of the across the board cutting of psychiatric R&D, leading to a new, inventive approaches.

In the place of pharmacological therapies for these treatment resistant patients, stimulatory surgical procedures have begun to fill the void. Neurostimulation treatments, such as Vagus Nerve Stimulation and Electroconvulsive Therapy (ECT), are becoming increasingly popular therapies for those who have exhausted psychiatry's pharmacological armamentarium against depression. ECT, a highly regulated and controversial treatment, is given to about 100,000 Americans a year.[10] A current is passed through the patient's body via electrodes placed on the skull, resulting in convulsions and a "rebooting" of the brain. The mechanism through which ECT acts is unknown and the treatment can carry side effects like memory loss and confusion. Even with these potential negative consequences, Dr. Wayne K. Goodman of Mt. Sinai School of Medicine has said that "for the acutely suicidal, treatment-resistant depressive who is not responding to other treatments, it is literally life saving."[11]

DIAGNOSIS IS CHALLENGING AND IT IS NOT UNCOMMON FOR PEOPLE SEEKING PSYCHIATRIC CARE TO BE LABELED WITH NOT ONE BUT SEVERAL CONCURRENT MENTAL DISORDERS, AN OCCURRENCE KNOWN AS COMORBIDITY, AS MOST CONDITIONS SHARE SEVERAL SYMPTOMS AND OFTEN HAVE IDENTICAL TREATMENTS.

To prevent ECT-induced convulsions from causing physical harm to patients, anesthesia and muscle relaxers are administered prior to application to decrease the unpleasant side effects of ECT. Despite its vilified role in movies like "One Flew Over the Cuckoo's Nest", ECT has achieved an 80-95% remission rate in some studies, although some patients relapse back into depression weeks after treatment[12].

NEW TOOLS

Deep brain stimulation (DBS) can be thought of as ECT for the 21st century; instead of flooding a patient's entire body with current, a specific section of their brain is targeted. DBS is a neurostimulatory technique currently being researched as a treatment for a number of disorders such as heroine addiction, obesity, Huntington's disease and MDD[13]. Currently, almost all DBS procedures focus on Parkinson's disease for which it is FDA approved. DBS was first successfully used to reduce the tremors, stiffness, and uncontrolled movements associated with this disease[14]. Parkinson's is a motor system disorder caused by the loss of dopamine producing cells[15]. Dopamine, a neurotransmitter expressed in the brain, is integral for the processing of reward and the refining of motor control[16].

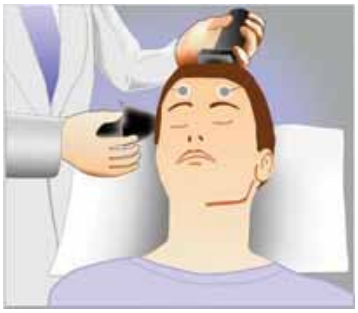
In DBS for Parkinson's, a pair of electrodes is implanted into dopaminergic areas of the brain. These electrodes continuously stimulate the section of the brain their distal ends are in contact with using current from a generator typically implanted into the chest[17]. Like ECT, DBS has been shown to be effective for treating certain enigmatic disorders but the mechanism through which it acts is unknown. Although this may sound alarming, it should be noted that many of the most popular classes of psychiatric medications, like Selective Serotonin Reuptake Inhibitors, operate through unknown mechanisms but are still considered to be relatively safe[18]. Most of the research being done with DBS has concentrated on stimulating parts of the brain associated with the "reward system" such as the nucleus accumbens, but other brain regions are being targeted as well.

Of these potential treatment applications being researched, DBS had gained some validation in the treatment of depression and obsessive-compulsive disorder. It is currently categorized as a Humanitarian Use Device (HUD) for these two conditions[19]. HUD's have conditional FDA approval in cases where conventional therapies have failed and procedures involving these devices can only occur in highly regulated settings like the Perelman School of Medicine[20]. Most importantly, these treatments do not have to prove clinical efficacy to be used. The HUD categorization allows healthcare companies and providers to circumvent the need to invest in expensive clinical trials, giving patients another

BRAIN STIMULATION THERAPIES

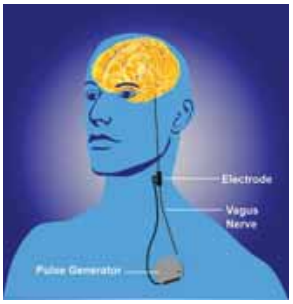
Brain Stimulation therapies involve the hyperactivation or touching of the brain using magnets, electricity or implants. These therapies have been used to treat depression and other disorders.

ELECTROCONVULSIVE THERAPY (ECT)



Involves passing an electric current through electrodes placed on precise locations on the head, which causes a brief seizure. This procedure has most often been used to treat patients with severe, chronic depression.

VAGUS NERVE STIMULATION (VNS)

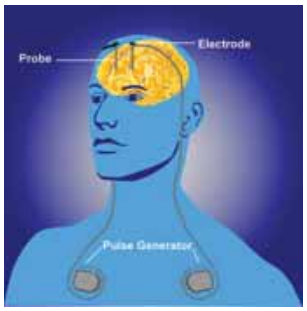


Provides electrical pulses to the left vagus nerve, half of a pair of nerves that run from the brainstem to each side of the abdomen, through a device implanted under the skin. This procedure has most often been used to treat patients with severe, chronic depression.

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS)

Uses a magnet to provide short magnetic pulses to specific sites of the brain. Has been approved by the FDA as a treatment for major depressive disorder patients who have not responded to at least one antidepressant medication. Though the effectiveness of rTMS is being debated, it lacks many of the unpleasant side effects of other brain stimulation therapies.

DEEP BRAIN STIMULATION (DBS)



Involves implanting a pair of electrodes into the brain that provide electrical pulses to a designated area. Pulse generators placed on the chest provide continual pulses. DBS has been used to treat Major Depressive Disorder and Parkinson's disease.

Source: http://www.nimh.nih.gov/health/topics/brain-stimulation-therapies/brain-stimulation-therapies.shtml

option if all else fails. In addition, having DBS as a treatment option for depression allows physicians and researchers to collect data from those who do elect to have the surgery, adding to our knowledge of this treatment option. In recent years many studies involving DBS have been authorized in order to investigate its efficacy in treatment of depression.

