Emory Undergraduate Medical Review

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Picture by Josie Chen

EMORY UNDERGRADUATE MEDICAL REVIEW

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MISSION STATEMENT

The Emory Undergraduate Medical Review publishes student-authored research review articles on the intersection of cutting-edge medicine and the sciences. Our interdisciplinary articles span all clinical fields and are peer-reviewed by medical professionals from leading academic institutions, including Emory University, Yale University, and the Mayo Clinic.

On campus, EUMR hosts a variety of medically-related events, including frequent collaborations with Emory's School of Medicine. Our projects have been featured by Emory's News Center and have caught the attention of former President Sterk.

LETTER FROM THE EDITOR

Dear Reader,

As we enter the ninth year of EUMR, we have sought to both maintain the journal's excellence and implement changes to improve the quality of our publication. While preserving EUMR's strong emphasis on being an academically rigorous organization, we also focused on creating opportunities for peer engagement within the Editorial Board to build a close-knit and supportive community. By fostering a positive organizational spirit and underscoring the importance of collaboration, we have seen the internal culture parallel the quality of our journal. To further increase engagement and streamline the publication process, we combined the copy and layout positions into one. Editors thus gained exposure to both important facets of EUMR's publication process and maintained close relationships with their writers throughout the semester.

Over the years, EUMR has consistently recruited strong writers from diverse backgrounds to cultivate articles for the campus community, and this year was no exception. We began the semester by recruiting eleven new members to fulfill writer, editor, and first-year positions. Through the combined efforts of our diligent Editorial Board, we produced a culmination of 21 exceptional articles across our digital platform and semesterly journal. As is tradition, this issue successfully highlights a critical attribute of EUMR: interdisciplinarity intertwined with advanced scientific and medical research. Readers can look forward to articles ranging from patent suits regarding the current COVID vaccine to an in-depth examination of the clinical research, diagnosis, and treatment of Interstitial Cystitis. We owe an enormous thank you to our Editorial Board members for consistently doing their part; this publication wouldn't be possible without their committed efforts.

One of our principal goals this semester was to be proactive earlier in the article creation process to produce a well-rounded journal. In addition to pitching their article topics to the rest of the Editorial Board, our writers also worked with Dr. Gregg Orloff in selecting strong, timely, and interdisciplinary topics. We would like to extend a special thank you to Dr. Orloff for taking on this new role and his continued support of EUMR.

Lastly, we'd like to thank our advisory board for their continuous support of our Editorial Board. Their expertise and assistance play a foundational role in the quality of our articles as well as the overall success of EUMR. We are pleased to announce the addition of two new advisory board members, Dr. Michelle Park and Dr. Jonathan Crane. They have taken the place of Dr. Jesse Soodalter, Dr. Lawrence Marks, and Dr. Kevin Li, who have been with us over the past few years. We will miss them dearly and wish them the best.

Next semester presents a new opportunity to do it all again. We look forward to working with our amazing team once more and seeing what's to come.

Cordially,
Josie Chen & Muriel Statman
Editors-in-Chief
EUMR 2022-2023

The predicament of clinical research, diagnosis, and treatment of interstitial cystitis

GRACE WARD
Staff Writer

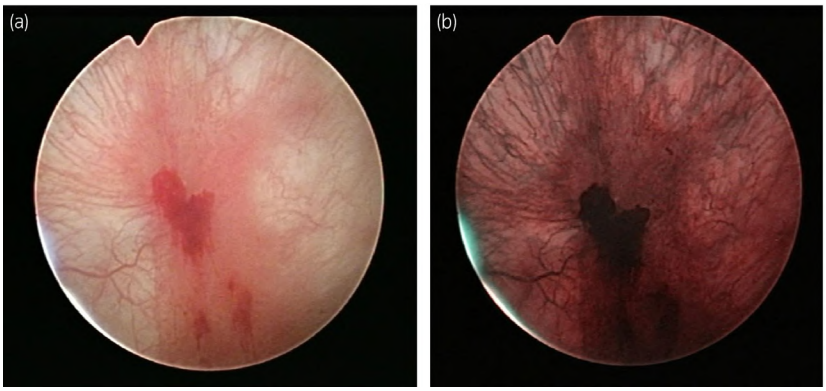

Figure 1. Cystoscopy (a) and narrow-band cystoscopy (b) images of Hunner lesions. Image from Akiyama et al., 2020.

According to the National Institutes of Health, interstitial cystitis (IC) affects an estimated three to eight million women and one to four million men in the US (Definition & Facts of Interstitial Cystitis | NIDDK, n.d.). IC is a chronic inflammatory condition associated with a variety of symptoms including – but not limited to – urinary urgency, frequency, pain, and incontinence, which significantly affect the quality of life of individuals with IC. The symptoms of IC are nearly identical to those of a urinary tract infection, but individuals with IC must live with this discomfort indefinitely. Unlike many other chronic pain conditions, such as rheumatoid arthritis or hypertension, IC is also associated with decreased vitality and mental health (Michael et al., 2000). IC predominantly affects women, and the mean age for IC patients is 53.8 ± 0.7 (Koziol et al., 1993). Thus, with the aging population in the US, treatment and diagnosis of IC are becoming even more essential. IC proves to be an exemplary case study on the complexities of nosological and statistical classifications of disease (Jutel, 2011). This complex condition is uniquely challenging to medical providers and researchers due to the nature of its symptoms, causes, and available treatments. This review compiles some of the multifactorial complexities of IC, explores the challenges and constraints associated with treatment development, and highlights the importance of current and future efforts to understand IC.

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Our current understanding of the pathophysiology of IC is largely inconclusive. The original understanding of IC pathogenesis was based on histological studies, specifically focusing on the presence or absence of Hunner lesions (lesioning and neovasculation of the bladder lining) (Figure 1). The presence of Hunner lesions is now collectively acknowledged as a significant clinical subtype of IC, but diagnosis proves to be more difficult than a dichotomous lesion/no lesion model. Many cases symptomatically indicate IC yet show no evidence of Hunner lesions. As such, various other physiological mechanisms for IC have been suggested, including upregulation of certain genes, neurogenic inflammation, downregulation of tight junctions, and defects in the urothelium (i.e. increased permeability of bladder lining) (Akiyama et al., 2020). Additionally, other evidence suggests that dysfunction of adenosine triphosphate (ATP) release from the lining of the bladder, which is associated with contraction/voiding of the bladder in normal physiology, contributes to the inflammation and urinary urgency associated with IC in some cases (Andersson, 2015; Silberfeld et al., 2020). In individuals exhibiting IC symptoms, there are numerous combinations of physiological pathways that may be contributing to their condition, making it difficult to define a "most important" cause for IC and causing the focus of the literature on the topic to be extremely varied.

Moreover and probably related, diagnostic guidelines are frequently incongruous. There is some contention over whether the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) "research" definition of IC should strictly be used as

the diagnostic guideline for IC. This NIDDK-based diagnosis involves cystoscopic evidence of IC (presence of Hunner lesions) and a hydrodistention measurement taken by filling the bladder with solution to measure pain and bladder capacity. A 1999 study found that only 32% of female participants diagnosed with IC by a medical practitioner met the strict NIDDK guidelines for IC diagnosis, despite the fact that they exhibited symptoms of IC (Hanno et al., 1999). As such, discrepancy persists regarding the appropriate medical and diagnostic definitions of IC, and there is some debate on whether diagnostics should be based on a more traditional understanding of root-cause indicators or symptomatic presentation. Either way, if clinical research – on which the development of treatments for IC depends – is based on a definition that is largely unconsidered in the diagnosis process, there will inevitably be a disparity in the efficacy of treatment on "research" IC and "real-life" IC.

Currently, diagnosis of IC is based on a holistic evaluation of symptoms and selected tests by a medical provider; in other words, the diagnostic process is catered to each individual. A simplified model of this diagnosis pathway and ensuing treatment can be seen in Figure 2. While holistic evaluation will always be an important component in IC diagnosis, it seems that at least some of the subjectivity of IC diagnosis arises from the lack of a comprehensive, universal set of diagnostic guidelines. Various national and international guidelines have been introduced in the past 14 years in response to the shortcomings of the NIDDK-based diagnosis. As of 2019, there are 10 major sets of guidelines for the diagnosis of IC of adequate quality (as classified by Pape et al., 2019). These guidelines hold varying degrees of consensus over the efficacy of each of the aforementioned treatment methods outlined by Pape. For

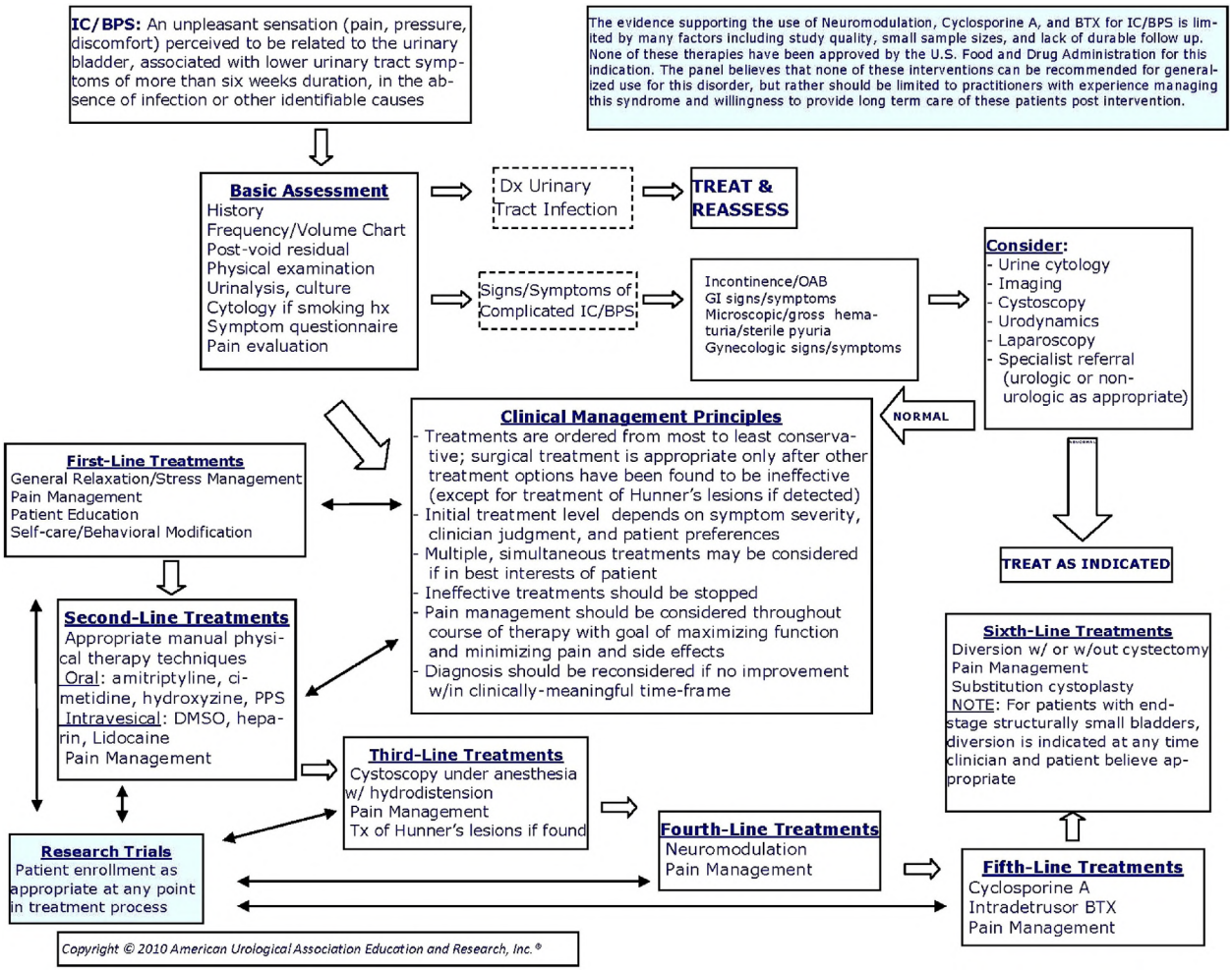

Figure 2. Visual representation of diagnosis and treatment processes for IC. Image from Hanno et al., 1999.

