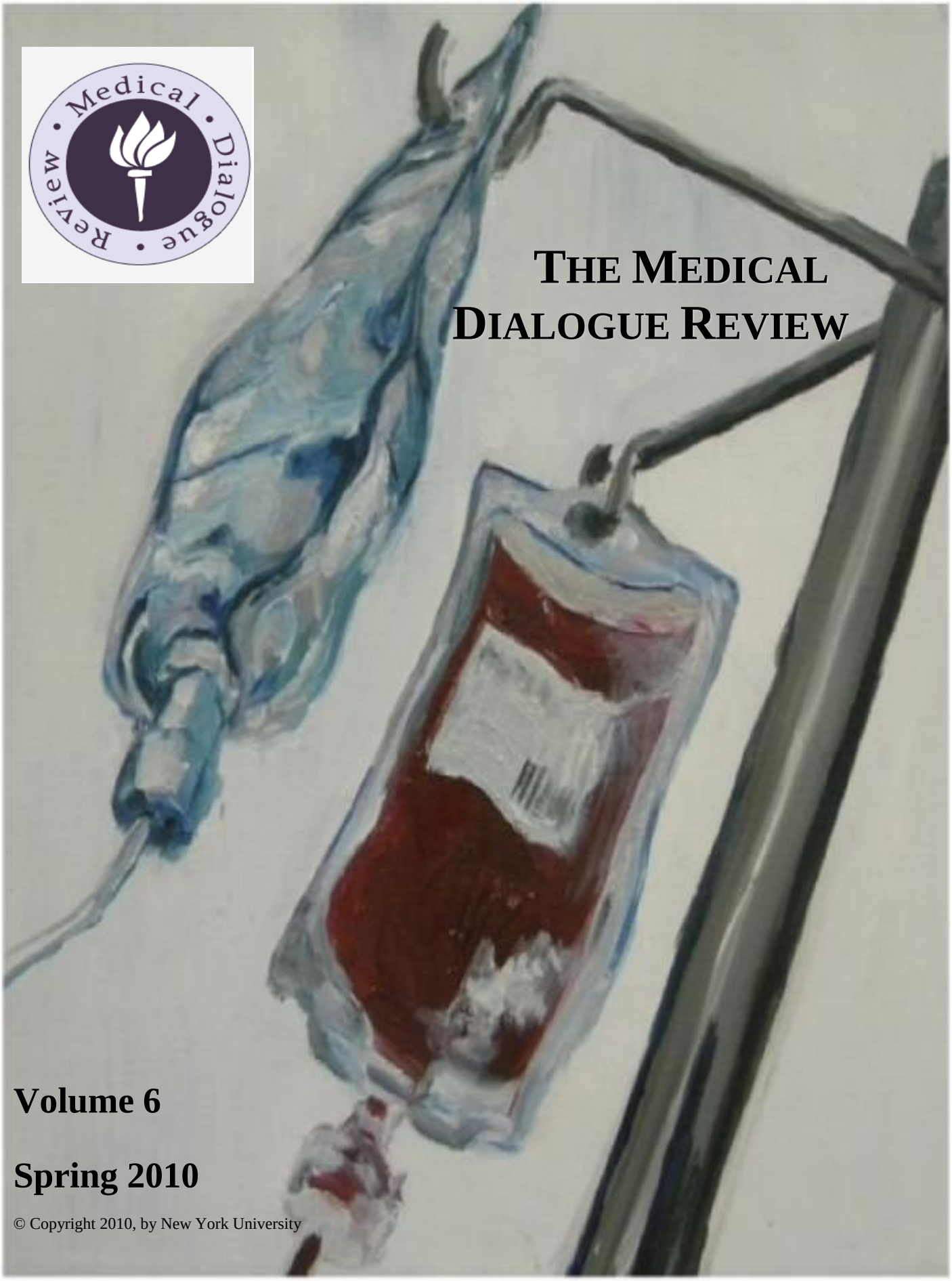

The Medical Dialogue Review

Volume 6

Spring 2010

Medical Dialogue Review
An undergraduate medical journal

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Letter from the Editors:

Dear MDR Reader,

We are proud to present the sixth edition of Medical Dialogue Review! We have more than succeeded our goal to bring together an amalgam of opinions and expressions that relate to the sciences and emphasize that science should not be viewed as an isolated discipline. It is the belief of MDR writers and reviewers that science, even as a general, widely encompassing field of study, is fundamentally intertwined with numerous other aspects of study and experience, from the political implications of a scientific development to how a health professional tells a joke. With this in mind, we always look to include a myriad of topics and opinions within the review.

Each issue contains its own set of unique and powerful articles written by enthusiastic individuals who are passionate about a specific cause. Some writers choose to focus on domestic issues, while others look abroad to topics on global health; some will delve into great detail about specific disorders and diseases while others choose to tackle the state of a constantly changing healthcare system. Whatever the issue at hand may be, each article is characterized by the thought and sincerity involved in its conception.

Thank you so much for all of your support. We hope that the contents of this edition will expand your understanding of science and its place in society as much as the last one and that you will maintain an inquisitive and earnest attitude towards learning and the field of science as a whole. Read on, see what catches your interest, and start a dialogue with others just as passionate as you about medicine and culture.

Sincerely,
The Editors of the Medical Dialogue Review

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Cover Image by Katelyn Norman
Oil on canvas
I am a problem solver by nature. I thrive on research, revision, data and thought. I consider things in large, abstract terms. The common thread in the issues I've been exploring for the last few years is the multi-faceted study of people. I want to understand how we work anatomically, from cells and atoms to complex organ systems, as well as how we relate to each other and ourselves. I once believed that the obvious path for me to follow was to become a doctor, yet recently, I have become more and more convinced that art and medicine are not mutually exclusive- in fact, they are very much co-dependent. They both rely on a deep commitment to addressing the problems latent in the human condition and to the pursuance of truths in this area.

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Introduction: A Look at What's in the Spring 2010 Issue

Living with ALS: A Patient's Perspective
ALS is prevalent, it is emergent, and it is a crisis," writes Parth Vaghasia in his insightful piece that documents the diagnosis and treatment, or rather, lack there of, of a brave man living with this fatal ailment. With a survival rate of 1% after 10 years of initial diagnosis, Varghasia describes ALS sufferers as driving down a "one-way street leading to a dead end." Treatment is limited to "trial and error therapy" and diagnosis remains elusive, where early symptoms resemble those normal of the aging process. Through the compelling tale of an ALS patient, Varghasia highlights the importance of doctors having an open mind when making diagnoses. And despite the grim prognosis attached to an ALS victim, Varghasia portrays the courage and determination some people are capable of possessing.

Does NYU Make You Crazy? The Effects of College Life on Mental Health discusses the sometimes-dire consequences that can go along with the increased freedom young people experience when they enter college. As college students "experiment with their lifestyles," many are putting their mental health at risk, says Iascone. He explains how the "disruptions in regular sleeping habits can alter both a person's mood and general alertness." He also discusses how the new college lifestyle can exacerbate previously existing conditions such as ADD and ADHD. Using anecdotal evidence from NYU freshmen, Iascone provides a compelling argument that makes you think twice about skipping out on those recommended 9 1/4 hours of sleep a night.

The Issue with Tissue--Alexandra Pappas takes us through the various ethical issues, including informed consent and property rights, surrounding the use of biological materials. Pappas discusses the Supreme Court case of Diamond v. Chakrabarty, which ultimately ruled that biological materials could in fact be patented (and capitalized on), so long as they are the product of "human ingenuity." This ruling opened the floodgates to the patenting of all sorts of biological materials. Pappas also informs us of the case of Moore v. Regents of the University of California, which ruled that "an individual does not retain an ownership interest in tissues after they have been excised from the body or discarded" and further, "medical institutions are not explicitly required to disclose any potential financial gain" of harvested biological materials. The implications these rulings have on the medical research realm are vast and Pappas opens the doors for a fascinating and thought provoking discussion.

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Living With ALS: A Patient's Perspective
"Living every day *literally* as if it's your last."

Parth Vaghasia

"Damn you, Lou Gehrig!"
-- George Yardley
NBA Hall of Fame, ALS Patient

The name: Amyotrophic lateral sclerosis, abbreviated ALS. Aliases: Lou Gehrig's Disease and Maladie de Charcot.[i] Definition: A progressive neurodegenerative disease, which, fatally targeting motor neurons – the nerve cells responsible for voluntary muscle movement – is one of the most deadly terminal ailments known today.[ii] What do I mean by "most deadly?" Well, if one requires statistics as a safe haven for belief: the average survival rate for the 27 major types of cancer is 40.2%.[iii] Ready for this? According to recent studies at Johns Hopkins's Robert Packard Research Center, the survival rate for patients after 10 years of first being diagnosed with ALS is 1%.[iv] If one is diagnosed with ALS, he or she has a 1% chance of living more than 10 years after the diagnosis. Do you believe Johns Hopkins? If not, tell that to the 5,000 patients who were diagnosed last year, the 416 that were diagnosed last month, the 96 diagnosed last week, or the 13 that were diagnosed yesterday.[iv] As much as it is overlooked by drug companies, researchers, and policy-makers because of seemingly "bigger" health problems such as cancer and cardiovascular heart disease, ALS is prevalent, it is emergent, and it is a crisis. It is a silent killer, one that often progresses undetected until near death for many patients. Those that *are* diagnosed are still vulnerable, since there are no known cures and therapy can be exceedingly expensive. To those who have been diagnosed with ALS, the disease is devastating. ALS stops for nobody, claiming 30,000 American lives each year.[iv]

Lou Gehrig's Disease has two major forms: "bulbar onset" and "limb onset."[ii] Each has specific onset symptoms – bulbar onset begins with speech problems while limb onset affects one or more of the extremities (an arm or leg).[ii] About 25% of the ALS population is affected by bulbar onset, experiencing difficulty speaking, slurred or jumbled words, nasality, loss of speech volume, difficulty swallowing, and loss of tongue mobility. The remaining 75% suffer from limb onset, encountering clumsiness while moving, walking, or running, and severe loss of manual dexterity. The typical age of a patient diagnosed with ALS is between 45 and 70.[i] Because ALS occurs disproportionately in the elderly, many of these symptoms go unnoticed or are disregarded as signs of aging.