One such study was recently published in the Journal of Neurosurgery. A trial jointly conducted by several institutions achieved a 50% reduction in patients' HAM-D score in half of the implanted subjects 6 months after DBS began, a significant and encouraging finding[21]. Furthermore, one year after the surgery all those who were still receiving treatment remained below their pre-treatment HAM-D score. At this same one year mark the data indicated that the treatment was becoming about 50% less effective. Unfortunately, one of the subjects committed suicide while another made an attempt. Patients with MDD are predisposed to such actions so these occurrences are not too surprising, but they do indicate that even in the most encouraging studies DBS is no silver bullet for depression. In 2011 an update to the paper was released which stated that after 6 years, over half the patients were benefiting from their treatment although another patient had committed suicide.[22]

IN ADDITION, HAVING DBS AS A TREATMENT OPTION FOR DEPRESSION ALLOWS PHYSICIANS AND RESEARCHERS TO COLLECT DATA FROM THOSE WHO DO ELECT TO HAVE THE SURGERY, ADDING TO OUR KNOWLEDGE OF THIS TREATMENT OPTION. IN RECENT YEARS MANY STUDIES INVOLVING DBS HAVE BEEN AUTHORIZED IN ORDER TO INVESTIGATE ITS EFFICACY IN TREATMENT OF DEPRESSION.

So, is DBS for depression effective? Small sample sizes and conflicting data have made it difficult to answer this question. We know from DBS treatment for Parkinson's that this technique does provoke a change in neurological function, but basic questions like what DBS does on the neuronal level and how safe it is over the long term have yet to be answered. Questions about DBS's efficacy and safety will not be answered all at once; it will take time and patience to generate and sift through the accumulating data. Despite "big pharma's" lack of interest in psychiatric illness, healthcare workers and researchers are acutely aware of the need for new treatment options for conditions like MDD and they will continue to search for them. As DBS is attempted for different disorders and in different brain regions, we will learn more about how to use this new tool, but right now the verdict is out on DBS as a treatment for depression.

References

1 NIMH · Statistics · Major Depressive Disorder Among Adults. (n.d.). *NIMH · Home*. Retrieved March 11, 2012, from http://www.nimh.nih.gov/statistics/1MDD_

2 Biali, S. (n.d.). DSM-V offers new criteria for personality disorders | Psychology Today. *Psychology Today: Health, Help, Happiness + Find a Therapist*. Retrieved March 2, 2012, from http://www.psychologytoday.com/blog/the-shrink-tank/201002/dsm-v-offers-new-criteria-personality-disorders

3 'I Wanted To Live': New Depression Drugs Offer Hope For Toughest Cases : Shots - Health Blog : NPR. (n.d.).*NPR : National Public Radio : News & Analysis, World, US, Music & Arts : NPR*. Retrieved February 27, 2012, from http://www.npr.org/blogs/health/2012/01/31/146096540/i-wanted-to-live-new-depression-drugs-offer-hope-for-toughest-cases

4 MacDonald, A. (n.d.). Harvard Health Publication. *New insights into treatment for depression*. Retrieved February 10, 2012, from www.health.harvard.edu/blog/new-insights-into-treatment-resistant-depression-20101209891

5 CDC Features - Preventing Suicide. (n.d.). *Centers for Disease Control and Prevention*. Retrieved March 13, 2012, from http://www.cdc.gov/Features/PreventingSuicide/

6 NIMH · Suicide in the U.S.: Statistics and Prevention. (n.d.). *NIMH · Home*. Retrieved March 13, 2012, from http://www.nimh.nih.gov/health/publications/suicide-in-the-us-statistics-and-prevention/index.shtml

7 Nutt, D. (n.d.). Estimating Drug Harms - A risky business?. *Crime and Justice*. Retrieved February 22, 2012, from www.crimeandjustice.org.uk/opus1714/Estimating_drug_harms.pdf

8 Miller, G. (n.d.). Is Pharma Running Out of Brainy Ideas? . *Science* . Retrieved March 13, 2012, from http://www.sciencemag.org/content/329/5991/502.summary

9 Lierberman, J. (n.d.). Medscape: Medscape Access. *Medscape: Medscape Access*. Retrieved March 13, 2012, from http://www.medscape.com/viewarticle/721671

10 Mental Health America: Electroconvulsive Therapy (ECT). (n.d.). *Mental Health America: Welcome*. Retrieved March 16, 2012, from http://www.nmha.org/go/information/get-info/treatment/electroconvulsive-therapy-ect

11 Lowry, F. (n.d.). Medscape: Medscape Access. *Medscape: Medscape Access*. Retrieved March 15, 2012, from http://www.medscape.com/viewarticle/736697

12 Gardner, A. (n.d.). FDA mulls future of electroshock therapy - CNN.com. *CNN.com - Breaking News, U.S., World, Weather, Entertainment & Video News*. Retrieved March 13, 2012, from http://www.cnn.com/2011/HEALTH/01/26/

13 Deep brain stimulation search results. (n.d.). *clinicaltrials.gov*. Retrieved February 20, 2012, from clinicaltrials.gov/ct2/results?term=deep brain stimulation&pg=3

14 New Guidelines Issued for Deep Brain Stimulation in Parkinson's - Drugs.com MedNews. (n.d.).*Drugs.com | Prescription Drug Information, Interactions & Side Effects*. Retrieved March 13, 2012, from http://www.drugs.com/news/new-guidelines-issued-deep-brain-stimulation-parkinson-s-27279.html

15 Parkinson's Disease Information Page: National Institute of Neurological Disorders and Stroke (NINDS). (n.d.). *National Institute of Neurological Disorders and Stroke (NINDS)*. Retrieved March 15, 2012, from http://www.ninds.nih.gov/disorders/parkinsons_disease/parkinsons_disease.htm

16 Florian, K. (2007). Modulation by dopamine of human basal ganglia involvement in feedback control of movement . *Cell*, *17*(15). Retrieved March 12, 2012, from http://www.cell.com/current-biology/abstract/S0960-9822(07)01506-0

17 Listing of CDRH Humanitarian Device Exemptions. (n.d.). *U S Food and Drug Administration Home Page*. Retrieved March 12, 2012, from http://www.fda.gov/medicaldevices/productsandmedicalprocedures/deviceapprovalsandclearances/hdeapprovals/ucm161827.htm