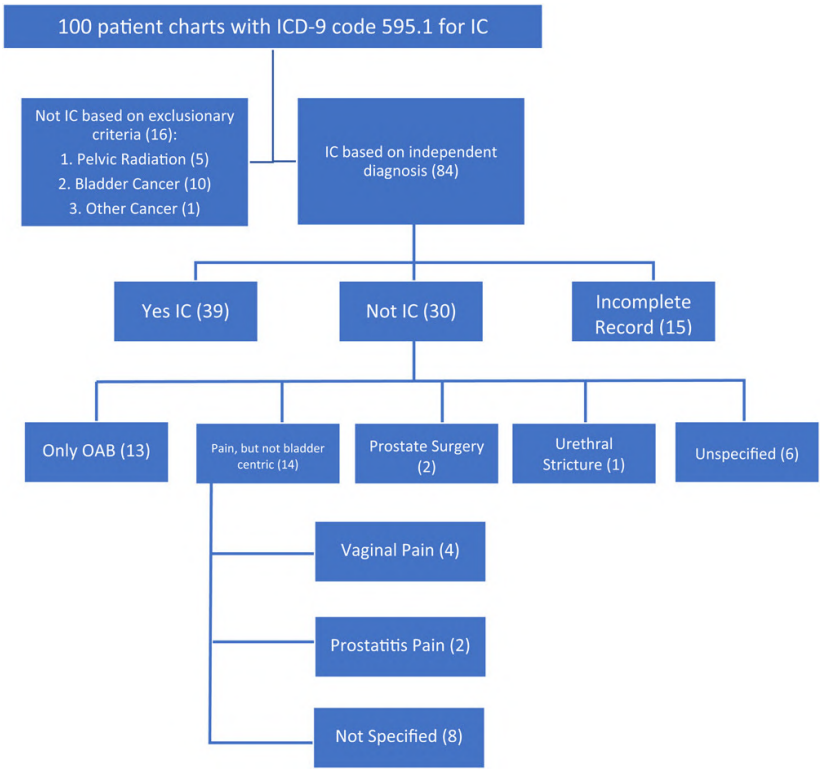

Figure 3. This breakdown of reevaluated IC cases demonstrates the high proportion of misdiagnoses. Image from Skove et al., 2019.

instance, evidence for the efficacy of treatment of IC via pentosan polysulfate sodium is assessed as "high" (A) by the Royal College of Obstetricians and Gynecologists guidelines but is deemed "very low" (D) by the Canadian Urological guidelines. As a consequence of nebulous diagnosis parameters, studies show that there is also a high rate of misdiagnosis for IC. As Figure 3 shows, a study determined that only 39 of 84 individuals with independent IC diagnosis actually had IC, while the remaining individuals had other forms of pelvic pain, overactive only, or other unspecified conditions and had been misdiagnosed with IC (Skove et al., 2019). On the flip side, evidence suggests that there may be a significant number of undiagnosed IC cases, especially since requirements for cystoscopic tests have become more lax due to the large number of individuals who exhibit the symptoms of IC but do not have a formal diagnosis (Clemens et al., 2005). The fact that IC is both frequently misdiagnosed and underdiagnosed emphasizes the flaws in the current diagnosis system.

The fact that IC is both frequently misdiagnosed and underdiagnosed emphasizes the flaws in the current diagnosis system.

Clearly, there are numerous possible causes for IC. Since treatments are meant to target an identified cause, the abundance of physiological causes of IC identified by biomedical research brings about a diversity of IC treatment options. To name just a few, current treatments for IC include mucosal surface protectants, antihistamines, antidepressants, pathway desensitization via DMSO, and even botulinum toxin injections (Chancellor & Yoshimura, 2004). Highlighting just how many treatments for IC are officially cataloged by diagnosis guidelines, Pape et al. (2019) identify over 40 treatment methods ranging from conservative therapies to surgical interventions; over half of these are oral and intravesical pharmaceutical treatments.

It could be argued that this flexible array of treatments would be well-suited to the current diagnosis model for IC (given that most cases have differing root causes or even no identifiable cause). However, while medical providers can predict which forms of treatment will work best for patients based on the specifics of their cases, this is not a perfected process. The lack of a broadly successful treatment pathway is a frustrating dilemma for healthcare providers and patients alike; for instance, one study found that 44% of women with IC and bladder pain syndrome had tried three or more prescription pain medications since their diagnosis (Tholemeier et al., 2022). Furthermore, significant issues arise in the efficacy of these treatments. As Chancellor and Yoshimura conclude in their review of current treatments, "Although there has been some success with these agents, [no pharmacologic treatment for IC] has been satisfactory" (Chancellor & Yoshimura, 2004). The available treatment options for IC are all associated with high risk, adverse side effects, low efficacy,

or a combination of the three. The seldom straightforward path to finding an effective treatment for an individual may further contribute to the stress and diminished quality of life associated with IC.

Ideally, the scientific community could eventually come to a "worldwide evidence-based consensus" on how IC should be diagnosed and treated (Pape et al., 2019). Our current understanding suggests that a straightforward answer simply does not exist, pointing to the importance of patients' lived experiences in the clinical diagnosis process (Jutel, 2011). Furthermore, greater consensus and clarity on the diagnosis of IC would help ensure more accurate diagnoses and allow more people with IC to access treatment. Most importantly, it is essential that research on new, innovative forms of treatment for IC is well-funded and supported. After all, while IC is often-overlooked due to the stigma surrounding it, it greatly impacts many peoples' everyday lives. While a path to clarity is far from simple, patients with IC deserve the quality of life that more comprehensive and effective treatment would provide. ❧

AUTHOR BIO

Grace is a second-year double-majoring in Biology and Anthropology with Human Biology. She is interested in biomedical research and plans to pursue a PhD after college.

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Placed by Claire Gong

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Neuroprosthetics and neuromorphic technology: Restoring movement to the paralyzed

ESTHER JUNG
Staff Writer

A life-threatening car accident on the highway, an accidental blow to the back during sports practice, or a bad fall from a 20-foot tall ladder can all change the course of a life within a split second. Spinal cord injuries (SCIs) are often caused by preventable incidents, like road traffic crashes, falls, or violence, yet they occur between 250,000 and 500,000 times every year worldwide (World Health Organization, 2013). About half of SCIs lead to chronic paralysis, which can result in partial or complete loss of sensory and motor function in the body. SCIs can also cause chronic pain and are associated with higher lifelong mortality rates and a loss of independence. In addition to the taxing physical impacts, SCIs are a financial burden for patients, averaging from 1.2 to 5.1 million dollars per patient over their lifetime for costly hospital stays, surgeries, medications, and rehabilitative physical therapy (University of Alabama at Birmingham, 2020). For decades, scientists and physicians have been trying to reverse damage to the spine and nervous system to improve patients' lives. In recent years, scientists have discovered how to make devices that mimic the structure and function of neurons using advanced prosthetic technology that integrates biomedical engineering, materials science, and robotics.

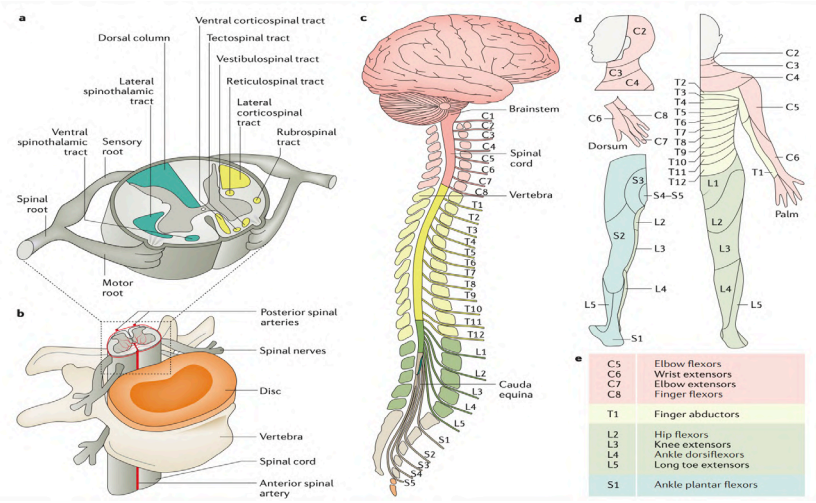

Figure 1. The spinal cord, made up of bundles of neurons, carries signals between the body and brain, and each region inervates a specific part of the body.

The spinal cord—a key component of the central nervous system—primarily consists of neurons that transmit information between the brain and peripheral nervous system, which innervates the rest of the body. This strand of nervous tissue, about a finger thick, delivers sensory information from the body to the brain and conveys motor signals from the brain to the limbs and organs (Schwab, 2002). To shield the neurons of the spinal cord from harm, a layer of cerebrospinal fluid cushions the neurons against the vertebral column made up of protective bone and ligament (Figure 1). When the spinal cord experiences trauma, neuronal cells are damaged and can take up toxic products released by dying neurons; sometimes, the spinal cord is compressed or even severed. The blood-spinal cord barrier, which separates the spinal cord from toxins, blood cells, and pathogens from the bloodstream, may also be compromised, allowing blood to leak into the spinal cord and cause hemorrhages (Ahuja et al., 2017). These events are collectively called the "primary phase of injury." This triggers a sustained, complex secondary cascade that causes the death of neurons and brings inflammatory cells to the site of injury (Ahuja et al., 2017). The persistent presence of inflammatory cells causes additional cell death, contributing to increased neurological dysfunction. Within weeks, nerve fibers at the site of injury are replaced by cystic cavities surrounded by scar tissue (Schwab, 2002). Each segment of the spinal cord innervates a specific region of organs and muscles (Figure 1). SCIs often cause loss of sensation and/or motor function below the level of the injury, as the region(s) of spinal cord below the damaged site

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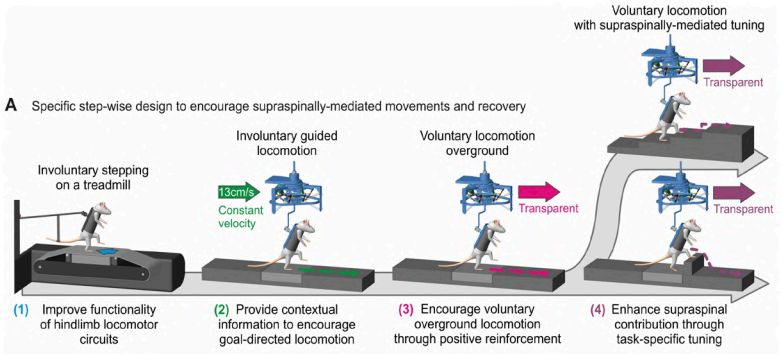

Figure 2. Multi-system neuroprosthetic training program, including robotic postural interface that supports rat vertically and laterally but does not facilitate movement to encourage the rat to initiate movement on its own.

cannot properly transmit signals between the peripheral nerves and brain.

Anatomically, SCIs can be defined as either complete, where the spinal cord is altogether severed by the injury, or incomplete, where the injury does not cut through the entire spinal cord and a portion of the spinal cord remains intact. Researchers believe that functional recovery is possible in patients with incomplete SCIs; plasticity, the ability of the nervous system to modify its activity by changing its structure or connections, is retained by strengthening the connections in the remaining intact bridge of neurons at the injury site (Raineteau & Schwab, 2001; Schwab, 2002). Patients with incomplete SCIs, as well as animal models of incomplete SCIs, have demonstrated functional recovery, although outcomes differ from patient to patient—recovery can take anywhere from months to years to fully develop (Raineteau & Schwab, 2001). In 2012, Dr. Grégoire Courtine and his lab developed a novel robotic neuroprosthetic and training program in rats by studying incomplete SCIs. Rats received two incomplete cuts to their spinal cords, one left of thoracic (T) vertebra T7 and one on the right side at T10. This SCI left a bridge of intact nerve tissue but caused a complete loss of hindlimb function in the mice with no sign of recovery over 2 months post-injury (van den Brand et al., 2012). After inducing the SCI, the same researchers administered electrical stimulation to intact spinal segments above and below the cuts while simultaneously introducing a cocktail of neurotransmitters, including serotonin receptor and dopamine receptor agonists, or drugs that bind to receptors to produce the same response caused by neurotransmitters. The stimulation paired with the drugs allowed sensory information to become a source of control for hindlimb stepping, and researchers observed the paralyzed rats display coordinated but involuntary locomotion on a treadmill.

Patients with incomplete SCIs, as well as animal models of incomplete SCIs, have demonstrated functional recovery.

Despite early progress showing that recovery of hindlimb movement is possible, Courtine's lab wanted to restore locomotion initiated by the rat rather than the involuntary movements triggered by the combination of the treadmill, electrical stimulation, and neurotransmitters. The rats were introduced to a robotic postural interface that supported the rat to be vertical and bipedal but did not facilitate locomotion in any direction. Even with the robotic interface, none of the rats were able to initiate hindlimb locomotion voluntarily without the treadmill. As a result, researchers introduced a training paradigm to the rats to encourage voluntary movement. The researchers utilized a positive reinforcement paradigm that forced the rats to voluntarily use their hindlimbs overground to reach a food target. The training paradigm, combined with electrochemical stimulation, was employed for 30 minutes a day for 5 to 6 weeks. Afterward, all of the rats could both initiate and sustain full weight–bearing bipedal locomotion for extended periods of time, but only during the electrochemically enabled motor states (van den Brand et al., 2012). The researchers even began introducing stairs and obstacles to the previously-paralyzed rats to fine-tune voluntarily mediated locomotion.