In August of 2009, Marc H. Nilssen, the father of a very close high school friend, was diagnosed with ALS. I recently had the opportunity to sit down with him and talk about the reality of the disease – what it is like to live every day *literally* as if it's your last.

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We started getting on track with the possibility of something serious in June of 2008. Mostly because of my

observations and [my wife]'s insistence that I see the doctor.

It began for me with a chronic cough that I had for nearly a year and a half. I figured I had gotten so much dust in my lungs from my work as a plumber that I had developed allergies and after many visits to my primary physicians and them playing off of that idea, I was on a regimen of many different allergy medicines. I used up drawers full of samples.

But during that process, and reflecting back, I had noticed that there were other things happening to me, but I mostly just brushed them off as signatures of old age. I was very physically active and athletic, but in time, I seemed to lack the ability to continue, and I attributed that to the process of just getting old. We had just bought a new house, I had changed jobs, I was working seven days a week, and I thought I was just stressed out, tired and aging.

In the early spring, March I think, I was putting together an awning that had tons of small nuts and bolts and I noticed how difficult it was getting for me to put them together. I was "clumsy," my fingers were weak and I would get cramps in my fingers, mostly my left arm. But again, I thought I was fatigued from working too much and it was still cold out.

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Just as patients can overlook such symptoms, so do physicians. It is a difficult task to diagnose something as radical as ALS if the symptoms are similar to those of normal aging. Marc went to multiple doctors, all of whom remarked how amazing the process of aging is, prescribed pain relievers and anti-allergenics, and overlooked the seriousness of the symptoms. "The process of being diagnosed with ALS is a long one. There is no distinct 'test' or specific 'signs or symptoms' that determine whether you have the disease or not," Marc says. Nevertheless, people do get diagnosed and their fate is a grim one.

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During one of the doctor visits, I had finally had enough and demanded to see specialists for my persistent cough. It was then that everything started to open up and one thing led to another. Immediately, I was referred to two doctors for two different suspected causes of my cough. A G.I. (gastrointestinal) doctor, in case I had chronic heartburn, and then an ENT, to see if I had a postnasal drip problem.

The GI did his thing and discovered I had Barrett's syndrome, which he attributed to my having acid reflux disease for such a long time. Finally an answer that made sense. That was why I was coughing all the time! Next stop the ENT, which was supposed to be a confirmation of what the GI had discovered.

He's the guy that really put me on the right track. If it weren't for him and his open mind, things may have taken a lot longer. During his exam, he noticed my tongue twitching. And that's how I was introduced to [my neurologist] because the ENT suspected something other than just what he specialized in.

And that's why I believe it is so important for everyone, especially doctors, to have an open mind when dealing with patients.

From then on, it was go time. A series of back and forth's, MRI's, X-Ray's, tons of blood tests, pulmonary function tests, trials and errors, basically all kinds of testing for everything else.

In August of 2009, I was diagnosed with ALS

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In my previous submission to this publication, I wrote a poem about how the practice of medicine is often rushed and how it has become industrialized, turning away from personalized treatment to a state in which every patient is a file on the shelf and a chart to be viewed before meetings. Physicians that practice this type of medicine surely would not be able to diagnose ALS. Today, given the high price of care, doctors are often reluctant to order expensive but necessary testing. This is especially problematic in the case of ALS patients, for whom their affliction carries a grave prognosis.

Still, technological advancements are making diagnosis easier. A recent study identified three proteins that are found in significantly lower concentrations in the cerebrospinal fluid of patients with ALS than in healthy individuals. Evaluating the levels of these three proteins proved 95% accurate for diagnosing ALS.[v]

But what happens after diagnosis? To date, there are no cures or even any real treatment for ALS. Instead, patients are monitored closely, usually by a team of specialists, and are subject to trial-and-error therapy. These experimental treatments can be prohibitively costly, especially if patients do not have health insurance, which is often the case. Only 22% of the current ALS patients in the United States have health insurance, and most patients, like Marc, are unable to work due to the degenerative effects of the disease.[iv]

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The costs are insane. I visit a specialized team at Columbian Presbyterian: a nurse, dietician, psychologist, physical therapist, speech pathologist, pulmonologist and the specialist. The bill is almost $ 8,000.00 for that one day, but thanks to insurance, we only have the co-pay of $50.00.

As far as medications, I have three right now: one for the pain and cramping, one for my excess saliva and drooling, and another for my acid reflux. All are covered under insurance and once a month I pay $20.00 for each medication.

I have a breathing device that I didn't pay for, but I saw that the mask was $365.00 alone, so the device, phew! And the speech communication device was $15,000! But again, thank god for health insurance, we didn't pay for that either.

That will change in March because my insurance with my employer ends and Medicare takes over. I don't know what's going to happen then but I've heard Medicare isn't nearly as helpful as most private insurances are. So far I know the acid reflux medication won't be covered unless they change their policy. That will cost $480 bucks a month. Not cool.

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While most sufferers, if they have insurance, are subject to experimental therapies, a few with the means are going to great lengths to increase their longevity or overcome the disease. Eric Edney is one of these people. Edney was diagnosed with ALS at the age of 58 and immediately changed his

lifestyle. He switched to an all-organic diet, alternative and all-organic medications and began a very expensive series of neurological treatments. He even moved – from Southern California to Arizona – after reading that it is the state with the cleanest air. Edney has been living with ALS for over twenty years now.

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I believe in [Edney's] methods, and have tried many of them. But, frankly, I don't have the will, the resources, or the fat wallet required to undertake such a regimen as demanding as his. It would require me to uproot my family and everything, and that I am not prepared to do.

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So then, what else is there for patients to do? Just sit and wait? But wait for what? There are very few labs and pharmaceutical companies that are offering any progress towards a cure. There are half as many ALS labs as cardiovascular labs in the United States and only a quarter compared to the number of cancer labs in North America.[vi] ALS patients fight every day for recognition. They seem helpless, but continue to hope for a cure.

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I think some of the cruelest information that I've learned from this disease is the inability of physicians and ultra large organizations to discover a cure for this disease. I've heard there is more focus on other neurological diseases because they affect children and others at much younger ages than ALS typically attacks. I've also heard there is a lack of funding to discover a cure because there 'is no money in it'. Because there aren't a lot of people that get this disease and that the life expectancy is so short for most victims, many major pharmaceutical companies are not motivated to spend money to find a cure. They are afraid they wouldn't be able to recoup their investment.

I really think that ALS is almost a 'self-inflicted' disease because of the way they explain what is happening to me. Apparently, it causes your immune system to basically attack itself. Something goes wrong inside the mind – something psychological. I think the cure is up to the individual and the sooner we learn how to control our own minds, the sooner we'll be able to find a cure for this disease.

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ALS patients must live with the knowledge that they have a terminal disease; they are on a one-way street leading to a dead end. With nobody helping them, no known cures, they spend the remaining days taking various medications and trying to live life to the fullest; they try to spend time doing things that matter.

***

One thing that may not be apparent in your research is this: ALS is not a disease that affects an individual; it affects the family as well. It's easier for me to deal with it because I have to; I don't have a choice. But a common trait in most people is the desire to help and to protect and care for their loved ones, and that's why I think it's harder on [my wife] than me. There's not much she can do to help and she can't always be here for me. She has her own life to live and needs to take care of herself, first and foremost, and the kids…and the kids, especially [my youngest son] because he's so young. He's not learning what is necessary to become a man from his father. He's not seeing me as the man I used to be, only what I've become. And that worries me the most.

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I have had the opportunity to speak with an inspiring, honest person: Marc H. Nilssen – a strong-willed man with lots of determination – but even he fears the future. Nevertheless, he holds his head high and marches on into the foggy, one-way street and continues to smile on a daily basis. He lives every day as if it were his last and cherishes the small things in life that matter – family and friends, mostly. Marc finds a reason to live when most in his position would not be able to. He truly is one of the bravest people I know. Many of you may not have the opportunity to meet such a person, though I hope you do. I have learned many things from Marc and I hope you have as well from what I have shared with you.

Thank you, Marc.