18 Prozac Package Insert. (n.d.).*lilly.com*. Retrieved March 10, 2012, from pi.lilly.com/us/prozac.pdf

19 Humanitarian Device Exemption. (n.d.). *U S Food and Drug Administration Home Page*. Retrieved March 3, 2012, from http://www.fda.gov/MedicalDevices/Dev

20 Reclaim Deep Brain Stimulation Clinical Study for Treatment-Resistant Depression - Full Text View - ClinicalTrials.gov. (n.d.). *Home - ClinicalTrials.gov*. Retrieved March 13, 2012, from http://clinicaltrials.gov/ct2/show/NCT00837486

21 Lozano, A., Giacobbe, P., Mayberg, H., & al., e. (2009). A multicenter pilot study of subcallosal cingulate area deep brain stimulation for treatment-resistant depression Clinical article. *Journal of Neurosurgery*, *116*. Retrieved March 12, 2012, from http://thejns.org/doi/full/10.3171/2011.

22 Lozano, A., Mayberg, H., Kennedy, S., & al., e. (2011). Deep Brain Stimulation for Treatment-Resistant Depression: Follow-Up After 3 to 6 Years. *American Journal of Psychiatry*,*168*. Retrieved March 12, 2012, from http://ajp.psychiatryonline.org/article.aspx?articleID=106984

Regenerative Medicine defines the Future of Organ Transplantation

A look at the current capabilities and future possibilities

BY RICARDO SOLORZANO

There are currently 122,843 patients on the waiting list for organs in the U.S. Specifically, there are 97,267 patients waiting for kidneys and 16,868 waiting for livers.[1] The wait for organs is a dilemma shared by many around the world. Even if these patients were to find a donor, they would still have to take toxic immunosuppressant drugs that have the potential to significantly hamper the quality of the patients' lives. To combat these difficulties, scientists and physicians in the field of regenerative medicine have been striving to engineer replacement organs for patients in need. While there is still much more to be investigated, recent discoveries in regenerative medicine have produced remarkable results. Engineered organs could soon become a viable treatment for patients with organ failure.[2]

HOW DOES ONE ENGINEER AN ORGAN?

When scientists were first attempting to engineer an organ, they had to consider the basic structure of tissue. Scientists have long known that tissues are made of cells. However, during the mid-twentieth century, they also found that tissues have a basic scaffold, an extracellular matrix (ECM), which holds cells together and promotes cell growth.[3] The initial challenge for scientists and engineers was to find the right type of material that could support cells and promote them to grow into tissues just as native ECM does. They found that synthetic polymers, such as poly-glycolic acid (PGA) and collagen to name a few, were viable replicas for native ECM.[4] With further research, scientists also found that they did not even have to synthetically produce ECM scaffolds. Instead, they could take donor tissue and wash away the living cells with detergents to leave the native ECM. Since matrices are typically identical among humans, the body would not reject the foreign transplanted ECM scaffold.[5]

THE ENGINEERED BLADDERS TOOK ABOUT 7-8 WEEKS AFTER BIOPSY TO BE READY FOR IMPLANTATION. ONCE READY, LUKE RECEIVED HIS TRANSPLANT AND AFTER THREE MONTHS, HE REGAINED NORMAL UROLOGIC FUNCTION.

The second challenge for scientists was to find ways to harvest specific cell types in large quantities for transplantation. Although some cell types can continuously divide in the body, when placed on a dish, they lose their high regenerative capacities. Scientists discovered that progenitor cells residing within certain organs could be used to overcome this limitation. In the body, progenitor cells are often responsible for tissue regeneration due to tissue injury, aging, and natural turnover. By isolating specific progenitor cells and by figuring out the conditions of differentiation and of self-renewal, scientists have made it possible to overcome the obstacles of in vitro survival for a few cell types. These harvested cells are advantageous because they can be transplanted into patients without the fear of rejection, since they are from the patient's own cells.[4]

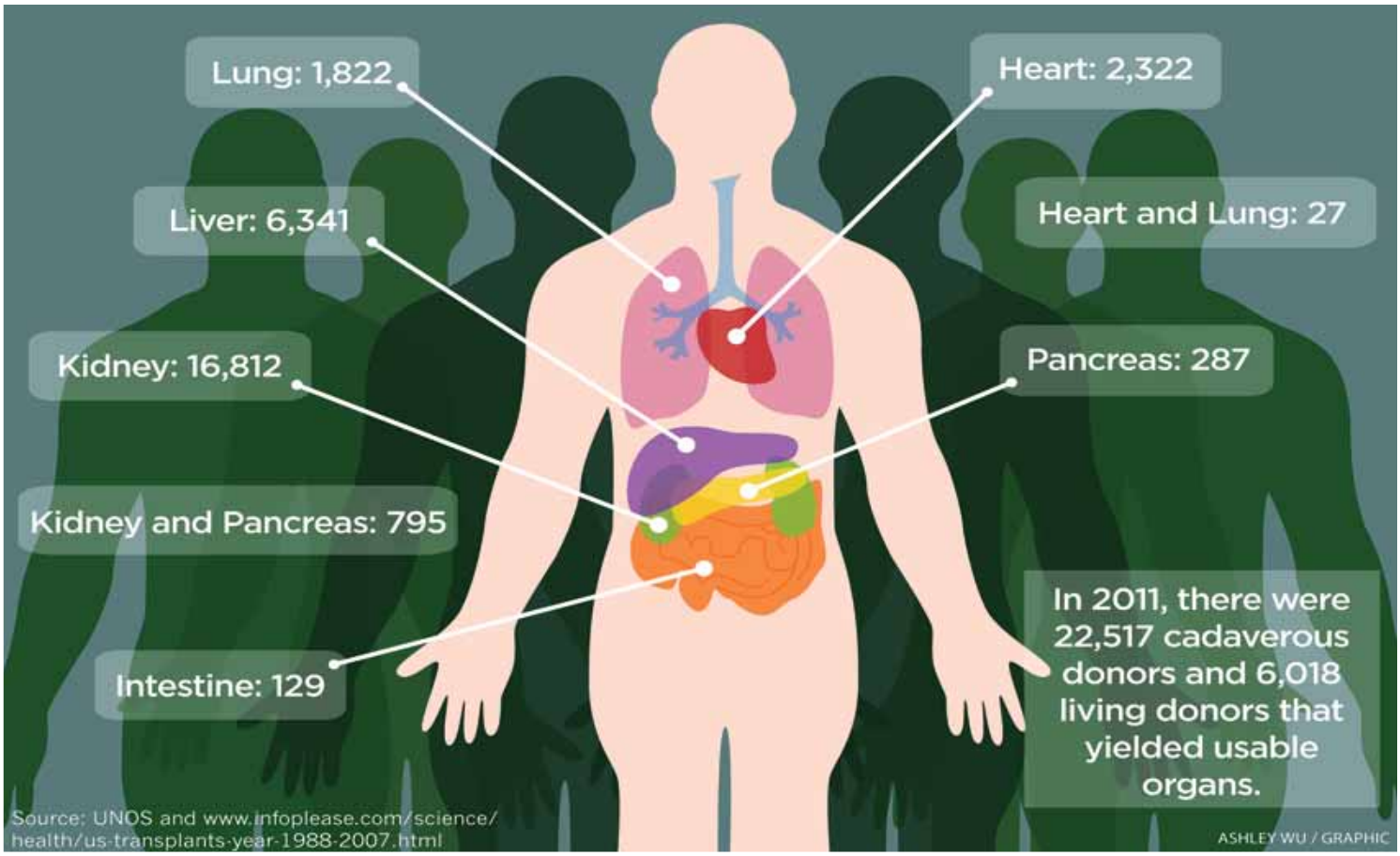
Having overcome these challenges, scientists began to combine either synthetic or native ECMs with a patient's own progenitor cell population to create tissues and ultimately organs.[6]