Some scientists argue that current neuroprosthetics are too clunky and require too much energy. This rationale spurred a team of researchers at Seoul National University to generate new implants that are less rigid than typical neuroprosthetics and require less power. The stretchable neuromorphic efferent nerve (SNEN) developed in Dr. Tae-Woo Lee's lab in Seoul improves

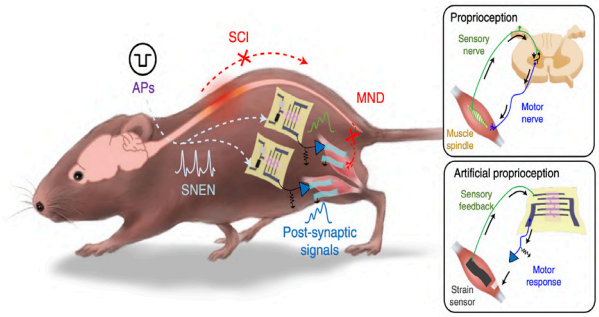

Figure 3. SNEN mimics organic electronic synapses that are able to bypass the damaged nerves and relay signals to the muscle while providing proprioception

current neuroprosthetic designs by acting as an artificial neuron that receives excitatory signals while providing proprioceptive signals (Figure 3). Proprioception, or the perception of the position and movement of the body, is key in motor functions like standing and walking, but neuroprosthetics rarely supply proprioceptive function to paralyzed subjects. The SNEN is made of a carbon nanotube (CNT) strain sensor in an artificial proprioceptor, an organic semiconducting nanowire and an ion gel in a stretchable synaptic transistor, and soft hydrogel electrodes (Lee et al., 2022). The CNT strain sensor can detect strain in the muscle and regulate its voltage to the transistor, which emulates excitatory postsynaptic currents typically found in a biological synapse. Together, these components allow voluntary movement to be restored through a closed negative feedback loop, enabling the mouse to prevent muscle damage due to overstretching of the muscles, which might otherwise be overlooked without proprioceptive feedback. Dr. Lee's lab found that in paralyzed mice supported vertically and laterally, similar to the support provided by van den Brand et al.'s robotic interface, mice displayed recovery of voluntary motor function for bipedal walking (Lee et al., 2022). This neuroprosthesis is more energy-efficient than other neuromorphic implants currently available. Its power consumption of 6.1 mW is significantly lower than comparable systems consisting of silicon integrated circuit chips with a microprocessor because the SNEN operates only in response to events, while the microprocessor system must operate continuously.

Although a diagnosis of SCI seemed like an irreversible predicament just a few decades ago, modern advancements in medicine and engineering enable breakthroughs in SCI research. Dr. Courtine's lab at the Swiss Federal Institute of Technology Lausanne (EPFL) continues to delve into the repair and rehabilitation of SCIs in patients, and some of their recent research has extended to human subjects as well. An article published by Courtine's lab earlier this year revealed that targeted epidural electrical stimulation (EES) is capable of restoring trunk and leg motor functions to paralyzed patients. Although the treatment requires patients to undergo extensive preparation and surgery, three previously paralyzed patients emerged from the study with recovery of standing, walking, cycling, swimming and trunk control (Rowald et al., 2022). The groundbreaking research done by Dr. Coutine and his team, as well as the achievements attained in Dr. Lee's lab in Seoul, brings to light incredible progress made for patients with SCIs. Some caveats still remain in SCI research; for example, patients with complete SCIs with a fully severed spinal cord face much more difficulty regaining function than those with incomplete SCIs. Another challenge researchers face is translating research done in animal models to human patients, a common barrier in many clinical trials. For example, the robotic support interface introduced by van den Brand et al. may be clunky and impractical for the everyday lives and activities of human patients with SCIs. However, with the tremendous progress that has been made within the last decade, it's clear that many life-changing treatments lie ahead.

AUTHOR BIO

Esther is a third year majoring in Neuroscience and Behavioral Biology. Her interests in medicine line in neurology, psychology, and genetics.

Edited by Alicia Yin, Daphne Ih and Dr. Gregg Orloff

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Good in theory: Inaccessibility of RU-486, the at-home abortion pill

ASHLEY ZHU
Staff Writer

In 1980, French company Roussel Uclaf discovered RU-486, better known as Mifepristone, a synthetic steroid that can be used for termination of an early intrauterine pregnancy. Mifepristone's high affinity for progesterone—a crucial hormone in the establishment and maintenance of pregnancy—allows it to block progesterone's action and terminate early pregnancy, particularly when used in combination with 800 mcg of misoprostol (Fiala, 2006). Its ability to induce abortion with only a small, 200 mg pill was revolutionary; it showed 96% efficacy and worked just as well as vacuum aspiration, the most widely used abortion technique at the time (Fiala, 2006).

Progesterone is a hormone essential in the preparation of the uterus for implantation of a fertilized ovum. During the second phase of the menstrual cycle, progesterone causes the proliferation of the endothelial lining in the endometrium—the mucous membrane that lines the uterus—leading to a thickened endometrial wall (Cable, 2022). This mucosal thickening in the cervix also plays an important role in innate immunity by establishing barriers to infections and secreting immune cells such as leukocytes (Cable, 2022). After fertilization, progesterone plays a role in sustaining pregnancy by suppressing ovulation, which decreases uterine smooth muscle contractility and lessens maternal immune response (Corey, 2012). Contrary to other steroid hormone receptors, the progesterone receptor is confined to a few specific organs and is found in especially high concentrations in early pregnancy and after estrogen exposure (Corey, 2012).

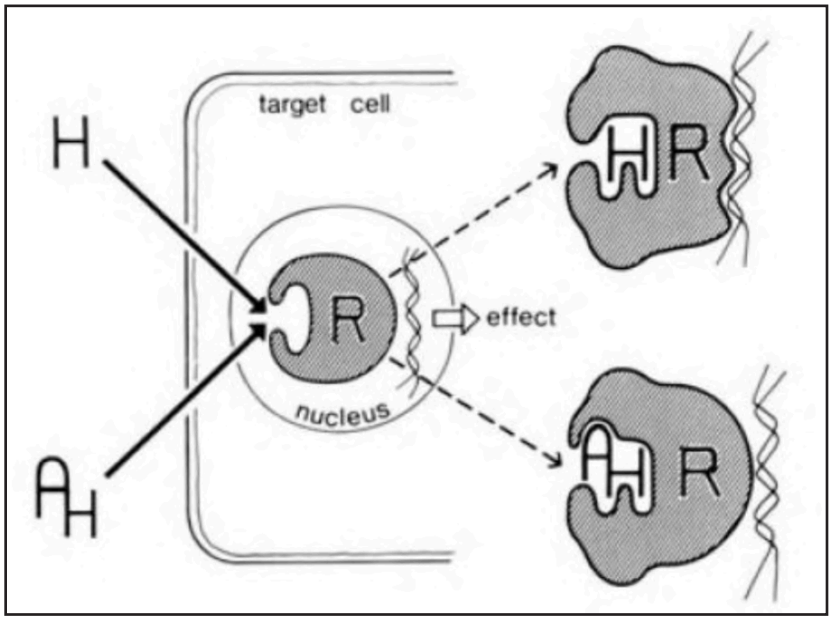

Figure 1. *The effect of a hormone compared to an anti-hormone is shown; the hormone triggers a conformational change, causing the transcriptional response of target genes, while the antihormone triggers a conformational change that does not cause any biological response. The progesterone receptor is essential for progesterone activity, and Mifepristone acts as an anti-hormone that inhibits its response.*

There is little evidence justifying restricting access to medication abortion based on socioeconomic factors.

Scientists discovered that Mifepristone perfectly antagonized progesterone action, binding tightly to the progesterone receptor and completely blocking its action. Mifepristone leads to degeneration of the decidua, the uterine lining, and causes the softening of the cervix, a normal process leading up to the start of labor (Corey, 2012). This causes detachment of the blastocyst, and decreased progesterone production results in further breakdown of the decidua (Corey, 2012). Prostaglandin levels are also increased and the sensitivity of the uterus towards prostaglandins is enhanced, leading to uterine contraction, ultimately causing the expulsion of the detached blastocyst (Corey, 2012).

Despite such advanced technologies, low-income women still remain disproportionately

impacted by unintended pregnancies. Abortion providers have been shown to be reluctant to offer medication abortion to certain populations, citing concerns of inappropriate use of emergency services and incorrect use at home (Teal, 2009). However, previous studies have demonstrated that adequate counseling results in safe and proper utilization even for women with limited health literacy or supervision (Teal, 2009). A study of 900 women in urban and rural India showed that perfect use and typical use rates rivaled those seen in European trials; another study of 1373 women in India, Cuba and China found that subjects receiving medication abortion were highly satisfied (Winikoff, 1997). A study by Teal et al. comparing adherence rates between a population of only Spanish-speaking Latinas and a bilingual English/Spanish population showed equally high rates of adherence to therapeutic regimen. There has been little evidence justifying restricting access to medication abortion based on socioeconomic factors.

Abortion providers have been shown to be reluctant to offer medication abortion to certain populations, citing concerns of inappropriate use of emergency services and incorrect use at home (Teal, 2009).

Internationally, a large number of countries uphold anti-abortion laws. Ireland, a country that legalized abortion in 2018, is a prime example of a state that has historically held a severe stance against abortion. The previously "Abortion-free Ireland" resulted in women travelling overseas to end pregnancies; but this changed with the advent of Mifepristone within Ireland (Sheldon, 2016). In 2001, an estimated 6,672 women gave Irish addresses when ending pregnancies in England, but by 2015, that number had almost halved, due in part to the availability of medications over the internet (Sheldon, 2016). Few women experienced serious side effects when using pills for early abortion, and pain was reportedly manageable using over-the-counter analgesia. In an interview with Women Help Women (WHW), an interna-

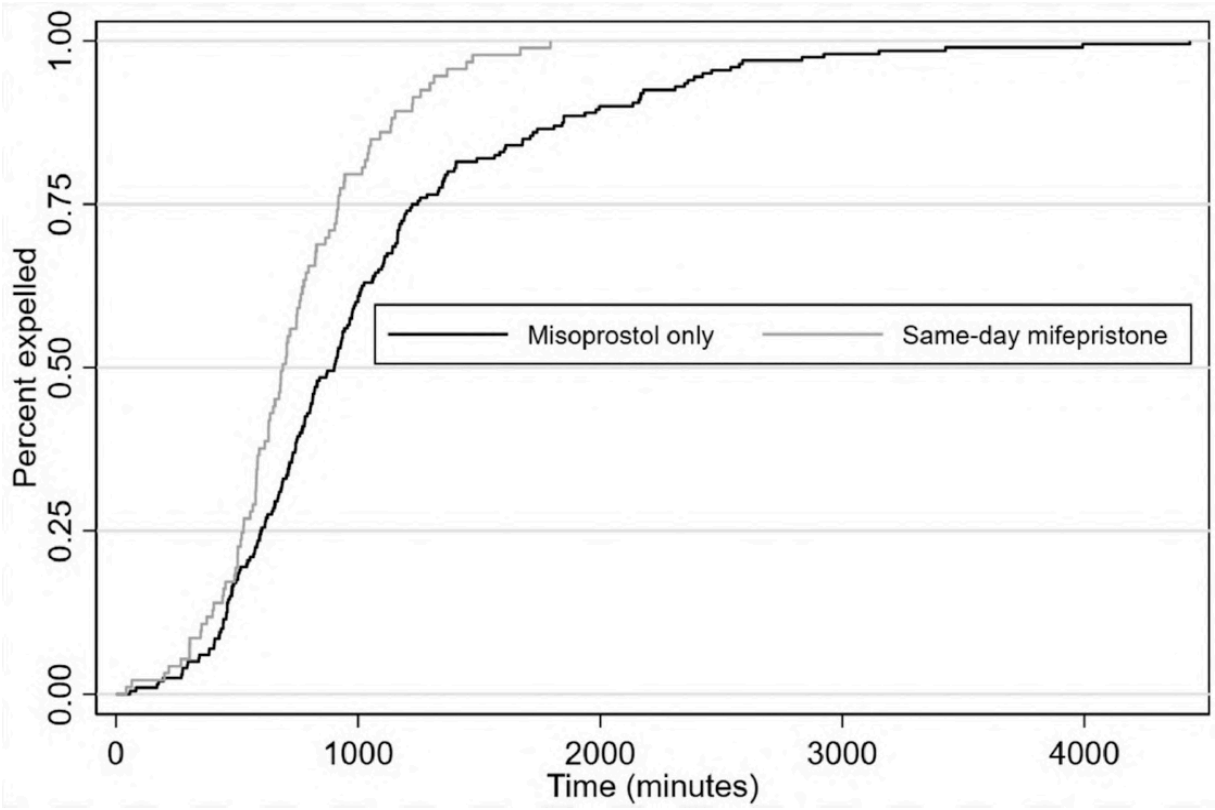

Figure 2. *While same-day Misoprostol results in around 95% fetal expulsion in a median time of 901 minutes, the Mifepristone + Misoprostol combination treatment resulted in the same percentage of expulsion in a median time of 689 minutes.*

	All subjects	Some English	Spanish only
	N=270	*n*=166	*n*=104
Compliance with procedure			
Took misoprostol correctly	95.8%	95.7%	96.0%
Attended first follow-up visit without prompting (no reminder call)	90.0%	91.0%	88.3%
Lost to follow-up	2.2%	1.8%	2.9%
Efficacy			
Complete abortion	97.7%	98.2%	97.0%

Figure 3. *The outcome of all subjects and subjects who identified as speaking some English-speaking vs. Spanish-speaking only. The efficacy of complete abortion and compliance with procedure was high and relatively the same between both groups, showing that there is little difference between English-speaking and Spanish-speaking only groups.*

tional non-profit organization working on access to abortion the importance of women having clear instructions on how to properly utilize the medication was underscored—however, there is no evidence that women struggle to follow the simple instructions. According to Kinga Jelinska of WHW, "The potential of the technology of self-administration of medical abortion is incredible. It can empower women and they can do it in the privacy of their own home" (Sheldon, 2016).

An interesting final case to examine is the implementation and acceptability of Mifepristone in the North Korea, where surgical abortion via vacuum aspiration is the only method of abortion available. Though the level of education is high and healthcare can be accessed in remote areas, major healthcare problems stem from a lack of resources and outdated principles and techniques (Tran, 2010). A study conducted by Tran et al. aimed to determine whether medical abortion using Mifepristone-Misoprostol is a feasible and safe mode of abortion for North Korean women. The result for the study was consistent with trends found in other international studies—the efficacy level of Mifepristone was at just above 95%. Bleeding was a concern, but it did not result in adverse events from any of the women in the study. Furthermore, all women fully complied with the protocol, demonstrating the value of comprehensive counseling in both urban and rural women. The addition of medical abortion served as an easily accessible complement to surgical services and improved access to high-quality abortion services in North Korea (Tran, 2010).