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[iv] Griffin MD, John W. "ALS Statistics." ALS. (2009)

[iv] Pasinetti G, Ungar L, Lange D, Yemul S, Deng H, Yuan X, Brown R, Cudkowicz M, Newhall K, Peskind E, Marcus S, Ho L (2006). "Identification of potential CSF biomarkers in ALS". *Neurology* **66** (8): 1218–22.

Running in Circles

Marcus Cimino

Running is not only the oldest sport, but also the oldest physical activity of our species and our recent hominid ancestors. Running has been the subject of works of art, has been intertwined with major events in history, and is involved in almost every sport that has been created. Recently, running, jogging and similar bipedal movements have sprung in popularity. The main reason for this increased prevalence: a plethora of health benefits. Yet there are concerns about how safe it is and how much running is too much. Furthermore, if is is considered safe, is there a right way and a wrong way to run so as to minimize its harmful effects?

It is not surprising to hear that someone died during a marathon, and it is even more common to hear of cases of dehydration, over hydration, exhaustion and myocardial infarction(heart attack). In fact, in the 2008 New York City Marathon, three people died(New York City Marathon). This past October, five more deaths occurred: three in a Detroit marathon(3 Runners) and two more in a San Jose half marathon(2 Runners). Another man died this past March in Dallas(Runner Collapses). Ages of these runners ranged from 26 to 66. Many of these people were considered to be in good health, but some had preexisting health conditions. Even if you are in good health, there is still the danger of getting injuries from the constant wear running can cause. Although the injuries and afflictions vary in severity, they should all be taken seriously.

Just how dangerous is it? According to experts, this remains to be seen. In an interview with Runner's World magazine, Dr. Paul Thompson discusses the likelihood of health problems during a marathon. He has said that the sudden rise of people of all different ages and health levels entering

the sport will increase the tendency of incidents. He maintains, "[I'm] confident that exercisers have lower heart risks than non-exercisers, but the truth is we don't know this for sure about marathoners"(Oct 19). His recent study shows a higher rate of atrial fibrillation among endurance runners than with sedentary people(Atrial Fibrillation). Atrial fibrillation is an irregular heart beat that can cause problems such as a stroke, though it does not often affect an athlete running.

While there appears to be at least one increased risk for a heart condition, Another paper's findings appear to contradict that of Dr. Thompson's study. In the *American Journal of Physiology – Heart and Circulatory Physiology*, they reveal the findings of experiments done on dogs and rats. The results show that a regimen of exercise with increased intensity over time showed improved heart health and function. Previous research included in the study claimed, "daily exercise (voluntary wheel running) … reduced arrhythmia formation" in rats. The research conducted by the author revealed that "[a] 6-wk daily exercise program (treadmill running) completely suppressed ventricular fibrillation in all eight [dogs] previously shown to be susceptible to sudden death" due to heart complications (Cardiac autonomic neural remodeling).

With these contradictory findings, we can not be sure whether or not running is completely beneficial or not. Perhaps addressing statistical findings can elucidate the risk of running. The risk of sudden death while running a marathon is 0.8 per 100,000 people (Triathalons, 1). For driving a car the risk is 1 per 6,700 (Causes of Death). For Diabetes, it is 23.3 deaths per 100,000 peopl e(United States). When compared to a common daily activity and a widespread disease, marathon running, considered by many to be the most strenuous running event, is considerably safe – safe enough to comply with the Center of Disease Control's recommendation of 30 minutes of exercise a day (Physical Activity and Public Health).

How should one run in order to stay healthy, while staying safe? Not everyone can run marathons or ultra marathons (50+ miles). Yet even if one chooses to run the number of ways it can be done is constantly increasing. Previously, many believed that short, high intensity workouts should be reserved for fit competitive runners. However, research done on elderly runners shows anything but this. Findings from these studies reveal that "doing interval training can double their endurance, improve their oxygen use and strength by more than 10 percent, and their speed by at least 5 percent"(Interval Training). The implications of this study indicate that people who once thought they did not have enough time to exercise properly may be mistaken. Still, many training programs such as the one provided by *Runner's World* magazine for marathons, requires significant effort and time, because they have shown to be effective(Come Run with Us). However, two months later, *Runner's World* published an article that took on time-tested approaches to running with alternative ideas, including not needing to run as much for marathons and putting longer breaks in the middle of high intensity workouts (The Rules).

In addition to theories on *how* to run, there has even been debate on what you should run *in* as well. Many shoe

companies have claimed the necessity for cushioning and motion control for years because if you foot is not perfect, it can lead to injuries from excessive use. Yet new findings show that running barefoot or with minimalist shoes is better for you and your running experience. It allows for natural movement and less impact on the joints. By minimizing the amount of material between your foot and the ground, your adjust to a proper gait, according to Harvard biologist Daniel Liberman (People Born to Run) whose research was published in *Nature*. In fact large companies such as Nike and up and coming companies like Vibram provide minimalist running shoes based on this rising trend all of which is backed by research from professionals like of Dr. Liberman.

So for runners of any level, or those maybe perhaps considering it, what does all of the research and articles tell you? Being an avid runner with 8 half marathons and 2 marathons and countless other races under my belt, I have tried a lot of advice; some of it has worked very well, and some of it has not worked at all. Instead of telling you what I think you should do, or who you should listen to, I will tell you to go out and see for yourself. Running, despite having team events in sports, is an individual activity. Only you are moving your legs and what works for you will not work for the next person. Spiridon Louis drank 2 glasses of wine during the first Olympic marathon. He also won. Thomas Hicks drank Brandy in the 1904 Olympics to deal with the heat (The Rules, 60). Is that recommended? No. Will it work for you? Maybe, but see what else works first and take it one step at a time. Only you will know what works for you.

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Does NYU Make You Crazy?
The Effects of College Life on Mental Health

Daniel Iascone

It is certainly true that the college experience is a pivotal stage of growth and development for many young adults. For most of these students, this four year interval is the first significant period of time in their lives in which they are both removed from their families and entirely surrounded by people their own age on a twenty-four hour basis. It therefore follows that shortly after the transition between high school and college, new cultural norms and social hierarchies are developed by the members of each incoming freshman class in order to compensate for the relative dearth of guidance or direction. To put it somewhat more succinctly: college is the freedom we always wanted. After years and years of complaining to Mom and Dad about what a big boy or girl you were and about how you deserved to have more independence, you finally got what you asked for. Many students who recognize the increased level of independence use this period to experiment with their lifestyles in various (and sometimes extreme) ways.

Given the drastic nature of the changes many new college students undergo, it is very unlikely that college life will have solely positive effects on mental health. This claim can be easily substantiated by looking at psychological research of mental illness in college students. Of the roughly 16 million people who attend colleges and universities in the United States, 2 million have experienced some sort of mental illness during the course of their time in college (Mental Health). Since mental illness can stem from a variety of sources, it is important to refrain from making broad generalizations about the effects of college on the mental health status of all students. It is possible, however, to analyze some of the leading causes of psychological disturbances and provide some suggestions for their alleviation. Lack of sleep, or irregular sleeping patterns, can cause disturbances that can manifest on top of existing disorders, such as ADD and ADHD, or from a genetic predisposition to become depressed.

According to Ted Coons, a psychology professor at NYU, sleep can be categorized as either slow-wave (quiet) or REM (active) by determining the frequency of the brain waves a person exhibits during sleep. He theorizes that growth-promoting hormones are secreted primarily during slow-wave sleep, and that this particular type of sleep has a restorative function, which might explain why more time is spent in this phase of sleep after intense physical exertion. In contrast, REM sleep, which is associated with restoring norepinephrine levels, may function to mend the fatigue of the mind. A person who is in REM sleep exhibits an EEG record that closely resembles that of a fully awake and alert individual. An individual alternates between slow-wave

and REM sleep over the course of each night. [1] It has been determined that disruptions in regular sleeping habits can alter both a person's mood and general alertness. In fact, it has been demonstrated that a person deprived specifically of REM sleep will later try to recover that lost sleep by spending a greater portion of subsequent nights sleeping, which demonstrates that REM sleep is a necessary component of good mental health.

Further studies of sleeping patterns have concluded that the actual amount of time spent sleeping is merely a single component of determining whether or not a person is getting adequate sleep. Along with the actual time spent sleeping, the quality of the sleep and regularity with which sleep is attained must be taken into account when attempting to analyze the effectiveness of an individual's sleeping habits. For example, Kyle Zinn, a freshman in the Stern School of Business, noted that, while he definitely enjoys life at college, the new ability to set his own schedule has led directly to his change in sleeping patterns. "Freedom is a big deal, being able to make my own decisions all the time, being in New York, and living with a group of my friends has definitely made me change some of my old habits," said Zinn. However, along with the positive aspects of being able to make all of his own decisions, he feels that "Maybe a couple of times a month I get really irritable because I was unable to get enough sleep the nights before." Although Zinn's sleeping patterns may not appear to be as drastic as others, even he is aware of the fact that changes in his sleeping patterns have led to petulant behavior.

As previously mentioned, the complete change in lifestyle that is intrinsic to the college experience can also exacerbate already existing disorders such as ADD and ADHD. Sam Freiberger, a freshman in liberal studies going into Tisch who has been diagnosed with ADD, can attest to the fact that college life can make his condition more severe. "It definitely gets worse when I don't get a lot of sleep," he says, "and I haven't been getting an awful lot of sleep since coming to NYU." He further states: "I used to skate by in high school, but the fact that I have a bigger workload here makes it harder for me to concentrate." Finally, with the ability to make all one's own choices, comes the decision of whether or not to take any medication for ADD or ADHD at all. Sam, for example, has decided to stop taking his ADD medication because he feels that it "dampens [his] creativity." Making such decisions is just another part of assuming responsibility for one's own well-being.