TREATING PATIENTS WITH ENGINEERED ORGANS

After successfully testing engineered organs in vitro, it was time for in vivo transplantation. One of the first patients to undergo engineered organ transplantation was Luke Masalla. Luke was born with spina bifida, a birth defect in which the backbone and spinal canal do not close before birth. Because of this, Luke received over a dozen surgeries while growing up and had bladder failure by the age of 10. The standard procedure at the time was a bowel-for-bladder replacement, which involves replacing the diseased bladder with a grafted segment from a patient's own bowel. This procedure causes several side effects, including reoccurring kidney stones in the long run. Dr. Anthony Atala, urologist and director of the Wake Forest Institute for Regenerative Medicine, found it senseless to perform this procedure on a child. He knew that there would be severe complications for Luke in the future.[7] Dr. Atala proposed a novel solution using regenerative medicine. He undertook combining a biomaterial scaffold and Luke's own progenitor cells to engineer a new bladder. His team first produced biodegradable composite ECM scaffolds made of PGA and collagen that closely resemble cloth material. The polymer squares were sutured together with biodegradable glue and shaped like a bladder. Then, a biopsy of Luke's bladder, the size of a postage stamp, was taken and separated into its two particular cell types, urothelial and muscle cells. Once the cells were grown, muscle cells were poured onto the exterior surface of the synthetic ECM scaffold and urothelial cells were poured onto the interior. As Dr. Atala describes, the process is "much like baking a layered cake." The construct was placed in a sealed container filled with media and growth factors and allowed to settle for 3-4 days. The engineered bladders took about 7-8 weeks after biopsy to be ready for implantation. Once ready, Luke received his transplant and after three months, he regained normal urologic function. After this surgery, Luke was able to start to live a normal life and has come to say that this surgery saved his life.[8,9]

The successful treatment prompted physicians around the world to use similar techniques to solve other complicated diseases. In Barcelona, Spain, Claudia Castillo, a 30-year-old mother of two, was hospitalized due to an acute shortness of breath that did not allow her to carry out simple domestic tasks and care for her children. Doctors diagnosed her with a collapsed left bronchi that was caused from a severe case of pulmonary tuberculosis. At the time, the only viable option

TRANSPLANTS PERFORMED IN THE UNITED STATES, 2011



was to remove her left lung, a procedure that would result in serious side effects and even the possibility of death. Dr. Paolo Macchiarini, thoracic surgeon and chairman at the Hospital Clinic of Barcelona, Spain, and his team carried out a procedure similar to that of Dr. Atala's. This time native ECM was used. His team utilized a seven-centimeter tracheal segment that was donated by a 51-year-old transplant donor. The trachea was decellularized over a six-week period to remove all donor cells, leaving only the native ECM scaffold. Progenitor cells were then taken from Claudia's own bone marrow and differentiated into cartilage cells. These grown cells were seeded onto the scaffold and allowed to grow for four days. When the engineered trachea was ready, Dr. Macchinarini transplanted it into Claudia. Just after a few days the transplant was indistinguishable from the right bronchi and Claudia was able to return home to continue a normal life.[3,10]

These two success stories depict the promise that engineered organs have to treat organ failure. The fact that both Luke and Claudia were able to regain full functionality of their diseased body parts without having to take immunosuppressive drugs is a significant breakthrough for regenerative medicine. It should be noted, though, that both of these organs were hollow. The level of complexity significantly rises when trying to engineer solid organs such as hearts, kidneys, and livers.[11]

THE NEXT STEP: SOLID ORGANS

Several challenges remain until fully functional solid organs are realized. The transplanted organs in the previous two cases were implanted without the reconstruction of blood vessel networks. The only reason they survived was because their thinness allowed for surrounding nutrients and oxygen to diffuse into the tissue. Solid engineered organs need a network of blood vessels in order to survive after transplantation - they bring essential oxygen and nutrients to cells deep within the tissue. Therefore, this vascularization is essential for solid organ construction.[12] Another major challenge is to create a synthetic 3D scaffold that can reproduce signals through which cells interact with one another and with the ECM. A Ideally, biomaterials in regenerative medicine should mimic the biological and mechanical functions of native ECM that is found in the body. Native ECM brings cells together to form tissues and communicates with cells to helps regulate cellular phenotype. However, no 3D engineered matrix has been able to successfully perform these specified functions.[12]

Researchers are striving to resolve these problems so that solid organ construction can become a reality. Jonathan A. Epstein, Director of the Penn Institute of Regenerative Medicine Program in Regenerative Cardiovascular Biology, has been playing a critical role in understanding the development of blood vessels. His lab has discovered new genes that play pivotal roles in guiding the growth and patterning of both

large and small vessels.[13] Furthermore, David Mooney, Professor at Wyss Institute for Biologically Inspired Engineering at Harvard University, and his lab have been attempting to create 3-D scaffolds that provide mechanical support while directing proliferation, differentiation, and gene expression.[14] Although great strides have been made in the field of regenerative medicine, decades remain before this technology is fully developed.[8] If researchers are able to meet these challenges, regenerative medicine has the potential to relieve individuals who may need organ transplants in the future as well the thousands that wait today.