Intertwined with a host of legal and psychological implications, the barriers that prevent women from obtaining abortion services continue to pose a key issue of accessibility.

Irregardless of any socioeconomic or moral considerations surrounding RU-486 one core fact remains clear: at the pharmacological level, Mifepristone is a highly effective progesterone inhibitor, and is undoubtedly a reliable mode of at-home abortions. However, intertwined with a host of legal and psychological implications, the barriers that prevent women from obtaining abortion services continue to pose a key issue of accessibility. ❧

AUTHOR BIO

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Doulas in the Black community: A possible solution to the Black maternal health crisis

KAYLA ROBINSON
Staff Writer

Table 1

Support Measures Provided During Labor

Physical		Psychosocial	
Nurse	**Doula**	**Nurse**	**Doula**
Holding legs	Massage	Verbal encouragement	Verbal encouragement
Vital signs	Counter pressure		Music
IV insertion	Assistance with bath/shower		Calm environment
Cervical exams	Coached breathing		Reassurance
	Positioning		Presence
	Walking		Focus
	Swaying		Love
	Homeopathic remedies		
	Ice chips		
	Birthing ball		
	Warm compress		

Figure 1. Doula support measures given during birth

In May of 2022, Republican Louisiana Senator Bill Cassidy, a co-sponsor of the Maternal Health Quality Improvement Act, stated in reference to Louisiana's maternal mortality rates: "If you correct our population for race, we're not as much of an outlier as it'd otherwise appear." He continued claiming that people of color have a higher maternal mortality rate for "whatever reason" (NBC, 2022). The dismissiveness and ambiguity toward health disparities in a state with a large population of color widen the healthcare disparity gap and continue to ignore a pressing issue that takes the lives of historically disadvantaged mothers each day across the nation. Louisiana has historically ranked low among other states when comparing health quality, with one of the highest maternal mortality rates, 31.8% of live births between 2018 and 2020 (CDC, 2021). However, Louisiana is not the only state with such concerning maternal mortality rates; it is a nationwide problem that has yet to be solved, especially for birthing women of color.

"If you correct our population for race, we're not as much of an outlier as it'd otherwise appear" (NBC, 2022).

The United States has an alarming maternal mortality rate compared to other first-world, industrialized countries, at 17.4 deaths per 100,000 live births compared to France at 8.4 and New Zealand at 1.7 (Tikkanen, 2020). The nation's Black maternal mortality rate is nearly 3 times the maternal mortality rate, with 41 deaths per 100,000 live births (Robinson, 2021). The disturbing statistics related to Black maternal mortality receive minimal legislative and healthcare attention outside grassroots movements such as the Black Maternal Health Caucus. The 2022 documentary, Aftershock is one of the few media depictions that portray the effects of Black Maternal Health disparities. The documentary follows the aftermath of the deaths of two Black mothers who died during childbirth within six months of each other in New York City. Directors Paula Eislet and Tonya Lewis Lee proposed possible solutions to the problem, citing midwifery and doulas as evidence-based interventions and removing the stigma around holistic maternal professionals having an active voice in the birthing process of a mother (Valenti, 2022).

The Biden-Harris administration released a blueprint outlining the federal agenda to address the Black Maternal Health Crisis (White House, 2021). The fact sheet acknowledges that the high Black maternal morbidity rates stem from systemic racism and are rooted in implicit biases. The Biden-Harris call to action included investing $200 million to implement implicit bias training in healthcare facilities, expanding insurance for postpartum care, and expanding and diversifying the perinatal workforce, including non-clinical professionals such as doulas (White House, 2021).

Theme	Description
1. Similarities of race, culture, and experience impact care	Racial, cultural, and experiential similarities between mother can help in the creation of a trusting mother–doula relationship
2. Doulas often step outside their role to provide mothers with extra support but cannot do it all	Doulas often link mothers to outside resources, such as nutrition and housing supports. At times find themselves as the provider of resources, such as clothing or rides to medical providers; however, taking on the extra tasks and services can lead to burnout and doulas feeling overextended
3. Doulas recognize the institutional biases that exist in the hospital system	Doula help prevent overt effects of institutional racism, such as ensuring mothers are asked consent of procedures and are addressed respectfully by medical staff

Figure 2. Themes shared among doulas of color in a 2019 study.

Doulas boomed in popularity since their introduction to postpartum care in the 1980s alongside the national trend of distress caused by Cesarean sections (Papagni, 2006). The Doulas of North America, DONA International, defines a doula as "a trained professional who provides continuous physical, emotional and informational support to their client before, during and shortly after childbirth to help them achieve the healthiest, most satisfying experience possible" (DONA, n.d). With childbirth intervention—specifically Cesarean sections—being at an all-time high with minimal infrastructural help from the government in comparison to other first-world countries, it is natural for North American women to seek non-clinical support to alleviate any negative postpartum feelings before prematurely returning to the workforce.

Doulas' duties have since expanded to pre- and postpartum care, with doulas providing support before, during, and after the birth of a child. Doulas have also become more integrated into the healthcare structure, working more alongside nurses and midwives to form a complete team for the mother-to-be (Figure 1). A 1999 study investigated the possible outcomes of providing hospital-based doulas and concluded that providing hospital-based doulas resulted in desirable outcomes for new mothers (Gordon et al., 1999). Gordon found that mothers provided with doulas used fewer epidurals and were more likely to have a positive birthing experience. A 2013 study had similar findings, claiming that women who had doula-assisted births were "two times less likely to experience a birth complication involving themselves or their baby, and significantly more likely to initiate breastfeeding" (Gruber et al., 2013). The effect of doulas in underserved communities has also been observed. Duke University graduate, June Eric-Udorie, recalls why she became a doula and stresses the importance of community-based doulas for marginalized women. She noted that doulas could play a critical advocacy role that many marginalized women—especially women of color—need when their needs are ignored or questioned by other hospital-based care providers (Abramson, 2019). Doulas can mediate, leading to fewer birth interventions and a satisfactory overall experience. There has yet to be a longitudinal study investigating the link between doula services and lowering maternal mortality. Still, the already studied positive impacts conjoined with the advocacy role that many women of color need already point to doulas being the solution to the United States' maternal mortality crisis and the Black maternal mortality crisis.

The demand for doulas may have increased, but there is an even greater demand for doulas of color. Diversifying the availability of doulas makes care more accessible to women of color; there is a greater chance of having an advocate understand the patients' nuanced experiences on a more personal level and allows for a more successful birthing plan. Dr. Kosette Kathawa explored how doulas of color conceptualize their work and found that most Black-identifying doulas stated that their identity strongly influenced their work and their want to close the gap between women of color and healthcare. One doula commented on the growing ambiguity of the term "natural birth" and how that phrase has been appropriated from women of color, stating how privilege enables specific non-Black demographics easier

Diversifying the availability of doulas makes care more accessible to women of color.

access to natural birth with minimal complications. The connection between sharing racial experiences and positive doula care was emphasized again in a 2019 study where Dr. Wint studied the relationship between low-income Black mothers and Black doulas and found a common line of thought. Doulas felt connected to their patients based on racial and cultural similarities while recognizing the impact of their actions on undoing institutional biases in the healthcare system (Figure 2).

...the significance in having an advocate who shares the same cultural and racial experiences as patients.

Sharing cultural experiences can provide great comfort for the mother, and doulas help prevent the effects of institutional racism and implicit biases in healthcare (Wint et al., 2019).

Doulas' positive effects on birthing outcomes should be further studied in the context of the Black maternal mortality rate and provide a remedy for the deaths across the nation, but anecdotal evidence, existing testimonies, and the standing body of knowledge already show the significance in having an advocate who shares the same cultural and racial experiences as patients. ❧

AUTHOR BIO

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The COVID-19 vaccine legal battle: Can Moderna even sue?

ETHAN ESSENFELD
Staff Writer

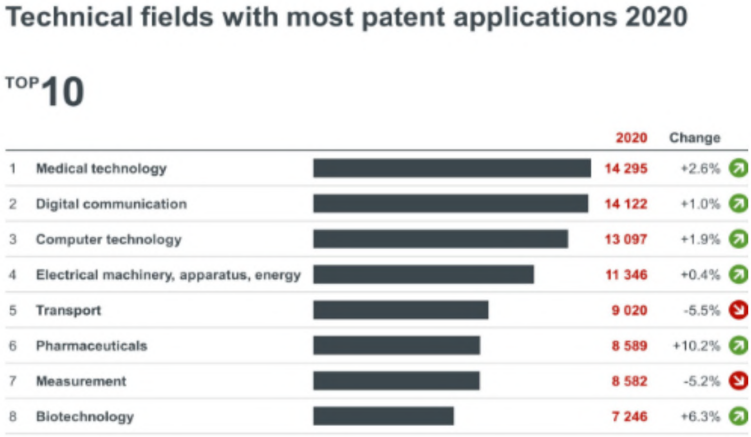

Figure 1. Patent applications by technical field in 2020. Pharmaceuticals, which the COVID-19 vaccines fall under, are the sixth most patent technology in 2020

COVID-19 controversy returns, but this time in the form of a high-profile lawsuit legal battle as Moderna sues Pfizer and BioNTech for stealing their patented mRNA technology in the creation of their COVID-19 vaccines (Modernatx & Moderna US, 2022). While patent infringement lawsuits, especially within the pharmaceutical industry, are not uncommon, this specific case is monumental since it pertains to the COVID-19 pandemic, the patent pledge Moderna made on the technology, and the future of mRNA vaccines.

In October 2020, during the height of the pandemic in the United States, Moderna made a public news announcement stating that for the duration of the pandemic, they "will not enforce our COVID-19 related patents against those making vaccines intended to combat the pandemic" while also stating that after the pandemic, they "are willing to license our intellectual property for COVID-19 vaccines" (Statement by Moderna on Intellectual Property Matters during the COVID-19 Pandemic, n.d.). However, on August 26th, 2022, Moderna filed a lawsuit against Pfizer and BioNTech on the grounds that three of Moderna's patents-US 10,898,574, US 10,702,600, and US 10,933,127-all of which have been infringed upon by the creation and subsequent commercialization and use of Comirnaty®, Pfizer and BioNTech's COVID-19 vaccine that has had over 3.6 billion doses shipped to 180 countries across the world (Cohen, 2022; COVID-19 Vaccine Equity | Pfizer, n.d.; Modernatx & Moderna US, 2022). This monumental lawsuit has come almost three months after Moderna released an updated patent pledge to "never enforce our patents for COVID-19 vaccines against companies manufacturing in or for the 92 low- and middle-income countries in the Gavi COVAX Advance Market Commitment (AMC)" while explicitly stating that they "expect those using Moderna-patented technologies will respect the Company's [Moderna's] intellectual property" (Moderna's Updated Patent Pledge, n.d.). These statements mean that Moderna will not prosecute any company that is infringing upon their patent rights if and only if they are doing so to serve the 92 countries in the Gavi Vaccine alliance. This also implies that any type of patent infringement occurring in any of the other 103 countries will result in Moderna taking legal action against those violating their patents, as demonstrated by their lawsuit with Pfizer and BioNTech in the United States and Germany.

It is undoubtedly an important part of the lawsuit to know what a patent is and how it is granted.

To understand what is happening in the lawsuit, it is undoubtedly an important part of the lawsuit to know what a patent is and how it is granted. Patents are the legal "right to exclude others from making, using, offering for sale, or selling" an invention (General Information Concerning Patents | USPTO, n.d.). It is critical to recognize that patent does not give the patent holders the right to make, use, or sell an invention, but rather exclude everyone else from making, using, or selling the invention (Patent | Wex | US Law | LII / Legal Information

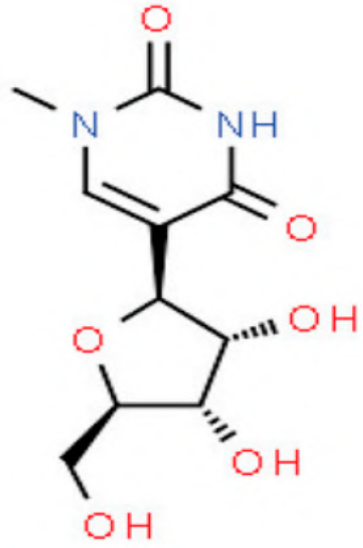

Figure 2. N1-methylpseudouridine, one of the RNA modifications in Moderna's patents that is also present in Pfizer's/BioNTech's COVID-19 vaccines

Institute, n.d.). Patents grant the patentee the right and option to sue anyone who is believed to be infringing upon the patent. They are issued by the government's federal patent office, known in the United States as the United States Patent and Trademark Office (USPTO) to inventors for their inventions.

The three types of patents are utility patents, design patents, and plant patents. Utility patents are granted to "anyone who invents or discovers any new and useful process, machine, article of manufacture, or composition of matter, or any new and useful improvement thereof" and are the patent type which medicines, such as the COVID-19 vaccines, are given (General Information Concerning Patents | USPTO, n.d.). It is extremely important that not everything is eligible for patentability. Specifically, abstract ideas, mathematical formulas, natural phenomena, natural laws, and anything that can be naturally found are ineligible for patenting. All inventions that don't fall into these categories must satisfy three requirements to be granted a patent: novelty, non-obviousness, and usefulness.