The correlation between insufficient sleep and poor mental health is the subject of a 2006 poll conducted by the National Sleep Foundation. This study concluded that 73% of the respondents who reported feeling unhappy, sad, or depressed also reported not getting enough sleep at night and being excessively sleepy during the day. Although it may not yet be determined whether it is the absence of sleep that leads to depression, or the depression that leads to the absence of sleep, it is easy to see that, at the very least, the two are closely related. The National Sleep Foundation further notes that under 15% of adolescents report getting at least 8 ½

[1] Electroencephalography or EEG records the electrical activity of neurons off firing within the brain.

hours of sleep a night (9 ¼ hours of sleep a night is recommended).

Some issues, however, cannot be solved merely by getting a few extra hours of sleep. Depression in college students is a major issue on campuses all across the United States, and is the subject of numerous awareness campaigns and college organizations. According to the Department of Health and Human Services, while suicide is the eighth leading cause of death for Americans, it is the second leading cause of death for college students. Fortunately, counseling is available to all NYU students who want it. The Wellness Exchange (212-443-9999) is available on a 24 hour basis to "help students address day-to-day challenges as well as any other crises they may encounter." Counseling and Behavioral Health Services (212-998-4780) at NYU can provide "short-term psychotherapy, group counseling, self-improvement classes, medication management, and off-campus referrals." All counseling is absolutely confidential and does not appear on any permanent records.

The bottom line is this: while going to college is an amazing opportunity to meet new people and do new things, there are some risks involved in making substantial changes in lifestyle. The purpose of this article is not to say that the negative aspects of college life should be avoided at all costs. On the contrary, a certain amount of experimentation is something in which almost all college students participate. Such new experiences often provide us with new perspectives and have lasting positive implications for the rest of our time in college. It is important, however, to be aware of the fact that some decisions can have adverse effects on mental health and that good mental health is something that can deteriorate over time if not cared for properly.

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Teacher First, Healer Second

Parth Patel

For centuries, the path taken by someone venturing into the field of medicine has been extremely grueling, challenging, and frustrating. Becoming a medical doctor generally requires four years of high school education, four years of undergraduate college education, four years of medical school education, and finally three to seven years of graduate medical education or residency in a chosen specialty. There are only a select few individuals who are capable of completing this path. Even though this process seems long and the years look packed, close analysis reveals that something still appears to be missing. Although students learn everything they need to become physicians, they also

need to learn how to become teachers in order to become successful, efficient, and well-rounded physicians.

The word *doctor* is derived from the Latin term *docere*, which means *to teach*. A doctor should therefore be more of a teacher rather than a healer. The interaction of doctors and teachers with the society has proved that the two professions of education and medicine have profoundly similar objectives. These include: assisting normal human development, preventing anything from going wrong by trying to stabilize the environment, and renovating and rehabilitating when disorder or chaos has occurred. Both doctors and teachers have known to practice and defend a vast, established body of knowledge. They are concerned with a human being's physical, psychological, and emotional state. Over the years, as human understanding of the world had deepened, the expectations from these two professions have increased as well.

Education, research, and clinical care are the three components that make up the mission of medicine. It is almost impossible to practice medicine without the incorporation of a teaching role. Whether as a primary care physician or a specialized neurosurgeon, this role as a teacher in the context of medicine applies to interactions with patients, residents, house staff, students, interns, and even fellow faculty and colleagues. Teaching, whether in the lecture hall, examination room, or rounds settings, is an elemental function of doctors who are seeking to deliver the best care possible and contribute to the preservation and improvement of the medical field.

Take, for instance, a patient coming in to the doctor's office for an appointment. One of the first things that will happen is that the patient will tell the doctor about the problem. The patient will discuss any signs and symptoms that need to be brought up. The doctor must then analyze this problem and tell the patient more about it. This is analogous to a student bringing up a problem for the teacher to solve. After trying all tricks, this student was unable to solve the problem and hence approached the teacher for better understanding. The teacher will then tell the student exactly what to do in order to attack the problem and solve it. This will require proper interaction and communication skills on part of the teacher. He or she must somehow teach the material to the student in a way that the student grasps it completely and is able to take care of similar problems. The student and teacher case is analogous to the patient and doctor one. It does not matter how the doctor approaches the problem, but in the end, he or she must calm the patient down and explain everything dealing with the problem systematically.

The issue of communication is also profoundly important, as it is the center point between the physician teacher and the patient. Researchers have looked at communication difficulties between doctors and patients from various disciplines and have tried to explore why these occur in the first place. Some have argued that doctors and patients talk to each other with completely different voices. The voice of the physician is usually characterized by complex medical terms and descriptions of physical symptoms. The voice of patients, on the other hand, is characterized by non-technical issues about the experience of illness and disease within the context of personal relationships and the social world around us. In most cases, doctors have more control than patients to structure the

interaction that takes place between them. As a result, patients may feel that their voice is not important enough, silenced, or stripped of personal meaning. Every medical practitioner, therefore, should be trained in the art of communication since this skill will prove invaluable when identifying problems and looking for treatment options for the patient. Interaction skills go hand in hand with communication and are necessary not only when talking to patients but also to nurses, pharmacists, or managers. To be an effective communicator and have a positive and beneficial interaction with people in a hospital setting, a doctor must strive to be a teacher who can clearly convey the message to the patient.

Besides efficient communicating and interacting, there are many other ways that the art of teaching can come in handy. One of these is the usually overlooked field of academic medicine. Around thirty years ago, there were no easily defined roles or set paths for physicians who also wanted to go into teaching. Teaching, unlike research, was rarely a source for advancement or achievement in the field of academic medicine. Physicians nowadays incorporate medical education into their practice of medicine in a variety of ways and with varying levels of time proportioned to each: some spend only nominal amounts of time teaching, while others devote most of their time to teaching. Participating in teaching more often than not depends on the medical practitioner's relationship with an academic institution as well as that institution's policies on compensating and reimbursing teachers. In some institutions like Harvard, physician-teachers are not paid for the hours they spend teaching classes. This sometimes makes it difficult for physicians who work for managed care organizations to participate in delivering education to medical schools. Such cases are especially evident when they must give up their time in the clinic in exchange for teaching time. This implies that the doctor would see fewer patients because he or she would be spending a fraction of time teaching. Some medical schools, though, are beginning to make serious efforts to obtain funding in order to financially compensate their physician teachers for the invaluable teaching hours they contribute.

While the art of teaching, especially with respect to teaching naive patients about their conditions and how to deal with them, is an integral part of practicing medicine, effective teaching often requires further training and experiences than those provided during the four grueling years of medical school. Doctors must deal not only with the logistical challenges but also with the reality that comes with caring for people while teaching. Aside from having an excellent understanding of the basic clinical skills, a doctor wanting to teach should also engage in the growing variety of educational courses that aim to improve the doctors' teaching ability. Teaching experience and knowledge complements the job description of doctors; it gives them a clear voice and helps others around the work area understand them better. A physician or surgeon who behaves like a teacher around patients will be much more respected, appreciated, and most importantly, successful.

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The Issue with Tissue

Alexandra Pappas

In 1995, President Clinton established a National Bioethics Advisory Committee (NBAC) to provide advice and recommendations in bioethical issues regarding research involving human participants and the applications of such research (Exec. Order No. 12975). In a 2001 report, "Ethical and Policy Issues in Research Involving Human Participants – Volume I", NBAC addressed the need to reform the system for the protection of human participants in research, deeming the system too narrow in scope to protect all participants and too bureaucratic to encourage ethically responsible research. With specific regard to human tissue research, another NBAC report, "Research Involving Human Biological Materials: Ethical Issues and Policy Guidance", concludes that for the advancement of health, it is critical that human biological materials remain available to the biomedical research community. But NBAC also concludes that the system of regulation in research involving human biological materials does not adequately provide clear direction of ethical conduct or ensure ethical use of biological materials. With this report, NBAC hoped to set a direction for a more regulated course in human tissue research. The NBAC charter expired in October 2001, but the issue of ethical execution of tissue research remains a topic of concern today. With its focus on informed consent and property rights, the ethical and legal issues regarding the use of tissue for research has relevance for many areas of medical research, not just research involving human biological materials.

The first immortal human cell line was established in 1951 from the cervical cancer cells of a young black woman from Virginia by the name of Henrietta Lacks. The cell line HeLa, named from the first two letters of her first and last name, has played a role in some of the most important scientific contributions over the last 50 years, like the development of the polio vaccine. Yet, the first decision to bear on the issues of human tissue research occurred nearly thirty years later with the Supreme Court case *Diamond v. Chakrabarty*, which addressed the question of whether biological materials could be patented.

Ananda Mohan Chakrabarty, a scientist working at General Electric, genetically-engineered bacteria capable of breaking down multiple components of crude oil (Skloot 201). Hoping to capitalize on his innovation, which would be instrumental in treating oil spills, in 1972, Chakrabarty filed an application to

patent the bacteria. At the time, though, patent law dictated that since micro-organisms are products of nature, living things are not patentable, and Chakrabarty's application was denied (Diamond v. Chakrabarty).