References

1 U.S. Department of Health & Human Services(2012). Overall by Organ. Organ Procurement and Transplantation Network. Retreived on Feburary 24,2012 from http://optn.transplant.hrsa.gov/latestData/rptData.asp
2 PBS (January 26, 2011) Replacing Body Parts. NOVA. Retrieved on February 12, 2012 from http://www.pbs.org/wgbh/nova/body/replacing-body-parts.html
3 Piez KA(1997) History of Extracellular Matrix: a personal view. *Matrix Biology.* Aug;16(3):85-92.
4 Atala, Anthony. (2009). Engineering Organs. Current Opinion in Biotechnology. Vol. 20, Iss. 5
5 Gilbert, Thomas et al. (2006) Decellurization of tissue and organs. Biomaterials, Vol. 27, Iss. 19.
6 Atala, Anthony. (2009) Anthony Atala on growing new organs. TEDMED, San Diego, Ca. Oct.
7 Parson, Ann (July, 11, 2006) A Tissue Engineer Sows Cells and Grows Organs. The New York Times. Retrieved on February 17, 2012 from http://www.nytimes.com/2006/07/11/health/11prof.html?pagewanted=1
8 PBS (January 26, 2011) Replacing Body Parts. NOVA. Retrieved on February 12, 2012 from http://www.pbs.org/wgbh/nova/body/replacing-body-parts.html
9 Atala, et al. (2006) Tissue-engineered autologous bladders for patients needing cystolplasty. Lancet, Vol 367, Iss. 9518. 1241-1246
10 Benjamin, C., et al. (2010) Regenerative Medicine: Basic Concepts, Current Status, and Future Applications. Journal of Investigative Medicine: Vol. 58, Issue 7. 849-858.
11 Adult Stem Cell Breakthrough: First Tissue-Engineered Trachea Successfully Transplanted. (Nov. 19, 2008) Science Daily. Retrieved on Feburary 17, 2012 from http://www.sciencedaily.com/releases/2008/11/081119092939.htm
12 Baptista, Pedro et al. (2008) Whole Organ Decellularization – A Tool for Bioscaffold Fabrication and Organ Bioengineering. 31st Annual International Conference of IEEE EMBS. Minneapolis, Minnesota, USA. Sept. 2-8, 2008.
13 Penn Institute of Regenerative Medicine (2012) IRM Programs – Regnerative Cardiovasuclar Biology and Cell and Tissue Engineering Programs. Retrieved on Feburary 24, 2012 from http://irm.upenn.edu/
14 The Mooney Lab(2012) Harvard Engineering and Applied Science. Retrieved on March 12, 2012 from http://www.seas.harvard.edu/mooneylab

Just Discrimination or *Just* Discrimination

Explicating bioethical dilemmas in organ transplantation

BY SALMON KADIVAR

Rivera recounts in her blog: "So you mean to tell me that as a doctor, you are not recommending the transplant, and when her kidneys fail in six months to a year, you want me to let her die because she is mentally retarded? There is no other medical reason for her not to have this transplant other than [that] she is mentally retarded!"

Imagine, as a parent, waiting impatiently at a hospital for treatment of your three-year-old's stomach ache, only to discover that your daughter requires a kidney transplant. This initial painful revelation is superseded by another trial— she does not qualify as a transplant recipient and will not be placed on the kidney transplant list; a list that already holds over 90,000 patients. This tragic situation faced Chrissy Rivera; her three-year-old daughter lives with Wolf-Hirschhorn syndrome, a disease that is estimated to occur every 1 in 50,000 births and causes growth and mental retardation, muscle hypotonia, seizures, and heart defects.[1,2]

Rivera claims that her daughter was denied a kidney transplant because of her mental disabilities and that the doctors would not perform a kidney transplant even if the parents themselves were eligible to donate a kidney. Soon after this story surfaced, many news agencies such as CNN and ABC News tried to address the issue of whether the doctor has the right to say no. Infuriated readers and friends of the family established a petition demanding that the Children's Hospital of Philadelphia (CHOP) allow the surgery, receiving over 40,000 signatures. Due to patient confidentiality rights, CHOP is not allowed to disclose information regarding its decisions or speak to the public about the case. However, CHOP has contacted the Rivera family to set up a new appointment to discuss the ongoing dilemma. While many readers may be unsatisfied with CHOP's decision, the truth is that cases like this are occurring all over the country and are not as straightforward as many individuals believe them to be.

When making life-changing decisions, doctors are meant to consider three of the main principles that govern medical science: autonomy, beneficence (*Salus aegroti suprema lex*) and justice. Autonomy in medical ethics refers to the principle that a person should be allowed to make his or her own decisions regarding their own life. However, there aren't clearly defined boundaries to autonomy. For example, persons who don't have full mental capacity are treated according to assumptions of their best interests. So if the child has a mental disability there is confusion as to

When making life-changing decisions, doctors are meant to consider three of the main principles that govern medical science: autonomy, beneficence (Salus aegroti suprema lex) and justice.

whose autonomy is in command: is it the parents', the doctor's, the hospital's, or the law's?