The novelty condition can be cleared if the patent is not known by the public in any capacity before the day it is filed with the USPTO. Any instance of the invention, or related invention with similar components or functions, is known as "prior art" and is always called upon in patent infringement lawsuits. If the invention is too similar to the "prior arts", then it is ineligible for patentability and is considered to be infringing upon the existing patents.

One crucial law that determines novelty is the Leahy-Smith America Invents Act which changes the U.S patent system from a "first to invent" to a "first to file" system (Leahy-Smith America Invents Act, 2011). Instead of the first documented inventors being given patent rights to the invention, the rights go to the first party that files, or applies, for the patents regardless of if they are the first inventors or not. This means that somebody who was not the first person to create this invention could legally prohibit the first inventors from making and selling the invention depending on who filed the patent application first. This change is critical in patent infringement cases as the original inventors no longer need to be determined, but rather who filed the patent application first.

This change is critical in patent infringement cases as the original inventors no longer need to be determined.

The non-obviousness element is that the invention is unable to be conceived by somebody with "ordinary skill in the area of technology related to the invention", meaning that only somebody with advanced education in the technology could be the inventor (General Information Concerning Patents | USPTO, n.d.). The final stipulation for patentability is usefulness which is defined as the invention being able to "perform the intended purpose" (General Information Concerning Patents | USPTO, n.d.). If the invention does not serve its intended function, it is unable to be patented. All these factors are considered by the USPTO when reviewing, and potentially granting, a patent application. Once a patent is granted, the inventor(s) have the exclusive right to prevent any other party from using the technology in the patent for 20 years after the patent is first filed before the technology becomes a part of public domain, or available for free use (General Information Concerning Patents | USPTO, n.d.).

Owning a patent for one's invention is always a critical component for any business plan as it is the most significant way inventors prevent others from stealing their market share and profits. Once a patented product is on the market, it can't legally be copied by the competitors until the patent protection runs out. Businesses take their patent space extremely seriously as they only have a

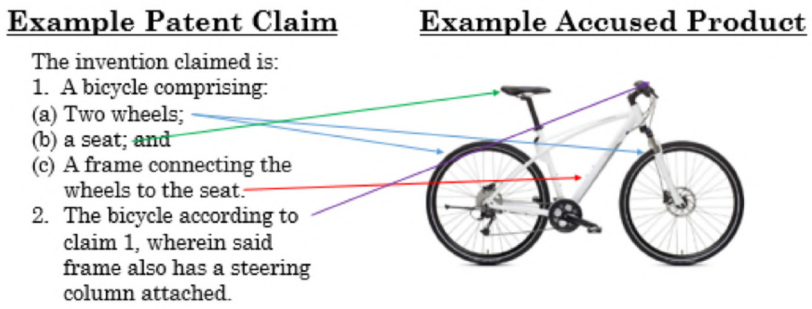

Figure 3. Example of how the claims in a patent define each component of an invention

limited time to capitalize on their exclusive rights to the invention before their competitors are allowed to legally replicate and sell their product. Owning the rights to a patent also gives the inventors the right to license the rights to other companies or giving limited permission to non-inventors to use the protected technology in exchange for money or simply sell the patent rights in its entirety. Patents, and thus patent rights, can only be awarded if the invention is filed with the USPTO. However, it is not mandatory to patent an invention, allowing others to make and use it without penalty. One common reason for a business to not enforce their patent rights is for philanthropic reasons, such as Moderna's claim in the height of the pandemic. Philanthropic patent pledges are rarely considered legally binding, meaning that whoever made the pledge is not legally forced to abide by their statement of non-enforcement. The primary contributor to making philanthropic patent pledges is to increase public perception of the company and not to influence the market, which is why they are not legally binding (Contreras et al., 2015). Moderna, in making a philanthropic patent pledge, did not establish a legal reasoning which would prevent them from creating their lawsuit against Pfizer and BioNTech.

Owning a patent for one's invention is always a critical component for any business plan.

Patents are composed of numerous sections, with the most important being the "claims". This section is where the inventors "define the scope of the protection of the patent", or list what parts of the invention are novel compared to everything else that has been invented (Non-provisional (Utility) Patent Application Filing Guide | USPTO, n.d.). The patent's protective rights are specifically for the claims. Patent infringement, when the inventors believe another party is violating these exclusivity rights, occurs if and only if the technology of at least one of the claims is found in the non-inventors' product. The inventors can then enforce their patent by suing the other party for patent infringement, which is then brought to court.

Moderna believes that Pfizer and BioNTech, with their COVID-19 vaccine, have violated three of their patents resulting in 472 million US dollars' worth of profit that should have gone to Moderna (Modernatx & Moderna US, 2022). Since Moderna believes that their patents have been infringed upon and have made a patent pledge that is not legally binding, they have sued Pfizer and BioNTech to recoup profits that they believe should be theirs. Moderna is within their rights to sue, but only time will tell if their arguments are strong enough to win the case and define the future of who owns the rights to make mRNA vaccines. ❧

AUTHOR BIO

Ethan is a fourth year majoring in Chemistry. His interests are in the drug development process and intellectual property components.

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Big pharma's middlemen: Pharmaceutical benefit managers

JUSTIN HAHM
Staff Writer

Three Pharmaceutical Benefit Manager (PBM) companies were in control of about 89 percent of the drug market as of 2022 according to the Center for Insurance Policy and Research. However, PBMs claim to be the American public's legal counsel in the fight against the pharmaceutical industry. Following the various antitrust violations of Big Pharma, the advent of Pharmaceutical Benefit Managers who would purportedly bring down medication pricing by mediating between manufacturers and vendors of pharmaceuticals picked up steam as a response to the general discontent with these large corporations. However, the emerging truth regarding the profits PBMs have garnered raises the question: whose side are they really standing for? The lack of transparency behind higher costs for medications and rebates negotiations have had rippling effects on the $369.7 billion industry of prescription pharmaceuticals in 2019 (Center for Medicare and Medicaid Services, 2020). Recent FTI investigations alongside Supreme Court cases have unraveled the ethical grounds and regulations PBMs have been subverting in the interests of their own profits and at the cost of a more equitable American healthcare system.

Health inequality in prescription medications is disproportionately higher in the U.S. compared to other countries. According to the United States Department of Health and Human Services (USDHHS) report on July 1st, 2022, U.S. prices were 256 percent of those in the 32 compared countries combined.

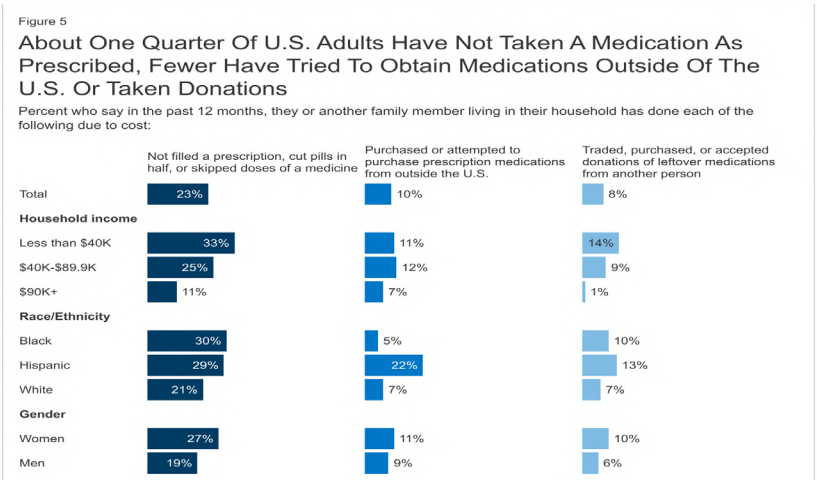

Figure 1. There are racial and socioeconomic inequalities in the accessibility of prescription-medicationns.

In comparison with individual countries, U.S. prices ranged from 170 percent of prices in Mexico to 779 percent of prices in Turkey. In 2021, among those taking prescription medications, one in four adults said they had difficulty affording the cost (Montero, 2022). This has led to deadly compromises for many Americans. Approximately a quarter of adults report that they themselves or a close family member have not filled a prescription, cut pills in half, or skipped doses of medicine due to high costs. Although this phenomenon affects even insured Americans, it exacerbates inequality within the healthcare system and disproportionately affects minority families. While affordability varies across the diversity of medications currently on the US pharmaceutical market, it is undeniable the general cost of pharmaceuticals will continue to rise despite newer innovations in analog drug manufacturing or more NIH investment towards research and development. PBMs have faltered while attempting to address this ongoing issue.

Health inequality in prescription medications is disproportionately higher in the U.S. compared to other countries.

PBMs function as a third-party administrator in the drug manufacturing supply chain. They contract with insurers to negotiate with manufacturers of drugs and manage costs on both ends. However, the major flaw in this process is their ability to profit off of spread pricing or the difference between the rebate to pharmaceuticals and their payment from health insurers. Rebates are refunds after the

transaction of a good to adjust back to its market price, which would theoretically help maintain reasonable prices. Drug rebates are usually paid after the point of sale by the manufacturer and vary based on the competitiveness of the product. Therefore, rebates effectively lower the prices of pharmaceuticals from large

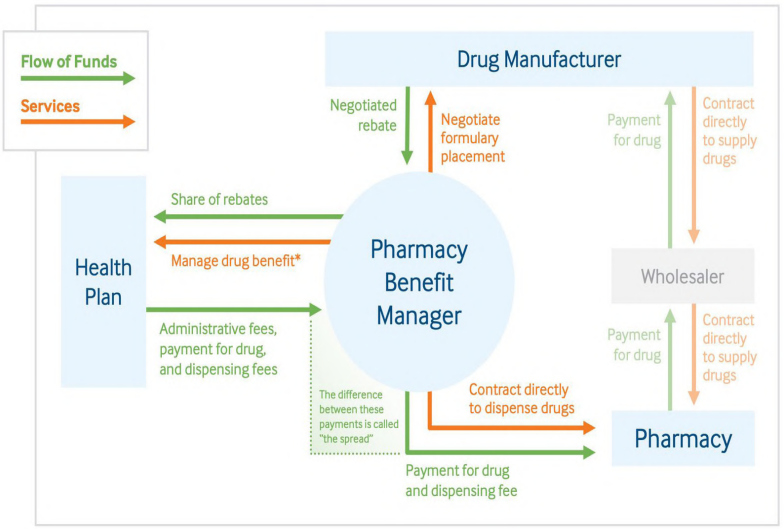

Figure 2. Pharmaceutical Benefit Managers (PBMs) manage rebates and payments from insurers and manufacturers allowing them to profit off of spread pricing.

name-brand companies. However, not all the rebates earned by PBMs are passed on to the health insurers. PBMs get reimbursed for rebates they obtain which incentivizes them to contract with high-priced brand-name drugs. Ethical models unanimously found the fluctuation of pharmacy reimbursement rates to be unethical (Drettwan, 2019). Essentially, the more expensive the drug, the more profit for the PBM. It can create the illusion that they priced down the highest quality drugs available when in actuality, there were cheaper and clinically equivalent medications in the market.

There are currently 66 PBM companies operating within the US, with Express Scripts, CVS Caremark, and OptumRx being the most notable and serving 270 million Americans (NAIC, 2022). Their services were valued as a critical cog in the convoluted world of health insurance with their conception in the 60s. However, many drug manufacturers such as CVS eventually began acquiring PBMs. Despite the conflict of interest, PBMs began to work under the very corporations that they were trying to negotiate with.

PBMs are a bandaid for an open wound in the pharmaceutical industry. Rutledge vs PCMA sets a precedent for state regulation of pricing practices that many PBMs have defaulted to in the past. The Respondent Pharmaceutical Care Management Association (PCMA) represented 11 of the largest PBMs in the United States in their legal suit against Rutledge, Attorney General of Arkansas (Supreme Court of the United States). Act 900 passed in 2015 by Arkansas required PBMs to reimburse pharmacies at a price equal to or higher than the pharmacy's wholesale price. The federal law ERISA contained a clause that prohibits states from regulating employee benefit plans. However, by upholding Arkansas Act 900, they continue to allow states to regulate the amount of PBMs reimbursements that are handed back to pharmacies. Under the dense legal technicalities surrounding this case, the fundamental issue that was resolved was the ability of states to maintain regulation of uninhibited practices that PBMs had been using to turn a profit. This Supreme Court Case exemplified how vital it is for the US government to remain vigilant in order to keep the pharmaceutical industry honest with its consumers.

Recently, the federal trade commission (FTI) announced an inquiry into the PBM industry, which required the six largest companies to provide the truth regarding their practices (Wehrein, 2022). The commission will be geared toward determining how practices have been used to potentially steer patients toward pharmacies that are consolidated with PBMs and specialty drugs. In addition, the inflow and outflow of rebates and fees will be scrutinized. This commission found bipartisan support of 5-0 even during the polarizing political spectrum (Cohen, 2022). It will take time, however, before the research is able to draw definite conclusions about the PBM industry. It leaves

PBMs are a bandaid for an open wound in the pharmaceutical industry.

the responsibility in the hands of healthcare professionals who will have to advise their patients about prescription medications.