Yet, Chakrabarty's bacteria did not naturally occur in nature, and so Chakrabarty appealed the rejection of these claims, and in 1980 the case was brought before the United States Supreme Court. Determining that Chakrabarty's bacteria constituted a manufactured organism as the result of human ingenuity, the Supreme Court ruled in Chakrabarty's favor and deemed his bacteria patentable subject matter (Diamond v. Chakrabarty).

After the ruling in *Diamond v. Chakrabarty*, it wasn't long before scientists started to patent all different types of biological materials, including cell lines. One of the earliest cell lines to be patented was Mo, a cell line developed from the cells of a man named John Moore.

In 1976, John Moore went to the Medical Center of the University of the County of Los Angeles (UCLA) to receive treatment for hairy-cell leukemia under the attendance of Dr. David W. Golde. After confirming Moore's diagnosis of hairy-cell leukemia through the collection of blood, bone, marrow aspirate, and other bodily materials, Golde recommended to Moore that his spleen be removed to slow down the progress of the disease (Moore v. Regents). After obtaining a written consent form from Moore authorizing the surgical procedure Golde removed Moore's spleen, and a few days later, Moore left the hospital to return home (Skloot 199). Over the course of the next few years, however, under Golde's instruction, Moore returned periodically to UCLA Medical Center for the withdrawal of additional samples of biological material, including blood, skin, and sperm, which, according to Golde, was necessary for Moore's continued health and well-being (Moore v. Regents).

It turns out that Golde used Moore's samples to develop and market Mo, which he patented along with several proteins that these cells produced. In 1984, Moore sued Golde and UCLA, claiming firstly that he was deceived and that his body was used in research without his consent, and secondly that his cells and tissues, including the cell line developed from them, were his personal property (Skloot 203). At this time, the estimated market value of Mo was approximately $3 billion (Skloot 201).

After several appeals, the case reached the Supreme Court of California, which rendered the following decision. The court agreed with Moore that there had been a lack of informed consent, and decided that in the obtainment of informed consent from a patient, a doctor must disclose personal interests unrelated to the patient's health, economic or otherwise (Moore v. Regents of the University of California). Not doing so, the court decided, is a breach of fiduciary duty (Skloot 205). With regard to the use of Moore's tissue in research, though, the court ruled that an individual does not retain an ownership interest in tissues after they have been excised from the body or discarded (Moore v. Regents of the University of California). Lastly, with regard to the Mo cell line, or any resulting product from research involving human tissues, the court referred back to the decision in *Diamond v. Chakrabarty*, stating that the application of Golde's inventive effort rendered the patented cell line and products derived from it factually and legally distinct from Moore's tissues (Moore v. Regents).

Moore v. Regents of the University of California presents the two main contentions of human tissue research, which are the use of informed consent and the rights of an individual to claim ownership of one's tissues.

The first line of the Nuremberg Code, a ten-point code of ethics on research involving human participants resulting from the horrific experiment on Jews by Nazi doctors during World War II, states: "The voluntary consent of the human subject is absolutely essential" ("Office of Human Subjects Research"). As *Moore v. Regents of the University of California* demonstrated complete informed consent is of the utmost importance. Yet, what any guideline or court decision fails to specify is the degree of completeness, or quality, necessary. Indeed, the Nuremberg Code stipulates that the responsibility for ascertaining the quality of the consent falls upon each individual who initiates, directs, or engages in the experiment ("Office of Human Subjects Research"). And, of course, since the decision in *Moore v. Regents of the University of California* is only case law, medical institutions are not explicitly required to disclose any potential financial gain (Skloot 326). Some institutions choose to disclose this information, some generally address its possibility, and others do not discuss it at all. This discrepancy exists in other circumstances as well, such as what kinds of research tissue samples might be used for or how researchers will maintain the confidentiality and privacy of any information they obtain, specifically genetic information (Strauss 191). As some point out, though, providing complete informed consent is inherently difficult. Apart from tissue research often dealing with esoteric scientific ideas, sometimes the possibilities for tissue research are not yet even known (Skloot 320; Strauss 191). As such, some argue that the rule about obtaining informed consent is being applied to rigidly today and that it is necessary for the quality of consent to be balanced against the different values at stake, such as values of time, confidentiality, or medical progress (M.O. Hansson 182).

Then there is the question of informed consent for archived tissue samples, whether consent must be obtained for every research study a sample is used for. One study assessing the public's attitudes toward informed consent for biobanking found that individuals want ongoing control and choices over access to their samples and information (Murphy, Scott, Kaufman, Geller, LeRoy, & Hudson 2128). Indeed, participants were split between wanting to provide broad or blanket consent and wanting to give consent for each study involving the biobank samples (Murphy 2133). A British study examining the practicality of obtaining explicit informed consent for archived tissue samples found that the vast majority of participants were happy for archived tissue samples to be used for research, yet that the opinions of 26% of participants remained unknown (Furness and Nicholson 561). In spite of these conclusions, many in the scientific community agree that complying with desires to obtain explicit consent for archived tissue samples would be too time-consuming and detrimental to research. It is supposed, though, that new technologies may make this option more viable.

With regard to property rights, in its decision in both *Diamond v. Chakrabarty* and *Moore v. Regents of the University of California* the United States Supreme Court aligns itself with the natural rights view of property. The

natural rights view of property posits that the mixture of labor adds value to an object, which defines a legitimate basis of ownership of that object (Björkman and S. O. Hansson 209). But many critics argue that this view is too rigid in its all or nothing determination of property rights. In their article "Bodily Rights and Property Rights", authors Barbro Björkman and Sve Ove Hansson propose five moral principles of bodily rights that should be used to determine a unique bundle of rights for each type of biological material (212). Another suggestion is for there to exist no property rights for transplantable human tissue, but that through the investment of labor such rights can be created (Swain and Marusyk 12). In this way, society's present ethical standards for the transplantation of human tissue are preserved and the potential to for laborers to claim property rights in their inventions is secured (Swain 15). Some still maintain, though, that there are numerous parties that can claim legitimate interests in any cultured cells, including the "donors" of the original samples, and have proposed several ways of compensating tissue donors, like tax write-offs or a royalty system (Skloot 204; 323).

All in all, as the issues regarding tissue research continue to be debated in U.S. courts, science continues to move forward. Recently, the National Cancer Institute (NCI) revealed plans to establish the first U.S. national biobank, following in the footsteps of countries like Britain, Canada, Norway and Sweden (Biobanks). The potential for medical research is limitless. But, this endless potential more importantly signals the pressing need for the issues surrounding tissue research to be more clearly defined and interpreted.

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Protein Folding

Rebecca Houston

Introduction

Proteins are macromolecules which may be envisioned as molecular chains, the links of which are comprised of uniquely ordered sequences of subsets of the twenty principal amino acids. The links of the protein chain are further arranged in space in one of several permissible three-dimensional (3-D) geometries or shapes. The process by which a protein transforms from one permissible shape to another is called "protein folding." The structure or geometrical shape in which a protein can interact with other molecules and specified conditions in its environment to perform certain task(s) is defined as the "native shape" or state of the protein.

Proteins are key components that contribute to defining the structural framework of cells. Proteins are also integral elements involved in virtually every part, process, and function that occurs within a cell. As such, proteins can be considered to be the building blocks from which life is created.

In their native states, proteins can interact with other proteins and molecules for a number of purposes, each having a weighty impact upon the health of a cell, and thus, of a person. One way in which proteins interact is to form 3-D mechanical scaffolding in which new cells can be created and which ultimately can be combined with other similar and different molecules and cells to form more complex, higher organisms. Proteins also facilitate interactions that occur between proteins, molecules, and cells. These interactions determine the energy, stability, and interactability of the resulting product, whether it is a cell or organ system. The resultant energy and stability determine whether or not the molecules, cells, and organ systems that the proteins folded into are able to perform specialized electro-mechanical and chemical tasks they respectively evolved to perform; such as the interactive contractile function of actin and myosin in muscle. Immune system responses like the production and dispatch of T-cells in the response of the body to infection, and processes like passing along genetics by way of RNA production are only possible because of successful cellular/organ function, which is in turn dependent upon successful protein folding.

Successful execution of the protein folding process depends upon many factors. Greater complexity of the protein leaves more room for error. Proteins are more complex depending upon the size of the protein amino acid sequence (the longer the "code," the greater the potential for something to go wrong), and the number and relative locations of the hydrophobic bonds in the sequence (the way the different pieces of the code attach to each other and where they do so complicates things). Next, there are environmental factors to consider. The temperature of the environment in which the protein

folding process occurs, the presence of solvents, and more play influential roles. Clearly, there is ample opportunity for failure of the folding process to achieve the protein's native state. When protein folding to the "native state" is disrupted, it can result in disaster. Misfolded proteins remain either inactive (often useless, at best), or may become toxic to the cell and organism as a whole. Ideally, the body's system of checks and balances steps in when things go wrong to prevent a protein in the process of misfolding from moving forward, or to remove those already misfolded. The current state of medical research focusing on the body's actions in dealing with protein misfolding has become highly specialized for intracellular studies, i.e. the interactions *between* two or more cells, but less is known about control systems for proteins in the extracellular domain.