Thus with autonomy comes beneficence, which states that a doctor should act in the best interest of the patient, whereas justice concerns the allocation of rare supplies of health resources and treatment determination.[2] Ideally, a doctor's goal is to help everyone, but when there are limited supplies of a drug, treatment, or cure one must decide who has the best chance of surviving and what constitutes a normal life. As a result, doctors must be mindful of the ethical decisions they make, taking into account the patient, the diagnosis, and the prognosis. For example, determining who should be placed on the kidney transplant list depends on factors such as organ availability, tissue matching, and conditions that would inhibit a transplanted organ's viability. A person with other medical conditions such as a mental disorder produces further hurdles. Doctors must ask important questions when considering the procedure. Will this person be able to handle the necessary medication? Will the medication have an impact on the patient's current neurological state? Will the patient require assistance with administration of medicine? Dr. Khadijeh Kadivar at Yale-New Haven Hospital explained that "many transplant teams look at patients and believe that the organs should be given to individuals whose lives can be prolonged the longest and who live in the healthiest manner possible. In doing so, some bias does occur, but it also has to do with a doctor taking into account a patient's history to ensure that complications are minimized." This is where justice, a third principal of medical bioethics, takes charge.

Justice is the moral obligation of a doctor to act on the basis of fair decision-making between competing claims. For example, the Rivera family wants their daughter to get treated as they have the right under autonomy, but the doctor did not believe that the candidate is suitable under the rules of beneficence due to a lack of supplies—this is where justice plays a role. Justice demands that patients be treated equally and have equal access to treatment. Many doctors believe that they have to choose which patients are the best recipients for organ transplants, while others claim that this 'bias' may not be legal.

As the question of legality arises, some wonder if doctors often ignore the Americans with Disabilities Act that prevents hospitals from discriminating against patients for treatment based on their disability. Despite the law, such decisions are not so easily made since "each case varies and some people with severe mental disabilities may not be able to handle the intensity of treatment," says Dr. Kadivar. Professor of Medical Ethics and Health Policy at the University of Pennsylvania Dr. Art Caplan states, "there are reasons why anyone with an intellectual or physical disability might not be considered a good candidate for a transplant. But those reasons, to be ethical, have to be linked to the chance of making the transplant succeed. Otherwise they are not reasons, they are only biases."[1]

While some doctors hesitate in donating organs to mentally disabled people based on health concerns and their fear that they will not be able to survive, there is some dissent within the scientific community. Marilee Martens, program director of Nisonger Center at The Ohio State University conducted a study to compare organ transplantation and mental retardation to test the difference of survival rate compared to the general population. To the surprise of some, the study found that the one to three year survival rate of mentally disabled people who received organ transplants was 100% and 90%.[4] While this finding is promising, some find it upsetting that the mentally disabled may not be getting full treatment as a result of previous bias. The National Work Group on Disability and Transplantation conducted a survey and found that 80% of people who are mentally retarded are discriminated against when it comes to transplant options.[4] Even more shocking is that the Joint Commission on Accreditation of Healthcare has expressed concern that many people with disabilities are denied evaluation and referral for transplantation and face hurdles in being assessed for, wait-listed, and eventually receiving donor organs.[5] These findings are worrisome, and the scientific community must re-evaluate the standards that have been established.

> "Due to patient confidentiality rights, CHOP is not allowed to disclose information regarding its decisions or speak to the public about the case. However, CHOP has contacted the Rivera family to set up a new appointment to discuss the ongoing dilemma."

Healthcare professionals are meant to act in the best interest of their patients, while balancing the responsibilities of distributing limited resources. Some patients will simply not be able to manage the complications of an organ transplant and a doctor should talk about these concerns with the family to make an appropriate decision. "Even though a doctor must take into consideration possible complications, he or she cannot rule out a patient from receiving a transplant simply because of a mental disability," according to Dr. Kadivar. Legally, everyone has the right to a transplant as long as it will prolong their life and give them another chance at survival. However, we cannot be certain that Rivera's daughter was denied a transplant because of her disability. There may be other medical complications we are not aware of, such as antibody deficiencies associated with Wolf-Hirschhorn syndrome that could lead to a negative outcome. Due to the complexity of these cases, greater transparency and dialogue as well as a systemized but flexible process of decision-making is necessary among doctors, patients, and bioethicists to ensure it's *just* discrimination.

References

1 Caplan, Art. (2012). Serious Issues in disabled girl transplant, *Vitals on msnbc.com*. Retrieved February 13, 2012 from http://vitals.msnbc.msn.com/_news/2012/01/17/10175611-serious-issues-in-disabled-girl-transplant-case

2 Battaglia A, Carey JC. Wolf-Hirschhorn syndrome and Pitt-Rogers-Danks syndrome. Am J Med Genet. 1998 Feb 17;75(5):541.

3 Beauchamp TL, Childress JF. (1994) Principles of Biomedical Ethics. *Oxford University Press, New York* 4th edition.

4 Marilee A. Martens, Linda Jones, Steven Reiss. (2006). Organ transplantation, organ donation and mental retardation. Volume 10, 658.664

5 Joint Commission on Accreditation of Healthcare Organizations. Healthcare at the crossroads: Strategies for narrowing the organ donation gap and protecting patients. 2004: 1–46

Elections and Emotions

The Framing Effect in (Political) Decision Making and Behavior

BY ANUP BHATTACHARYA

It is impossible to avoid the political ads incessantly airing on television. A voter may think that his or her mind is made up in terms of whom to vote for, though chances are that one negative ad before voting could change this decision. As a result, political campaigns often seek to influence our emotions in the hopes of winning our vote. The framing effect is the phenomenon in which subjective stimuli cloud our decision making-abilities.[1] It may be surprising to find out a brain's allegiance is not quite so certain, so it is very likely that one's brain will do a couple flip-flops of its own. Studies have shown that political ideologies and identities are often given root back in the control center in the central nervous system.[2] Dopamine, a catecholamine neurotransmitter, is influential in affecting our reward-driven learning. Dopamine has been shown to directly affect decision making through its intricate relationship with our emotions.[3]

The framing effect is a phenomenon in which people make irrational decisions based on whether a scenario is framed to focus on losses or gains. Biologically speaking, the associations made in the brain when responding to a negative choice cloud our natural cognitive ability and thereby lead us to potentially choose an unwise outcome.[1] Studies on the framing effect suggest that emotional shocks significantly affect our decision making, whether we invite them to or not. Dopamine is the critical neurotransmitter that plays a key role in determining our mood. It has been found to increase our attention and alter our expectations in specific scenarios. Furthermore, people are more likely to make irrational decisions when they have high levels of dopamine in the brain. Through dopamine's intricate relationship with emotions and subjective understanding, together with the emotional control center amygdala, our emotional responses influence our decisions. The existence of emotionally charged events and memories is given root in the amygdala.