In conclusion, despite the potential benefits that PBMs have to offer, the lack of transparency in the industry has left much to be desired in the accessibility of pharmaceuticals. It encourages the government and healthcare workers to remain inquisitive about the accessibility of medication vital to America's health. As pricing for Epi-pens and other prescription medications continue to take the headlines, there needs to be greater consideration of how the dollar is invested in the healthcare system. ❧

AUTHOR BIO

Justin is a second year majoring in Biology and Economics. His interests are in autoimmune conditions, controversial Big Pharma policies, and economic issues pertaining to healthcare equity.

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Chronic traumatic encephalopathy: The long-term consequences of chronic head injuries

CLAIRE ZEGGER
Staff Writer

Although many college students would agree that football is a fundamental part of the collegiate experience, the lack of a football team at Emory University might be saving lives. Playing contact sports, like football, shows a strong correlation with the development of Chronic Traumatic Encephalopathy (CTE), a neurodegenerative disease caused by repetitive traumatic brain injuries (McKee et al., 2015). In addition to professional athletes, CTE has been found in military veterans and blast victims. Some of the clinical characteristics of CTE include increased levels of aggression, depression, and anxiety, as well as cognitive symptoms such as dementia (Mayo Clinic, 2022). Although signs and symptoms of CTE can be identified in living patients, a diagnosis can only be confirmed post-mortem through brain tissue analysis (Corrigan et al, 2021). While there is currently no treatment for CTE, researchers are continuing to study the pathophysiology of the disease with the goal of developing drugs to prevent its progression.

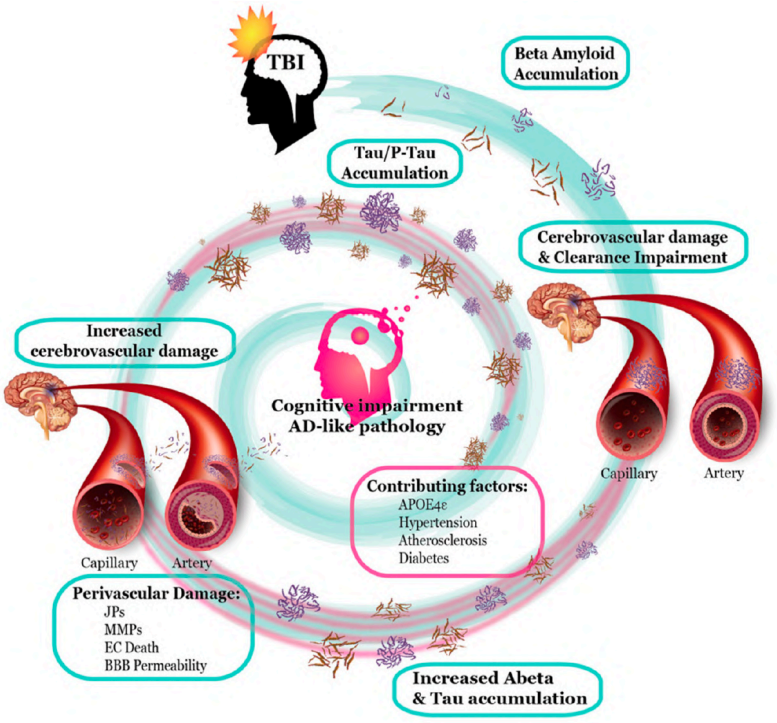

Figure 1. Schematic of how TBI disrupts cerebrovascular function, leading to the characteristics of Alzheimer's disease (Ramos-Cejudo et al., 2018)

Information about CTE has existed in medical literature for nearly a century, but it has taken many decades to identify its neuropathological features. The behavioral characteristics of CTE were first medically described by Dr. Harrison Martland in 1928, long before the condition held a scientific name (Ramos-Cejudo et al., 2018). During his years as a medical examiner, Martland noticed a common pattern of neurological symptoms in professional boxers, including confusion, mental deterioration, and loss of balance (McKee et al., 2015). Martland called the condition "punch drunk" syndrome, and it wasn't until the 1940s that the term "Chronic Traumatic Encephalopathy" became popular (McKee et al., 2015). In the 1970s, researchers first began to study the underlying structural changes in the brain caused by CTE, such as the formation of neurofibrillary tangles, which occur when piles of hyperphosphorylated tau proteins collect inside of neurons (McKee et al., 2015). The study of CTE and its potential risk for professional athletes in high impact sports gained prominence in the early 2000s when neuropathologist Dr. Omalu published the first pathological evidence of CTE in an NFL player (Omalu et al., 2005). Since then, public awareness of the disease has rapidly spread, prompting further research into early detection methods.

Playing contact sports, like football, shows a strong correlation with the development of CTE.

The clinical symptoms of CTE can be divided into two categories: mood/behavioral and cognitive (Stern et al., 2013). Behavioral/mood symptoms include increased aggression, impulsivi-

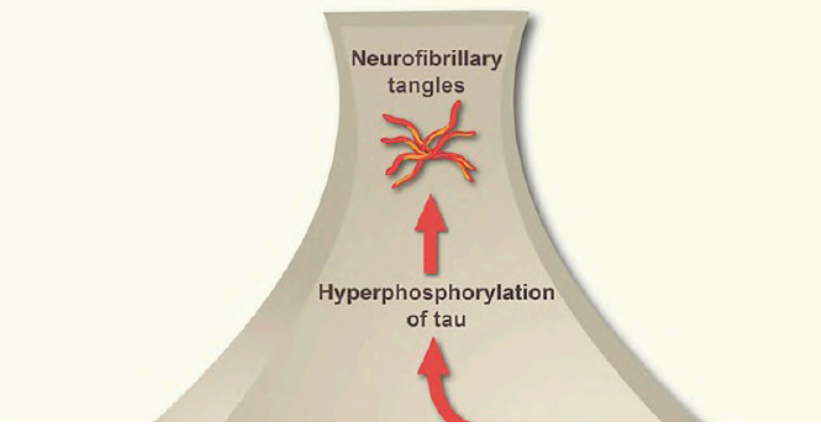

Figure 2. Diagram depicts steps of NFT formation from TBI at the neuronal level (Corrigan et al., 2021)

ty, and depression, whereas cognitive symptoms include declining motor control and memory loss (Stern et al., 2013). In young CTE patients, the first symptom is commonly behavioral or mood related, but many CTE patients do not experience any symptoms until much later in life. In the latter case, the first detected symptom is typically cognitive in nature (Stern et al., 2013). These two categories of symptoms are not, however, mutually exclusive, and many individuals who initially exhibit behavioral or mood-related symptoms eventually develop cognitive symptoms (Stern et al., 2013). In a study of 81 subjects with pathologically confirmed CTE, the average age of the subjects who initially exhibited a behavioral/mood symptom was 34.5 years, which was significantly younger than the average age of 58.5 years for the cognitive symptom cohort (Stern et al., 2013). Although the reason behind this distinction in symptoms remains unclear, it is possible that the cognitive symptoms of CTE may be tied to age-related neurological deterioration.

As stated above, CTE in older individuals commonly presents with cognitive symptoms that closely mimic dementia as seen in Alzheimer's disease. Beta amyloid plaques, a pathological hallmark of Alzheimer's disease, are also occasionally found in CTE brain tissue (McKee et al., 2015). These plaques occur when broken down proteins build up in the brain, disrupting neuronal functions. Given the pathological similarities between CTE and Alzheimer's disease, researchers are currently investigating how these two conditions might be related. In a 2018 review, Ramos-Cejudo and colleagues explored how reduced cerebral blood flow might be the causal link between traumatic brain injuries (TBIs) and Alzheimer's disease (Ramos-Cejudo et al., 2018). TBIs can lead to ruptured blood vessels, inflammation, and abnormal blood clotting, as well as neurofibrillary tangles, which cluster around blood vessels and restrict blood flow to the surrounding cells and neurons (Ramos-Cejudo et al., 2018). Based on their findings, the researchers from this study proposed that a TBI potentially initiates a chain reaction of devastating neurological events including beta amyloid accumulation, which, in conjunction with cerebrovascular disruption, ultimately leads to Alzheimer's-like cognitive impairment (Figure 1).

Given the pathological similarities between CTE and Alzheimer's disease, researchers are currently investigating how these two conditions might be related.

A central pathological characteristic of CTE is the presence of neurofibrillary tangles (NFTs), also known as tau tangles. These tau tangles are believed to be implicated in the behavioral and neurological symptoms of CTE (Corrigan et al, 2021). The role of normal tau proteins is to stabilize microtubules, which operate like highways for cellular transportation. However, when tau proteins become hyperphosphorylated, this process is disrupted– as well as cellular function (Corrigan et al., 2021). The exact mechanism by which an external head injury causes NFTs is still not entirely clear, but researchers believe that the process is mediated by substance P, a neuropeptide involved in the brain's pain and inflammatory response systems. Head injuries stimulate the release of substance

The results of this study reflect promising prospects for the development of a drug that might be able to prevent tau angles in individuals who area who are at risk for CTE.

P, which binds to a receptor that activates the phosphorylation of tau proteins, forming neurofibrillary tangles (Figure 2).

Through extensive examination of CTE brain tissue, researchers have identified characteristics to divide the disease into four stages of severity. It should be noted that the brains used in these studies were donated by former CTE patients after their death, and that without their contributions many of these discoveries would not have been possible. Stage I brains rarely show macroscopic differences compared to normal brains, but microscopic tau-tangles are found in the sulci of the cerebral cortex, particularly in the frontal, temporal and parietal lobes (McKee et al., 2015). In stage II, more dispersed patterns of neurofibrillary tangles appear throughout the cerebral cortex (McKee et al., 2015). Stage III is the first stage in which amyloid beta plaques can be found, though they are more common in CTE brain tissue from patients who were older at their time of death (McKee et al., 2015). The fourth and most severe stage is characterized by macroscopic changes, most notably a reduction in brain weight (McKee et al., 2015). NFTs are also widely spread throughout the cerebrum, brain stem, and diencephalon (McKee et al., 2015).

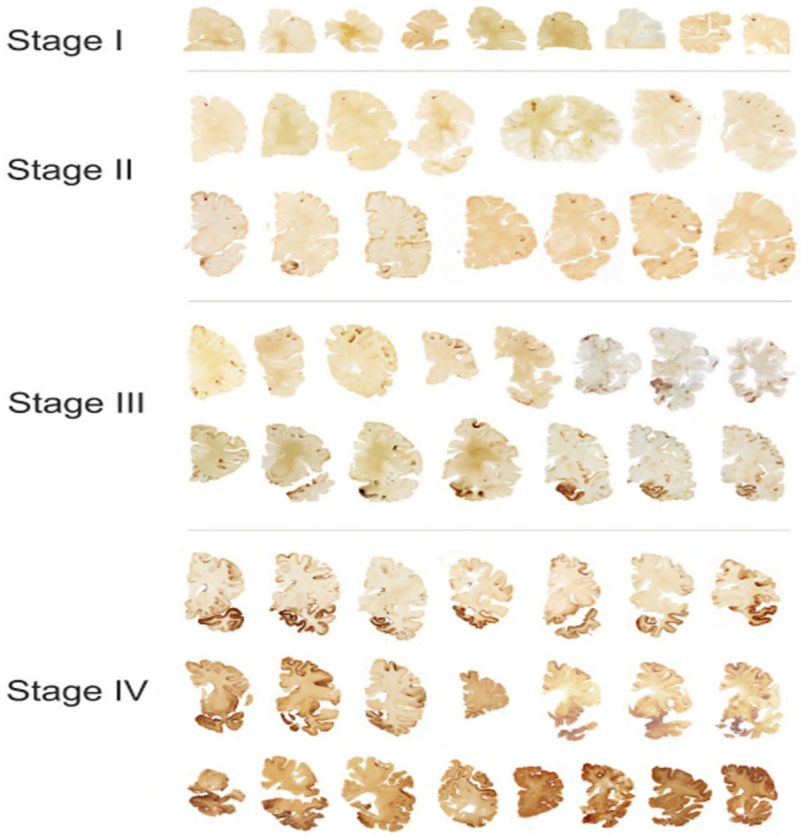

Figure 3. Images of brains in each of the 4 stages of CTE (McKee et al., 2015)

In her review of the pathophysiology of CTE, McKee notes that there is a "significant correlation between the pathological stage of CTE severity and the duration of the football career, age at death and years since retirement among our series of former American football players" (McKee et al., 2015). While this news may come as a relief to young athletes who play contact sports, it should be of significant concern to professional athletes.

As of 2022, there is no treatment for CTE. However, in 2021 a group of researchers studied the ability of a drug to prevent TBI-induced tau tangle formation with promising results. The drug was an NK1 receptor antagonist, which blocks a step in the process of tau tangle formation initiated by a TBI. The researchers divided mice into three groups, each receiving a different type of TBI: single mild (smTBI), repeated mild (rmTBI), or single moderate (ModTBI) (Corrigan et al., 2021). Within each group, some mice received the drug directly following the TBI, and

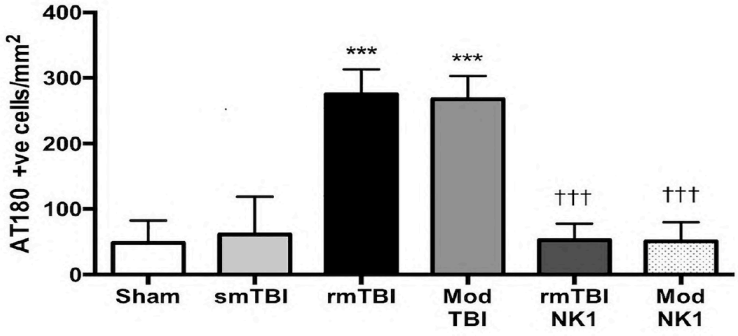

Figure 4. Levels of tau Phosphorylation (AT180+ve) in mice after repeated mild (rm) or single moderate (Mod) TBI with and without NK1 antagonist administration compared to baseline (Sham) (Corrigan et al., 2021)

some did not. 24 hours following the TBI, the researchers measured the amount of tau tangles in each group. In the group of mice who received a single mild TBI, there was no significant difference in the amount of tau tangles present compared to baseline (Corrigan et al., 2021). However, in all other groups, the mice who had received the drug had significantly lower levels of tau tangles compared to those who had not (Figure 4). Furthermore, the levels of tau tangles in the mice who had received the treatment was nearly equivalent to the non-concussed mice (Corrigan et al., 2021). The results of this study reflect promising prospects for the development of a drug that might be able to prevent tau tangles in individuals who are at risk for CTE, such as professional athletes and military personnel. However, further research is necessary before this drug can progress to clinical trials.