Sometimes however, these control systems fail. Because of the widely varied functions of proteins, from structural significance to enzyme activity, misfolding may disrupt cellular and thus human life in many ways. Among the potential consequences of misfolding are interference with cell-structure, regular chemical processes, and out of place proteins interacting adversely with surrounding molecules and processes. The consequences of misfolded proteins for human health range from decreased cellular efficiency to more dire outcomes.

Technology and Protein Structure

As previously mentioned, proteins play a role in most aspects of cellular life, and their ability to function is closely tied to their form. While the amino acid sequence of many proteins are known, much less is known about the complex three-dimensional structure of proteins. Challenges abound in mapping protein structure, and progress is hindered by the fact that it is more expensive to accurately determine structure than it is to study protein sequence. Some technologies have been developed which have contributed significant insight as to how proteins fold into their unique structures instead of the tremendous amount of other possibilities. However, these technologies have their limits, as the time frame during which protein folding occurs is minute, and many proteins are immune from these techniques based upon where they "live."

To study protein folding, we must be able to fold and unfold proteins at will. Studies thus far have used a number of methods to unfold proteins. Examples of such methods include exposure to elevated temperatures, an acidic pH, or exposure to urea as a denaturant, which allows for observation during refolding. Another option is the atomic force microscope (AFM), which unlike previous technologies, can image detail to the atomic level and can be used on biological materials. Second generation AFM technology, also known as frequency-modulation atomic force microscopy (FM-AFM), increases "spatial resolution," and our knowledge of the forces between molecules.[2] Use of the AFM allows for new controls in the unfolding process, and allows for single-molecule experiments, and the application of constant force.

Protein Mechanics

Researchers are also investigating the 3-D mechanical properties of the native and "permissible" folded states of proteins. Some examples of mechanical properties

being studied are how folded proteins respond to pushing and pulling applied by AFM's, forces from magnets, and different environmental stresses. Different aspects of the proteins' response to these stresses are studied. Some characteristics observed are the structural stiffness of the various folding states of proteins; the energy levels and stabilities of proteins' folded states; differences in energy levels between starting and end states. Additionally, they watch how the respective energy levels and transitional differences and various environmental factors affect proteins' stability, and their level of activity (ability to perform specialized functional task(s)) and their interactivity,(e.g., their ability to interact with other molecules as required by their natural function). Results from these observations have been used in efforts to study the effects various adverse environmental factors can have on the protein folding process and the errors they can introduce therein, producing malefic, unusable and often harmful "misfolded" byproducts.

The various 3-D structural configurations and architectures taken on by different proteins are also being investigated. How the structural configurations assumed by given proteins' in their native states differ from those assumed by the proteins in their other permissible folded states affect the energy levels and mechanical stability of the proteins' respective states, the degree of their interactivity with other proteins and molecules in their environment, and the rate with which they undergo successful foldings are under study.

Protein Misfolding and Disease

Many well known diseases are caused by protein misfolding, and may be divided into two large groups, each with many subcategories. Firstly, there are diseases which result from the inability of regular processes to be completed due to misfolding. Subcategories of this stop-process malfunction include the absence of necessary proteins, present but ineffective proteins, and toxic interactions of a malformed protein with its environment. Some diseases caused by the disruption of regular biological processes from misfolded proteins are cystic fibrosis, Marfan syndrome and Fabry disease. Notably, the von Hippel Lindau (VHL, p53) protein contributes to the tumor suppressing processes and is prone to misfolding and being omitted. Therefore, in the case of p53, protein misfolding may be linked to some cancers.

Additionally, various diseases result from the buildup of misfolded and insoluble protein "plaque." Protein aggregation is responsible for Type II diabetes, Alzheimer's disease, Parkinson's, and Creutzfeldt-Jakob's disease.[3] The protein ubiquitin is associated with the degradation of the cystic fibrosis transmembrane conductance regulator (CFTR), whose malfunction and aggregation are associated with cystic fibrosis disease. Ari Helenius of the Swiss Federal Institute of Technology's Institute of Biochemistry has, in his work focusing on the mechanisms involved in supervising what may go wrong during the protein folding process, compiled a table of diseases solely involving the endoplasmic reticulum of a cell and their corresponding protein mishaps.

Each protein malfunction and their associated disease(s) have their own unique folding "lives" and deaths. Notably, universal traits among proteins

(as well as the traits shared by certain groups based upon location in the cell, function, structure and composition) serve as opportunities in which progress in knowledge of one protein may reap rewards exponentially.

Progress

Advances in technology lead the discussion to the protein titin. Titin is an exception to the sequence-without-structure commonality, as both its amino acid sequence and three-dimensional structure have been mapped. Titin serves as an excellent example of the rewards that come with knowing both the sequence and structure of a protein. Found in cardiac tissue, titin plays a significant role in the mechanics of contracting muscles. Structural knowledge of titin in its functional state has furthered understanding of tension and contraction in the sarcomere region of muscle filaments, and thus, heart disease. [4]

Notably, the protein with the most exemplary performance in the field of folding is ubiquitin. Ubiquitin has been a favored choice in protein research because it is small, stable across a broad range of acidities and temperatures, , and has a highly structured native state (N). Much is known about the folding energy landscape of ubiquitin, including that of its native, denatured, partially structured, alternatively folded and locally unfolded states as well as the transitions between said states of being. Because ubiquitin is the ideal protein for experiments, progress with ubiquitin folding is progress which may be applied to many other proteins, and by extension, battling their associated diseases

Ubiquitin as a Model for Folding

Ubiquitin's short length makes it ideal to work with. Ubiquitin's structure is stable and commonplace, known as a β-grasp fold. Ubiquitin has a hydrophobic (water "scared") core, which may make it harder for proteins to return to the native state once denatured, studies suggest. Ubiquitin's intrinsic characteristics make it easy to work with, and because its β-grasp fold structure is not unique, early studies isolated fragments of ubiquitin in an effort "to identify potential nucleation sites for folding," (sites that other proteins with β-grasp folds may have in common).[vii]

Significantly, because ubiquitin is so stable structurally, it makes it simpler to study the "partially structured states of ubiquitin," or put simply, what happens on different parts of the protein during the folding process, known as local folding processes. Because we can "pause" the folding process in different areas and stages, we can also study the energy landscapes of each transition stage and state.[viii] For example, studies have documented the effects of changes at a place called the C-terminus of the α-helix resulting in the finding of "more than 70 mutants...which have a range of stabilities," both greater than and much less stable than wild-type ubiquitin. [ix]

Local folding processes are important to study and understand because "in highly localized structural change," it is often the case that "the molecule is plastic enough to accommodate local deformation without global reorganization."[x] In other words, as the protein folds or misfolds, it is unlikely that any single mistake in one minute area of the protein will cause the entire protein to misfold. However, if that were the case, because ubiquitin is so stable, we could isolate and identify

the single faulty folding area. As such, "if the primary determinants of conformation are realized locally, then the massive complexity of the folding problem can be reduced substantially by factoring it into smaller, more tractable problems."[xi] This is especially relevant to single residue (or highly localized) mutations.

Thus, as we continue to learn which local processes are more commonplace in specific mutations, we may be better equipped to predict the future on a cellular scale and possibly for the organism itself.

For these reasons this paper will focus upon protein folding in ubiquitin—what is known, notable experiments and major players in the ubiquitin specialized field, and what has yet to be done.

Specific Experiments

A number of experiments on ubiquitin have provided results that can only be used for ubiquitin-specific purposes, while many others have also furthered progress in the protein folding field in general. Frauke Gräter and Helmut Grubmüller of the Department of Theoretical and Computational Biophysics at the Max Planck Institute for Biophysical Chemistry utilized AFM technology to denature ubiquitin in order to better understand the factors involved in protein folding. The unfolding process began with the application of a "very high force (e.g. 100 pN)," followed by a much weaker force.[xii] The most notable results of the experiment were observed after the weaker force was applied and the unfolded state was reached. At this point, researchers found "a long lived intermediate state."[xiii] In other words, they found a point at which the protein was neither folded nor completely unfolded nor was it in the transition process. This new state can be identified by its unique intermediate structure, and the presence of hydrophobic clusters which are constantly reforming. The latter characteristic is the source of the name given to this newly identified state, as it is " 'molten-globule' like."[xiv]

The molten globule (MG) state differs from the native (N) and unfolded (U) states in a number of significant ways. The MG state has a "very broad ensemble of non-native conformations," and, perhaps even more significant, ubiquitin in its MG state goes through a number of interactions because its hydrophobic spots are exposed—the MG state "[presents the] formation of salt bridges."[xv] Hydrophobic clusters form which are temporary in nature and constantly reforming. The "clustering of hydrophobic residues" result directly in fluctuations of the end to end distance (size) of the protein.[xvi] Essentially, the MG state is dynamic, constantly moving and changing the size of ubiquitin. Eventually, the protein *was* able to return to its N state, and as a result, the researchers concluded decisively regarding the intermediate states that "we interpret these fluctuations as folding attempts."[xvii] So, we find that while ubiquitin is able to "hang-out" in a partially folded state, it will never stop trying to fold.