Other studies have looked into specific emotional states and how they affect our decision making. In one study, participants were divided into two separate groups, and each group was instructed to write about a recent incident that triggered either anger or fear. Participants were then instructed to assume the role of a sales manager at a large equity firm and were given the task of choosing between two candidates for an opening in the firm. Their decisions were based off contrived reports concerning the performance of each prospective candidate over the past few years. After this task, the participants were then intentionally informed that the candidate chosen ended up performing terribly, regardless of which candidate was chosen. Investigators found that those participants who had been stimulated to think about anger were significantly more likely to continue supporting their initial candidate and were less willing to admit to a mistake as compared to those in the fear-conditioned group.[5] Furthermore, it was found that patients who exhibited anger sustained higher dopamine levels for extended periods of time. This study links excessive emotional arousal with higher dopamine levels and, in turn, the clouding of emotions.

As a student you are more likely to be choosing between a Republican and Democratic presidential candidate in the coming year. Campaign chairmen realize that winning an election is more firmly based in presentation (the framing effect) of the candidate than what he or she stands for.[4] Here lies the campaign manager's most important role: should campaigns run ads that promote their candidate or attack the opponent? Perhaps the better question is: which would appeal to voters more? Studies have shown that consistent negative advertising can help win a primary battle but in the long run the candidate's overall message gets distorted. The larger battle is lost here and overall voter appeal and likeability will diminish. Yet, it has been well documented that a well-timed negative ad will in most cases turn the voter against the person featured in the negative ad if it is viewed within a few hours prior to voting. So perhaps the best choice would be to run a mostly positive campaign with a few negative ads interspersed throughout the election.

So the next time you are trying to make any serious decision, be aware of the subtle effects of emotion that influence your ultimate decision. As stated, this all has a foundation at the molecular level where your dopamine receptors are likely to be highly activated. If you want to make an entirely unbiased decision, one based entirely on reason, try to cloud out associations, subtleties, and emotions, and more often than not, you will come out with a decision you will not regret in hindsight.

References

1. Choi, C (2006, August, 6). 'Framing effect' influences decisions. retrieved February 20 2012, from MSNBC Web Site: http://www.msnbc.msn.com/id/14170927/ns/technology_and_science-science/t/framing-effect-influences-decisions.
2. Choi, C (2011). Politics on the Brain: Scans Show Whether You Lean Left or Right. LiveScience, . retrieved March 1, 2012, from http://www.livescience.com/13608-brain-political-ideology-liberal-conservative.html
3. Hutchings, C (2009, October 28). The Straight Dope: The Role of Dopamine in the Brain. The New York Times.
4. London, S How the Media Frames Political Issues. (n.d) retrieved March 3 2012, from Scott London Web Site: http://www.scottlondon.com/reports/frames.html
5. Palmquist, M (2009). How Emotions Affect Decision Making. Strategy + Business, 57. retrieved February 20, 2012, from http://www.strategy-business.com/article/09413d?gko=25b9b

Stimulants: The Not-So-Smart Pills?

BY SHEILA SHANMUGAN

With admissions to colleges, graduate schools, and medical schools more competitive than ever before, stimulant use among students is becoming an all-too-common trend in schools and across college campuses. We have all heard of the high school senior who took a dose of his sister's ADHD medication to earn a higher SAT score; of the college sophomore who bought Adderall® from her roommate to ace her organic chemistry final; of the premed who traded a few meal swipes for a dose of his friend's Ritalin® the day of his MCAT. The pattern is undeniable. The percentage of college students who report having used stimulants in the past year for non-medical purposes is alarming. Up to 35.5% of college students are estimated to have taken stimulants without a prescription in the past year.[1] Studies have found that weekly rates of non-medical stimulant use among these students are as high as 15.5%.[2] Not surprisingly, the strongest predictor of illicit stimulant use among college students is competitiveness of admissions criteria.[3,4]

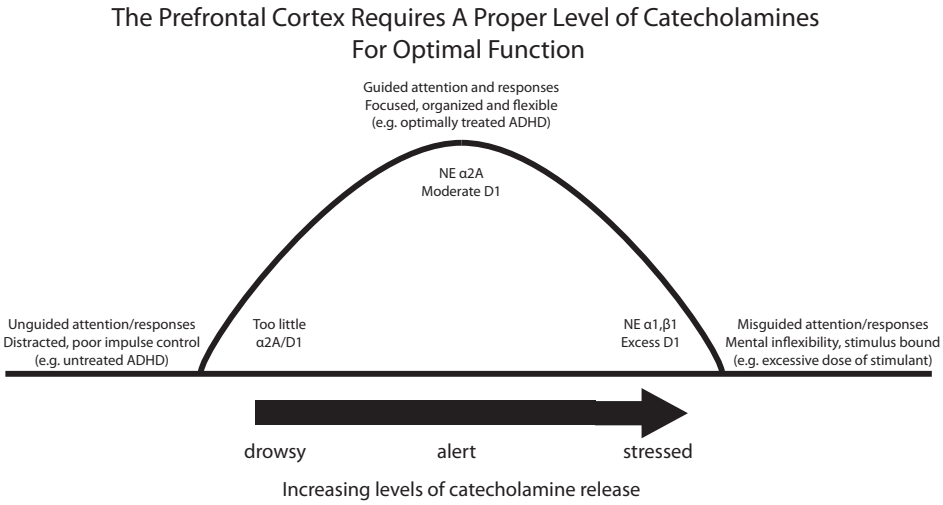
But the question remains, are these "smart pills" really offering students the edge they think

they are gaining? The true answer, according to hard science, is that stimulant use may actually worsen short-term cognitive performance.