Sports are not only beneficial physical health; they are biologically critical to the development of cognitive, emotional and social skills, particularly in children (Neale et al., 2018). Professional sports are also a central part of American society and provide a valuable source of entertainment. There is a difficult tradeoff when engaging in activities that improve physical fitness and social wellbeing, but may also have a detrimental neurological effect in the long run (McKee et al., 2015). CTE appears to be more of a concern for professional athletes than young adults who only play contact sports for a short period of time. Nevertheless, it is important for everyone, regardless of age or duration of athletic career, to be aware of the potential long-term consequences of head injuries so that they may take appropriate preventative measures. ❧

AUTHOR BIO

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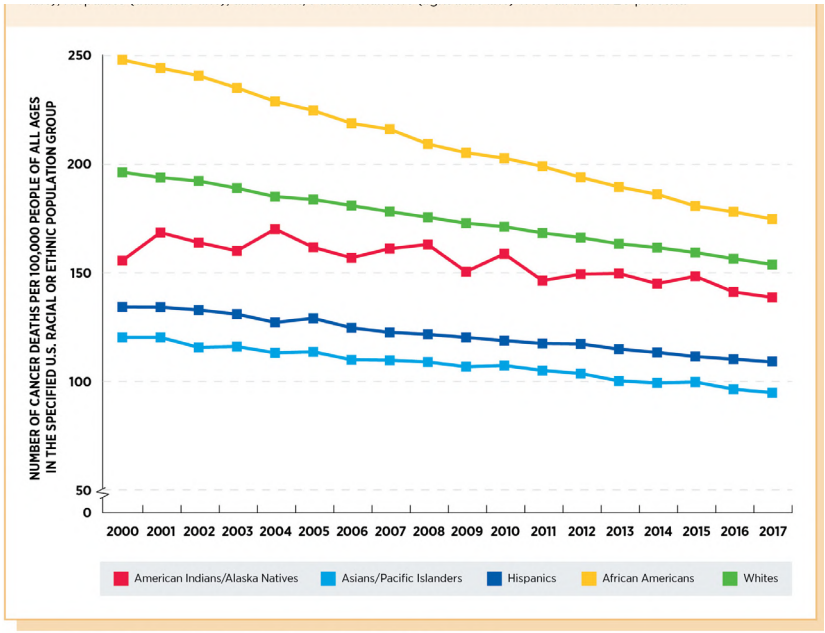
Disparities in cancer screening and occurrences in the US

UMA OBALAPURAM
Staff Writer



American Association for Cancer Research (AACR) Cancer Disparities Progress Report 2020

Figure 1. This graph shows the decline in cancer deaths by race from 2000-2017

Cancer is one of the leading causes of death worldwide. Particularly in the United States, it is second only to COVID and was the largest cause of death from disease before the pandemic's outbreak (World Health Organization, 2022). Though it is one of the most common causes of death in the U.S., the burden of fatalities within the American population is not equally shouldered by all racial and ethnic groups. African Americans have the highest rates of cancer deaths followed by Whites, while Asians/Pacific Islanders have the lowest percentages of cases (Figure 1) (AACR, 2021 1). These disparities could be caused by a variety of environmental or lifestyle factors and differences in rates in screening, which should be evaluated to find solutions and create more equitable cancer care in the U.S.

There are many factors that can increase the likelihood of cancer, the most easily identifiable and measurable are environmental factors and lifestyle choices. Researchers estimate that about 40% of cancer related deaths in the U.S. are due to avoidable risks such as tobacco usage, alcohol usage, poor diet, lack of exercise, obesity, infection, and exposure to UV radiation (AACR, 2021 2). Smoking and tobacco usage are associated with increased probabilities of multiple different types of cancer and exposure to secondhand smoking increases the risk of tumors, recurrence, and toxicity of treatment on the body. Smoking and secondhand smoking are also associated with a decreased response to treatment, increasing the difficulty to overcome the disease (National Center for Chronic Disease Prevention and Health Promotion (U.S.) Office on Smoking and Health, 2014). Another contributing factor which increases the likelihood of cancer is obesity. At the time of diagnosis, obesity is associated with an increased risk for developing multiple forms of cancer and early-stage death for certain types (Lauby, 2016). Obesity is also more strongly associated with cancer risk for African American than White men (Barrington, 2015). Diet is another lifestyle choice which can increase the risk of cancer. About 5% of cancer cases are caused by poor diet (AACR, 2021 2). Often, people in lower socioeconomic groups or those who live in ethnically or racially diverse neighborhoods are more at risk. These neighborhoods are located in "food deserts", where access to nutritious food is limited, but unhealthy fast food is readily available (AACR, 2021 2). All of these factors are important when considering why patients develop cancer and provide avenues to reduce its occurrence.

Often, people in lower socioeconomic groups or those who live in ethnically or racially diverse neighborhoods are more at risk.

In addition to lifestyle choices and environmental factors, another factor contributing to disparities in cancer prognosis and survival rates is cancer screening. Cancer screening is the process of checking a patient's body for various signs of the disease before symptoms start presenting. Cancer screening can take on many forms such as physical exams, lab

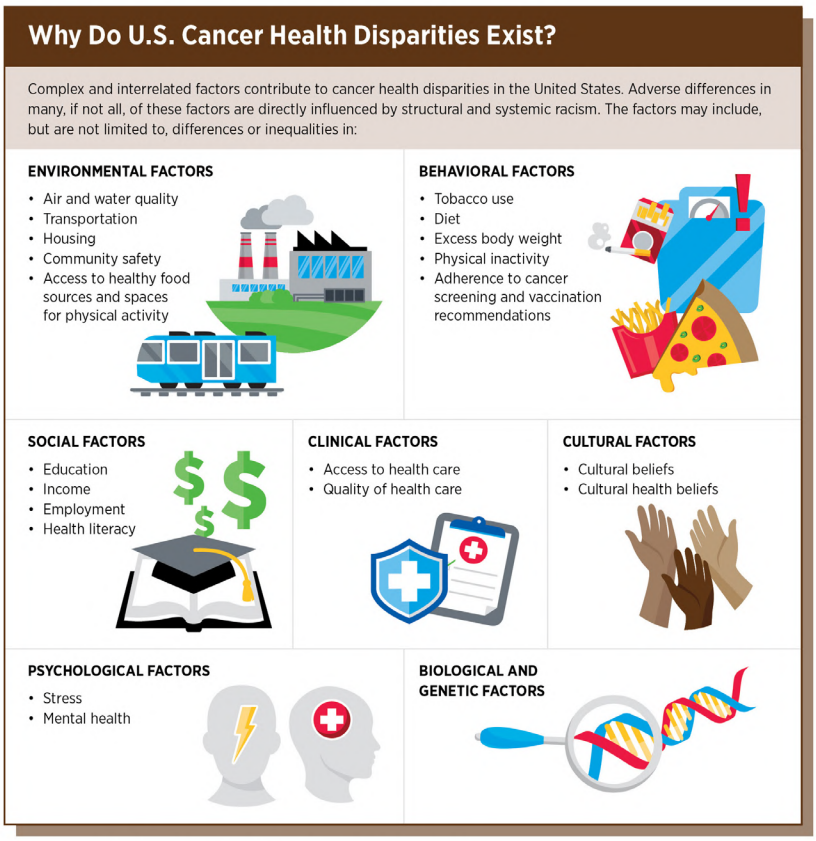


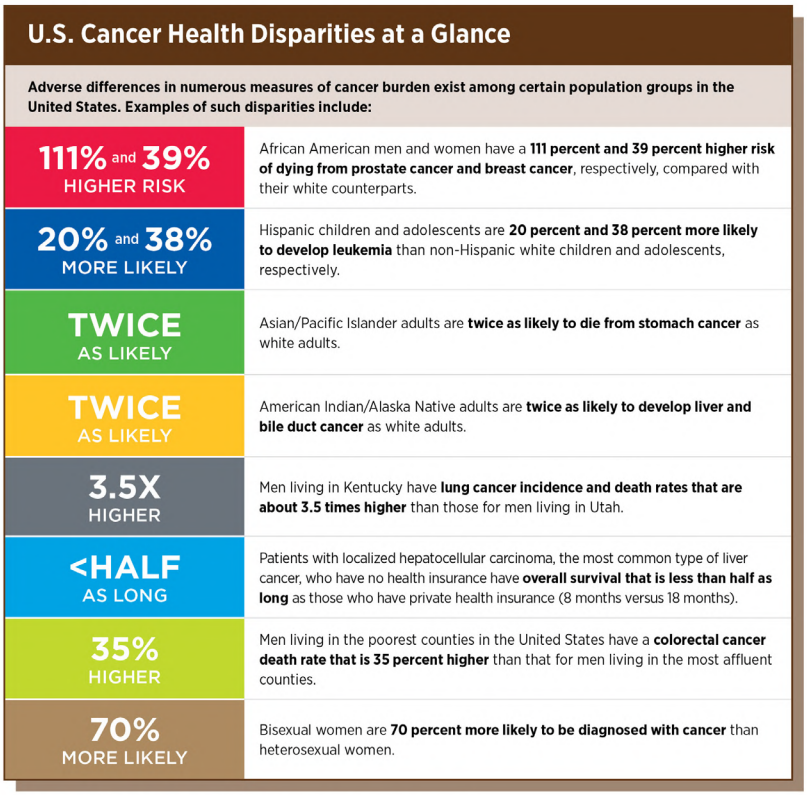
Figure 2. This graphic summarizes the various factors which increase the risk of cancer.

tests, imaging procedures, and genetic tests. (National Cancer Institute, 2019). Though this testing may seem straightforward, people of minority groups will be redirected or dismissed when requesting screening (Newsome, 2021). Minority groups also have less opportunities and access to screening services, which can cause otherwise treatable tumors to become a fatal diagnosis. Additional barriers for minorities include transportation concerns, cost of screening, and mistrust of tests and healthcare providers (Gray, 2017). The age at which recommended screenings should occur also changes based on ethnicity and race. African Americans as a whole in the U.S. are the most likely group to be diagnosed with cancer, followed by Whites (Figure 1) (AACR, 2021 1). More specifically, African American men have a much greater risk of developing prostate cancer (Figure 3). The age at which most men are recommended to get screened for prostate cancer is 55-69, but many physicians advocate that African American men get tested as early as 45 to ensure the cancer is caught before it becomes too serious (Blanchard, 2022). Though African American men should get tested earlier in life, many of these men do not know this and get tested at the recommended age, which may be too late to catch the disease before it becomes fatal.

Cancer screening disparities also occur based on sex and gender. Men are more likely to develop cancer and to die of the disease even after treatment, though the discrepancy varies with the form of cancer in the U.S. (Najari, 2013; Siegel, 2019). There are also disparities in cancer screening care with transgender and gender non-conforming individuals. Many that identify as such have a mistrust of the healthcare system due to history of discrimination or lack of proper care in the past. Additionally, many previous cancer research studies stratify their results based on heterotypical designations of the participants, leaving no representation for people outside the gender binary. Thus, there is not substantial research or statistics for how gender non-conforming individuals react to and survive cancer (Tabaac, 2018). Researchers found that disparities continue to exist outside of socioeconomic and healthcare factors; these need to be investigated to ensure all people are getting adequate cancer screenings.

Many previous cancer research studies stratify their results based on heterotypical designations of the participants, leaving no representation for people outside the gender binary.

Despite all of the environmental factors and lifestyle choices discussed above, there are tangible ways the healthcare system can provide preventive measures against cancer occurrences. First, in the case of lifestyle choices, many countries have implemented laws to discourage people from smoking



American Association for Cancer Research (AACR) Cancer Disparities Progress Report 2020

Figure 3. This chart provides insight into the disparities that exist in cancer diagnoses.

and forcing secondhand smoking on others. The percentage of smokers in the U.S. has significantly reduced - an approximate 62% decrease - from 1988 to 2014 and will hopefully continue to to do so (Tsai, 2018). In addition to tobacco laws, there are many campaigns, many of which are particularly focused on children, to encourage healthy eating and an active lifestyle to reduce the risk of cancer (World Health Organization, 2022).