In light of these results, researchers took note of a few conclusions pertaining to ubiquitin in particular and protein folding in general. Various folding mechanisms such as folding under force, temperature, or urea-induced folding "might share intermediates along the folding pathway."[xviii] Thus, experiments which monitor "several folding variables in parallel" (such as end to end distance,

conformation coordinates, force, thermal or chemical denaturation, etc) would be useful. [xix] These variables should be noted in observance of the N, U, and MG states.

Professor Sophie Jackson of the University of Cambridge published a ubiquitin-specific perspective in 2006, with a number of interesting conclusions. Our knowledge of ubiquitin has come a long way, such that we know "the folding energy landscape is…uniquely characterised with a plethora of information available on not only the native and denatured states, but partially structured states, alternatively folded states and locally unfolded states, in addition to the transition state ensemble." [xx]

Thus, we now know what "being there" for each state looks like in terms of energy, as well as the energy it takes to "get there," through transitional states. But what does "being there" look like structurally for each state? Progress in structure studies over the last two decades has been profound. Ubiquitin's structure has been mapped and was found to be quite simple, compared to many other proteins, and one aspect of the structure, termed a β-grasp fold, is widespread and many proteins and protein families are found to adopt this topology.

"Ubiquitin has been used extensively as a model system for investigating the factors governing the stability of proteins," and while the Makhatadze and Privalov groups have done quality work in this area, potential for study remains open-ended. The group made another significant observation—in analyzing charges on the surface of the protein, they found that it affects the stability of the entire protein, the groups "have produced a stabilized variant of ubiquitin by the optimization of charge-charge interactions on the protein surface. This group has also demonstrated that removal of surface charge-charge interactions leaves the protein folded and very stable." [xxi]

Generally speaking, "ubiquitin's intrinsic stability makes it an ideal system for stability studies enabling a comprehensive programme of protein engineering. To date, more than 70 mutants have been made and characterized which have a range of stabilities." [xxii]

Not only does the small, stable ubiquitin provide an exemplary model for protein study, but so do localized regions of the protein. Considered individually, Ms. Jackson titles these as ubiquitin's "partially structured states." These states "provide important information on the intrinsic stabilities of substructures within the protein as well as local unfolding events, both of which help to define the energy landscape for the folding/unfolding of this protein." [xxiii]

Likewise, Ms. Jackson chronicles the progress and usefulness of localized studies. Limited by earlier technologies, previous studies focused on specific ubiquitin segments which represented "different regions of the full-length protein. Evidence for intrinsic structure in the absence of the rest of the polypeptide chain was sought in order to identify potential nucleation sites for folding." [xxiv] As previously mentioned, the manipulation of local folding sites to demonstrate how they may affect the protein as a whole have shown just how resilient proteins, especially those as stable as ubiquitin, truly are. Ms. Jackson continues in stating that "some quite striking results were obtained when a fragment… of ubiquitin was produced

in order to test whether this portion had a propensity for independent self-assembly."[xxv] It was found that even in a "chopped up" state, it could fold successfully. Essentially, not only has the protein ubiquitin evolved for its varied purposes supporting eukaryotic life, but also for its own evolutionary advantage.

Next, there is the Chekmarev group, a three-way collaboration between the Institute of Thermophysics at SB RAS in Russia, the Laboratoire de Chimie Biophysique at the University of Louis Pasteur, and the Department of Chemistry and Chemical Biology at Harvard University. The Chekmarev group has worked to gain insight into the protein folding mechanism in general by conducting experiments which study the transitions between the main states of ubiquitin during the folding process. Just as Gräter and Grubmüller found, they determined that "the presence of long-living intermediates could not be ruled out."[xxvi] Their study focused upon the energy aspect of protein folding, as they examined the energy needed to transition from one state to another, and the energy associated with each state.

The Outlook

Because of the numerous and diverse roles played by protein in cellular function, gaining insight into protein structure and protein misfolding will be useful in learning about many diseases and possible therapies. Objectively speaking, funding for a wide range of topics within these categories may be sourced from pharmaceutical and biotech companies, who have already poured resources into creating a Alzheimer's vaccine, (AN-1792). Alzheimer's research, for example, is currently focused upon preventing protein "plaque" buildup in the brain, either by blocking the formation of proteins or directing deposits away from the brain.

Because misfolding diseases are so diverse across all significant categories (such as bodily location, scale of misfunction, time frame of deterioration, etc.), strategies for developing therapies will be just as varied. Thus, a better understanding of the underlying problem, protein misfolding, will be hugely impactful. Thus far, ubiquitin is the best model. While further advancements in technology may bring alternate proteins to the forefront of protein folding modeling research, the dearth of information already available on ubiquitin for an immense and varied amount of controls is unparalleled.

There is a biological aspect of misfolding to explore on a molecular level. Parameters such as size, crowding, function, and concentration of the protein and environment are all worthy of attention. Notably, less is known about the energy landscape of folding proteins, though thermodynamics are understood to be hugely influential. Another possible topic deserving of attention may be the influence of the stage of "life" during which a protein folds—natural folding varies: some fold during synthesis, while some fold afterwards. Is misfolding more likely to occur in proteins folding at a specific stage of "life"? Do the aforementioned "quality-control systems" exist at certain stages of protein "life," and can they be replicated? Answers to these questions and many more will be greatly impactful in battling disease.

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[xiv] Ibid, 1.
[xv] Ibid, 2.
[xvi] Ibid, 2.
[xvii] Ibid, 2.
[xviii] Ibid, 2.
[xix] Ibid, 2.
[xx] Ibid, Jackson 1845.
[xxi] Ibid, 1846.
[xxii] Ibid
[xxiii] Ibid, 1846-1847.
[xxiv] Ibid, 1847.
[xxv] Ibid
[xxvi] Chekmarev S.F., S. V. Krivov, and M. Karplus. ""Strange Kinetics" of Ubiquitin Folding: Interpretation in Terms of a Simple Kinetic Model." *The Fifth International Conference on Bioinformatics of Genome Regulation and Structure* 2006 243-246. Web.3 May 2009. <http://www.bionet.nsc.ru/meeting/bgrs_proceedings/papers/2006/BGRS_2006_V1_055.pdf>.

Depression

Lucy Chou

Depression is defined by the National Institute of Mental Health as a feeling of sadness that lasts more then a couple of days. It is like any other disorder; it requires treatment in order to get better, otherwise it can interfere with daily life and cause pain to suffering to those around. What is shocking is that many people with the illness never seek help. It could be because they are unaware that they are suffering from depression, that they feel there is no point in seeking help, or that they are financially unable to do so.

Depression is an interesting illness in that it is so variable in terms of the circumstances in which it develops and in the symptoms that patients face. It is ubiquitous in that it is able to strike all parts of the population, but it seems that the diagnosis and pubic awareness of the illness remains low. Thus, due to its span of infection and low detection rate, it would be worthwhile to look at how depression affects various segments of the population in terms of age groups.

There are several forms of depression, the most common being major depressive disorder and dysthymic disorder. Major depressive disorder interferes with a person's daily life, takes the pleasure out of normally enjoyable activities, and can plague a person for their entire lifetime.

Dysthymic disorder is characterized by long term suffering (2 years or longer) and less severe symptoms that may not disable them from functioning normally, but certainly make them feel depressed. (1) Yet, it is hard to say which segment of the population is more vulnerable to any form of depression.

Depression could develop as a result of a break with reality resulting in delusions (psychotic depression), the experience of childbirth (postpartum depression), or the lack of natural light during the winter (seasonal affective disorder). (1) In fact 10-15% of women experience postpartum depression after giving birth. (2) Those who suffer from seasonal affective disorder can be treated with light therapy, medication, and psychotherapy. Light therapy treatment hinges on the idea that the depression is less likely during the spring and summer. (3) It is safe to say that depression is dangerous because of its ability to target all segments of the population. Considering the stress that many feel in their lives today, it is not surprising that people feel overwhelmed and often depressed. However, it is incredibly important to recognize this stress and depression and try to treat it early on.

Regardless of the type of depression, diagnosing and treating patients remains an issue because symptoms are varied in terms of the severity and frequency, so it is often overlooked in a medical diagnosis. Symptoms of various depressions can include overeating, pessimism, and insomnia. Compounded with the fact that depression can often co-exist with other illnesses, the treatment and diagnosis is even more difficult. (1) Despite this presumed setback, it can actually be easier to treat patients suffering from a depression that is influenced by another illness, since the other illness may be more obvious and simpler to cure.

General anxiety disorders typically accompany depression, and include post-traumatic stress disorder, panic disorder, and social phobia. (4+5) Other problems like alcohol and substance abuse often occur alongside depression, and are a growing trend in the US. (6) This might actually be good news because we can re-evaluate patients diagnosed with alcoholism, and find that they were improperly diagnosed and treat the depression which will in turn solve the intertwined illnesses.

The problems arise when it comes to treating people with depression in conjunction with serious illnesses, like heart disease. These patients tend to have more serious symptoms, more difficulty adapting to their medical condition, and greater medical costs. (7) However, treating the depression will also improve the outcome of treating the co-illness. (8)

The symptoms and treatment of depression are well understood although the cause is still unknown. What is known is that MRI brain scans of people with depression show that there are parts of their brain that function improperly. These areas tend to control mood, thinking, sleep, etc…. The neurotransmitters that the brain uses for communication are also shown to be out of balance. (1)

Some argue that depression tends to run in families and suggest a genetic inheritance of the disease, but the confounding fact is that depression can occur in people without a family history of depression. (9) Actually, the risk for depression results from the influence of multiple genes acting together with the environment. (10) Other times the cause of depression might be the loss of a loved one or other stressful situation that will trigger later episodes of depression.