Stimulants, such as methylphenidate and amphetamine (known more commonly by their brand names, Ritalin® and Adderall® respectively), are the most commonly prescribed treatments for patients with Attention Deficit Hyperactivity Disorder (ADHD). Individuals diagnosed with ADHD have difficulties with tasks that involve sustained attention and focus, which for the everyday college student translates to studying for exams, paying attention in lectures, staying organized, and even following casual conversations. In individuals with ADHD, stimulant medications, when taken as directed, alleviate attentional difficulties and allow for normal cognitive functioning on par with the average college student.[5]

The majority of college students, however, do not have ADHD, which is to say that their capacity to complete tasks requiring prolonged focus is not impaired in any significant manner, biochemically speaking. Whether they use this capacity effectively turns out to be entirely a matter of motivation rather than brain chemistry. For these students, stimulant use may in fact pose effects contrary to what its users may believe it to as far as cognitive ability is concerned.[5] Although stimulants may offer the user the feeling of enhanced focus through heightened alertness and an augmented sense of motivation, research has shown that prescription stimulants in healthy individuals may actually worsen performance on tasks requiring critical thinking and sustained attention.[4]

The explanation for the counter effects of stimulants in healthy versus attentionally-impaired individuals lies at the neurochemical level. The region of the brain underlying symptoms of ADHD, and consequently the region of the brain targeted by prescription stimulants, is the prefrontal cortex (PFC). The PFC lies at the anterior of the frontal lobes and is critical for executive function, a specific domain of cognition. Executive functions include tasks requiring sustained attention, focus, organization, planning and inhibition of distracting information. The neurochemical environment, specifically levels of the neurotransmitters dopamine (DA) and norepinephrine (NE), in this region determines an individual's functioning in these cognitive realms. Individuals with ADHD have insufficient levels of these neurotransmitters within this region of the brain. Stimulants alleviate symptoms of inattention in these individuals by increasing levels of DA and NE in the PFC. In healthy individuals who already have sufficient concentrations of these neurotransmitters, stimulant use causes neurotransmitters to reach concentrations at which they begin to impair cognitive functioning within the PFC and impose mental inflexibilities.[5]



Source: J. Pediatr. 2009 May 1; 154(5): I-S43

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Excessive neurotransmitter concentrations result in executive dysfunction because the dependence of PFC function on neurotransmitter levels exhibits an inverted U-shaped dose response curve. When present at ideal levels, as in healthy individuals, NE maintains network connectivity (i.e. keeps a certain piece of information in mind) through the stimulation of postsynaptic a_{2A}-receptors, while DA inhibits inappropriate stimuli through stimulation of D_1 receptors. Insufficient activation of these receptors at lower concentrations can lead to symptoms of executive dysfunction, such as fatigue, distractibility and impulsivity as seen in individuals with ADHD. When neurotransmitter concentrations exceed ideal levels, as in healthy individuals under stimulant effects, receptor stimulation is altered. The excessive D_1 stimulation and inappropriate NE a_1 and b_1 stimulation that occur at elevated neurotransmitter concentrations can cause executive dysfunction, such as mental inflexibility and the inability to think critically.[5]

Interestingly, the contrasting effects of stimulants can be monitored in real-time through brain imaging. Using functional magnetic resonance imaging (fMRI), researchers are able to discern which parts of the brain are being activated as well as the extent of activation in those regions when a person is performing a particular task. Several fMRI studies to date have investigated the effects of stimulants on PFC activation. These studies typically ask subjects to perform tasks such as the n-back task, which requires them to keep certain information "on line" for appropriate recall, while inhibiting extraneous information. Individuals with ADHD not only perform worse than healthy individuals on such tasks, but also show greater activation in the PFC while doing so as a result of having to work harder to stay focused and inhibit distractions. Interestingly, when given a stimulant, PFC activation in individuals with ADHD decreases to levels seen in healthy individuals, while PFC activation in healthy individuals increases to levels seen in untreated individuals with ADHD.[6,8] These results suggest that stimulant use in healthy individuals over-activates the PFC to the point of executive dysfunction.

While there are a variety of non-medical reasons why college students use stimulants, several studies have shown that the most common reasons are related to cognitive enhancement, namely the desire to improve concentration, attention and intellectual performance.[4] What most students do not realize, however, is that, for them, stimulants are likely to have the opposite effect of what is intended. So the next time a friend considers reaching for a pill before a big exam, let him know that he might end up behind rather than ahead of the curve.

References

1 Low, K. G., & Gendaszek, A. E. (2002). Illicit use of psychostimulants among college students: A preliminary study. *Psychology, Health & Medicine, 7*, 283–287. doi:10.1080/13548500220139386

2 White, B. P., Becker-Blease, K. A., & Grace-Bishop, K. (2006). Stimulant medication use, misuse, and abuse in an undergraduate and graduate student sample. *Journal of American College Health : J of ACH, 54*(5), 261-268. doi:10.3200/JACH.54.5.261-268

3 McCabe, S. E., Knight, J. R., Teter, C. J., & Wechsler, H. (2005). Non-medical use of prescription stimulants among US college students: Prevalence and correlates from a national survey. *Addiction (Abingdon, England), 100*(1), 96-106. doi:10.1111/j.1360-0443.2005.00944.

4 Smith, M. E., & Farah, M. J. (2011). Are prescription stimulants "smart pills"? the epidemiology and cognitive neuroscience of prescription stimulant use by normal healthy individuals. *Psychological Bulletin, 137*(5), 717-741. doi:10.1037/a0023825

5 Arnsten, A. F. (2009). The emerging neurobiology of attention deficit hyperactivity disorder: The key role of the prefrontal association cortex. *The Journal of Pediatrics, 154*(5), I-S43. doi:10.1016/j.jpeds.2009.01.018

6 Sheridan, M. A., Hinshaw, S., & D'Esposito, M. (2010). Stimulant medication and prefrontal functional connectivity during working memory in ADHD: A preliminary report. *Journal of Attention Disorders, 14*(1), 69-78. doi:10.1177/1087054709347444

7 Tipper, C. M., Cairo, T. A., Woodward, T. S., Phillips, A. G., Liddle, P. F., & Ngan, E. T. (2005). Processing efficiency of a verbal working memory system is modulated by amphetamine: An fMRI investigation. *Psychopharmacology, 180*(4), 634-643. doi:10.1007/s00213-005-0025-4

8 Willson, M. C., Wilman, A. H., Bell, E. C., Asghar, S. J., & Silverstone, P. H. (2004). Dextroamphetamine causes a change in regional brain activity in vivo during cognitive tasks: A functional magnetic resonance imaging study of blood oxygen level-dependent response. *Biological Psychiatry, 56*(4), 284-291. doi:10.1016/j.biopsych.2004.06.008