Now looking at depression from a different perspective, it might not be all that surprising that depression is more common in women than men because of the biological and hormonal changes that occur

through a female's life. Hormones can affect the brain, which controls emotions and mood, so when there is an increase of these hormones after birth along with the new stressors of rearing children, it can trigger a depressive episode. (1) Then again, hormonal changes cannot be argued as the sole cause of depression in women because other women that face the same situation do not always suffer from depression.

Men experience and cope with depression in a very different manner than women. Men are more likely to acknowledge fatigue, show irritability, and lose interest in previously enjoyably activities, whereas women feel sadness, worthlessness, or excessive guilt (12,13) Men in the U.S. are more likely to turn to drugs and alcohol, become abusive, throw themselves into their work, engage in risky behavior, and successfully commit suicide. (14)

Although some may believe that the elderly are more likely to be depressed because they are aging, they actually have no greater likelihood of succumbing to depression than the rest of the population. Depression in seniors is a more difficult situation to diagnose because they show different symptoms and are less likely to acknowledge any sadness or grief that they may feel. (15) Additionally, the elderly may be more prone to medical conditions that cause depressive symptoms, take medications with depression as a side effect, or suffer from vascular depression. Vascular depression is when blood vessels harden over time and prevent normal blood flow to the rest of the body and organs like the brain (this also contributes to other conditions like stroke). (16) The sad statistic is that many elderly who commit suicide visit the doctor within one month of their death. (17) This shows that this treatable illness is often going undiagnosed in the US and leads to deaths that are preventable.

Childhood depression is an emerging risk that researchers are taking a closer look at because it tends to persist into adulthood, often leading to more serious illnesses later in life. (18) Some of what we would consider "typical" childhood behavior may actually be symptoms of depression. Children pretending to be sick, refusing to go to school, and clinging to a parent are all symptoms found in young children that may be indicators of depression. In older children, sulking, getting into trouble at school, and feeling misunderstood are also symptoms. (1) Some instances of childhood depression may be due to the various hormonal changes that they experience as they approach adolescence. Depression is a disease that can affect every area of the population and in the most serious cases lead to death as a result of suicide. Since depression does not discriminate in the people that it targets and can have lethal outcomes, I think it's important to focus on the detection of the illness. Depression has been studied enough that there are countless effective treatment options depending on the patient but identifying the sufferers still remains an area of weakness. In fact, even in cases where it is obvious that a person is suffering from depression, treatment is trial by error. Many simply shrug sadness off as a necessary part of life that is normal. It is time to focus on depression because even though it can be treated, the real problem is detecting it.

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An Extension of Fetal Viability

Christopher Bailey

It seems farfetched to begin to imagine a world where fetal viability, or the ability for a fetus to survive outside of the womb, could be pushed back to conception, but with the onset of in vitro fertilization and an increasing premature infant survival rate, the idea of an artificial womb is quickly becoming a reality. An artificial womb, in addition to in vitro fertilization and donated reproductive cells, introduces the possibility of creating a child externally without the direct involvement of either sex. Although the research is innovative, scientists must consider the ramifications that an artificial womb would have on society before introducing it as common practice within the medical field.

The most significant impact of the artificial womb would be on gender roles. A gender role is a "set of behaviors, expectations and values (norms) associated with either males or females" (Myers S-5). Traditionally in Western society these norms include male dominance and female dependence in normative family relations. Archaically put, the male earns the money and the females raise the children. These roles were largely determined by biology since women are engineered for pregnancy and men are not. Using such logic to interpret the roles of men and women, it could be easily assumed that the female is responsible for the care of the child leaving the man to provide the necessities the female and child need to survive. Today, such chauvinistic ideals have declined and both men and women have the ability to both provide and care for a family regardless of their biological differences. The artificial womb, however, would eliminate the biological responsibility of females. How would the absence of female pregnancy redefine the roles of both males and females within American society?

Take for instance a single male in his late forties who has given up on relationships but desires a child. With the artificial womb, this male would no longer need to have any ties with a female, either a companion or surrogate mother, to produce a child. Theoretically he could select a donated female egg at random and combine it with his sperm in the artificial womb to produce a child of his own. Once the child is born, his role as a father is similar to that of a single parent. However, not only has the father taken on both the maternal and paternal social roles of raising a child, but also the biological responsibility of obtaining both the male and female reproductive cells, egg and sperm, and having them combined and nurtured to term (Sexual Reproduction pars. 6). Although his biological role in conception is not exactly the same as a mother naturally carrying a child to term, the fact that he can have a child without explicitly using a woman gives him the power of both sexes. Conversely, a woman in the same situation could create a child without a man, also granting her the power of both sexes. In terms of gender roles, both sexes now have equal biological capacities and thus equal gender roles. Even in situations where two parents conceive a

child together via the artificial womb, the same type of biological equality remains; both sexes donate one gamete and share the same amount of responsibility while the child develops. Overtime, a hybrid of maternal and paternal gender expectancies to accommodate the new biological abilities of both sexes will be developed. Most likely the concept of gender roles will become androgynous or "neither specifically masculine or feminine" in terms of parental roles (Androgyny pars. 1). In turn, the androgyny would spread to other aspects of society where gender expectancies segregate male and female abilities into different categories. This is because the biological difference that created many gender roles would be greatly diminished.

The androgyny caused by the use of the artificial womb could create equality within the workplace by promoting gender integration. In Jerry Jacobs's article *Detours on the Road to Equality: Women, Work and High Education,* he identifies that certain careers are "skewed toward either men or women" (239). For example, jobs such as registered nurses and childcare workers are more than 90 percent female while men dominate the fields of engineering, construction, and business (Jacobs 239). These segregated fields are the result of gender expectations as well as "a web of social factors that tends to press women into traditionally female occupations" (Jacobs 241). Many of the gender stereotypes that segregate male and female occupations are instilled in children at a young age through mimicking ideal male and female behavior**.** If we consider the effect of artificial wombs creating androgynous gender roles, it can reasonably be assumed that this androgyny would create some degree of equality within the workplace by eliminating the gender expectations that pressure women into stereotypically female careers. Gender expectations, however, are not the only limiting factor for women. According to Jacobs, "demanding fields limit the opportunities of those with parental and other care giving obligations, especially mothers" (241). Again the artificial womb provides a solution for such obligations by limiting the effects of a child's conception on the mother's career. Woman need not be hindered by pregnancy if they desire a demanding career since the child would be developing externally and thus eliminating any recovery time. With this in mind, employers could hire women regardless of their personal agendas and be more open to promoting them to higher status positions. Another possibility is a large influx of single men having children via the artificial womb. As a result, these men would have similar obligations as women. Employers would then be more likely to evaluate both sexes based more on merit rather than on personal commitments. (Jacobs 239-245).

The artificial womb would also alter gender roles in terms of sexuality. Sexuality is "the gender gap in sexual attitudes and assertiveness" associated with social and reproductive sexual behavior (Meyers 169). An artificial womb would make reproductive sexual behavior superfluous, fundamentally changing the primary reason many choose to have sex. Moreover, over time the artificial womb could become the primary means for reproduction causing sexuality to be limited to our behaviors during social sexual behavior. With no biological motivation, having sex would solely be associated with pleasure, allowing our conceptions of normative sexual behavior to be completely altered. In American society "people tend to think of males and females and heterosexual and homosexual as distinct and opposite categories" (Taylor and Rupp 247). However, in Verta Taylor and Leila Rupp's article *Learning From Drag Queens,* the drag queens at the 801 Cabaret were able to

elicit a range of sexual identities from Americans that usually define sexuality in terms of two categories straight and gay (247). For instance, during a drag show a straight woman was asked to come on stage and represent another sexual identity. While on stage, the woman became "eager to have a lesbian touch her" (Taylor and Rupp 250). Other's reported being turned on by the drag queens yet claimed to be completely straight (Taylor and Rupp 250). Although these behaviors are limited to this specific social situation, the drag queens demonstrate that sexual identity can be more than just two categories. Androgyny coupled with sex purely as a means for pleasure would create a similar social situation as in the drag club by where the norms of society are not in line with biological necessity but rather sexual desire. As a result, this would allow various countercultures (gays, lesbians, bisexuals and transgender) to emerge, furthering the idea of diverse sexual identities as a normative attribute to American culture. (Taylor and Rupp 247-253).

Although the implications of the artificial womb extend far beyond this discussion, one must consider that it would take decades if not centuries to see the changes that would result from the widespread use of artificial creation. Also one must consider the legal and moral barriers that would restrict or inhibit the use of an artificial womb. Regardless, an artificial womb would create a new society that could possibly fulfill "the official Key West philosophy that we are *One Human Family*" not to be segregated or limited by our purposed gender roles, but free to define our own gender and sexuality (Taylor and Rupp 247).

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Editor-in-Chief: Erika Ryan, erika.ryan@nyu.edu

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