To address inequities in cancer screening processes, the U.S. healthcare system should implement policies to help patients from all socioeconomic and racial backgrounds receive better, more thorough cancer screenings. The Center for Disease Control and Prevention (CDC) has implemented programs in the past to help people who could not afford screening ensure their screenings were up to date, including the CDC's National Breast and Cervical Cancer Early Detection and Colorectal Cancer Control Programs, and covered the costs of millions of screenings (Fiscella, 2011). Enacting a similar policy for more types of cancer will help patients who previously would have had trouble getting checked ensure they are healthy or discover the tumor early before it can do much harm. Increasing the reach of such programs into remote areas that do not normally have immediate access to a physician or healthcare professional will ensure that more people are screened, thus eliminating another possible barrier to healthcare (Fiscella, 2011). To make sure healthcare providers are giving the best care they can and working to improve the care they provide, they should collect more information on "race, ethnicity, primary language and disability status, and underserved rural and frontier populations (to enhance monitoring of disparities)" (Fiscella, 2011). It will also be especially important for these healthcare providers to develop and implement culturally sensitive education models (Gray, 2017). This will best equip healthcare workers with the skills to make everyone, even those who may not have previously had this level of access to healthcare, comfortable in the examining room and with screening. These will help physicians and researchers better understand the factors going into a patient's life and diagnosis and will help them gather data to aid in better prediction of tumors in the future.

The best way to improve cancer care and decrease the rates of incidence and fatality in the U.S. is to ensure the care given to all people, regardless of race, gender, socioeconomic states, etc., is equitable.

Overall, there are many different factors that can contribute to a cancer diagnosis, both controllable - lifestyle choices, cancer screenings - and uncontrollable - environmental factors, genetics. The best way to improve cancer care and decrease the rates of incidence and fatality in the U.S. is to ensure the care given to all people, regardless of race, gender,

socioeconomic states, etc., is equitable. There are many ways that the U.S. can go about fixing these disparities , with the first being a start of positive change. With these avenues for improvement addressed, cancer diagnoses and fatalities will continue to decrease significantly (see Figure 1). ❧

AUTHOR BIO

Uma is a third year majoring in Biology. Her interests are learning more about alternatives to traditional forms of medicine, as well as our neurological responses to them in comparison to common treatments seen today.

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Moving beyond medication: Holistic interventions for the treatment of patients with psychiatric disorders

HELEN GRIFFITH
Staff Writer

Current models of psychiatric care in the United States have failed patients who suffer from mental illness. Today, approximately one in five U.S. adults live with psychiatric illness, and this number only continues to rise ("Mental Illness," 2022). There are a number of complex factors which have contributed to the astronomical increase in mental illness that can be seen in the general public. For instance, social media and the COVID-19 pandemic have both been associated with the skyrocketing rates of anxiety and depression in the United States (Karim et al., 2020; Xiong et al., 2020). The standard medical model of psychiatric care is used most often by physicians to categorize symptoms of mental illness according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). While this system remains useful for the purposes of distinguishing between different psychiatric illnesses, there are many flaws with its rigid structure, as mental illness manifests in a more fluid nature than previously thought (Young, 2016). Furthermore, current standards of treatment for psychiatric disorders, including medication and psychotherapy, remain limited in terms of efficacy and scope. Therefore, future treatment of mental illness should move beyond these methods to incorporate alternative, evidence-based wellness interventions that focus on integrating exercise, mindfulness, sleep, social connection, and nutrition to better patient mental health.

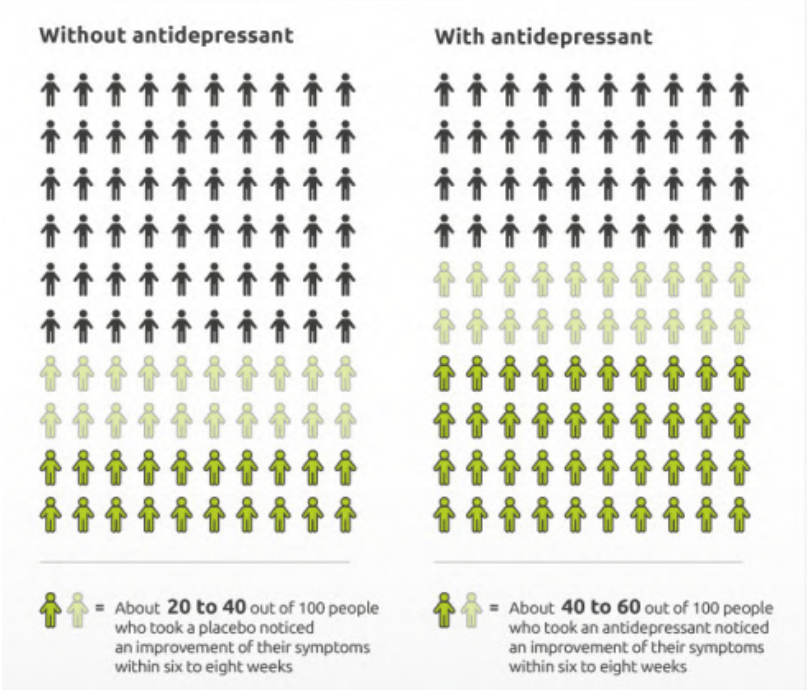

Figure 1. The efficacy of antidepressants in treating patients with moderate to severe depression ("How well can antidepressants," 2020).

Approximately one in five U.S. adults live with psychiatric illness, and this number only continues to rise.

The idea that treatment for mental illness should solely revolve around the administration of medication is inherently flawed and often does more harm than good to patients. In fact, in patients with moderate to severe depression, it has been found that only one in five will respond positively to any given antidepressant (Figure 1). For this reason, more emphasis should be placed on other treatment options, such as psychotherapy in combination with research-based wellness interventions. It is absolutely crucial that mental health professionals consider the immense variability between patients who struggle from psychiatric disorders in order to formulate a more personalized, holistic approach to treatment.

As rates of mental illness have increased, so too have the number of people who have been prescribed psychiatric drugs. While these medications can be incredibly useful for some patients, they may have overall neutral or even negative effects on others. In other words, given the level of efficacy that they provide, psychiatric drugs are being overprescribed, sometimes to the detriment of patient health and wellbeing. Even if the drugs

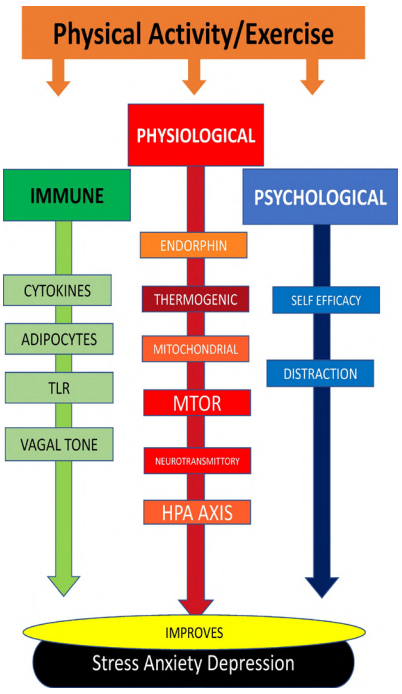

Figure 2. The physiological, immune, and psychological effects of physical activity on stres, anxiety, and depression (Mikkelson et al., 2017).

have a net neutral or positive effect, it is often not enough to bring patients within a standard range of mental well-being (Paris, 2011). According to the Mental Health Quotient (MHQ), a mental health assessment tool, normal mental health scores range from 0 to 200, whereas negative scores indicate at-risk or clinical patients. Furthermore, there are many instances when psychiatrists are unable to predict how patients may respond to a certain medication; as a result, patients are essentially subjected to various forms of experimentation until a seemingly effective psychiatric drug or combination of drugs has been found (Sparks, 2016).

Along with psychiatric medications, psychotherapy serves as a standard form of treatment for mental illness. Psychotherapy, also known as talk therapy, functions as a way to help people who are suffering from mental illness or other emotional difficulties (What is Psychotherapy?, 2019). In fact, psychotherapy in general has been shown to be significantly more effective than psychiatric medications in treating mental illness (Cuijpers et al., 2013). Additionally, in patients with treatment-resistant depression, psychotherapy may contribute to symptom improvement when medication does not (van Bronswijk et al., 2019). Nonetheless, the effects of psychotherapy depend on a number of factors, including psychiatric diagnoses and types of psychotherapy (Cuijpers et al., 2013).

As powerful as combinations of psychiatric drugs and psychotherapy can be for the treatment of mental illness, standard models of psychiatric care have not generated significant enough improvements in patient mental health. It is important to consider all possible avenues of treatment for a patient's mental illness, besides psychotherapy and medication, which could help to improve mental wellness. That is not to say that current psychiatric practices should be abandoned; however, there is more that healthcare providers, specifically psychiatrists, can do to promote mental health and treat psychiatric illness that does not involve expensive or exploratory treatments.

In other words, given the level of efficacy that they provide, psychiatric drugs are being over-prescribed, sometimes to the detriment of patient health and wellbeing.

Dr. Saundra Jain and Dr. Rakesh Jain developed the WILD5 program for this very reason. Their intention was to provide an evidence-based model of incorporating wellness interventions into standard psychiatric care. This program involves encouraging participants to center on five facets of health and well-being: exercise, mindfulness, sleep, social connectedness, and nutrition. While this specific program has been supported by research studies, it does not necessarily need to be followed precisely in order to see benefits in patients with psychiatric illness. Placing more focus on these areas of wellbeing would ultimately lead to a transformation of patient care and outcomes in psychiatric medicine (Rolin et al., 2019).

Exercise regimens have been shown to be highly beneficial for peoples' mental health, regardless of whether or not they suffer from psychiatric illness. Benefits include improved cognition, reduction in depression and anxiety symptoms, decreased risk of developing neurodegenerative diseases and of experiencing drug addiction (Ruegsegger and Booth, 2018). These improvements are hypothesized to result from increased circulation of blood in the brain during exercise as well as modulation of the hypothalamic-pituitary-adrenal (HPA) axis, which controls the stress response. Furthermore, some of the benefits of exercise may potentially be attributed to the social interaction that it can provide as well as feelings of

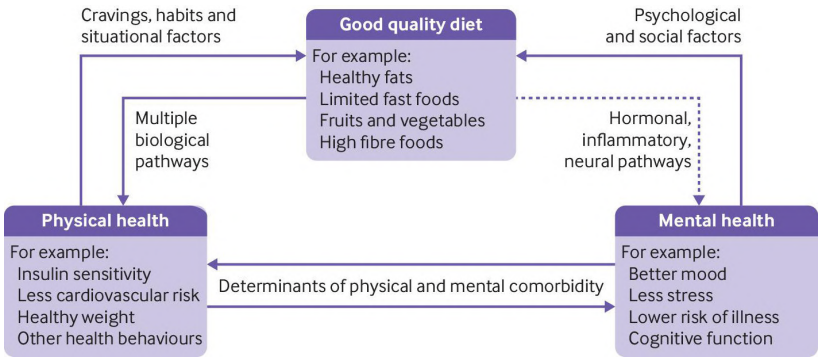

Figure 3. The relationship b/w diet, physical health, and mental health (Firth et al., 2020).

self-efficacy (Sharma and Petty, 2006).

Mindfulness promotes mental health and is associated with the development of a positive sense of self as well as a greater sense of autonomy and life satisfaction. It is also negatively correlated with psychiatric disorders such as depression, social anxiety, and neurosis, as well as rumination (Ngô, 2013). These benefits are proposed to be a result of enhanced self-awareness and attentional control (Tang et al., 2015; McGee, 2008), but the exact neural mechanisms activated by practicing mindfulness have not yet been discerned (Wielgosz et al., 2019).

Sleep plays a significant role in mental health status, with many common symptoms of mental illness including sleeping too little or not enough. Studies have shown that ensuring a quality night's sleep can reduce psychotic episodes as well as insomnia and depression (Riemann et al., 2020).

Additionally, social connectedness is important for maintaining mental health. In fact, loneliness has been shown to be both a cause and consequence of many psychiatric illnesses (Hare, 2017). Establishing strong social ties can provide individuals with support during hard times and help create a sense of security for them (Taylor, 2020).

Lastly, nutrition can have a large, positive impact on mental health. For example, consuming a largely Mediterranean diet has been associated with decreased risk of developing depression. This may be attributed to a reduction in inflammation, increased immune system activation, and favorable interactions between the brain and gut microbiome. On the other hand, diets which consist of mostly foods with a high glycemic index are associated with an increased risk of depression (Firth et al., 2020).

When considering wellness interventions for treatment of psychiatric illness, it is also important to acknowledge the sociological factors that can impact mental health, including but not limited to race, income level, religion and culture. For example, the killing of unarmed, black Americans by the police has been correlated with a decline in mental health among black citizens, especially in the location where the instance of violence occurred (Williams and Etkins, 2020). Additionally, poverty can be both a predictor for and symptom of mental illness (Murali and Oyebode, 2004). There are also times when a patient struggling with psychiatric illness could benefit from meeting with a religious figure, such as a chaplain, or even by introducing some component of spirituality into their daily lives (Cook et al., 2012). Finally, different cultures possess varying definitions of and perspectives on mental health and the ways in which psychiatric illness should be treated; this could impact whether, for instance, a patient is open to going to therapy versus taking psychiatric medication (Eshun and Gurung, 2009). All of these sociological factors should be taken into account when considering the ways in which patients' mental health could be improved and what forms of treatment would benefit them based on their individual history (Wong and Cloninger, 2010; Zaman et al., 2019). It is also important to note that a patient's medical history, for example, previous eating disorders, should be taken into consideration when prescribing a course of treatment.

In most cases, introducing wellness interventions into psychiatric treatment plans can only benefit the patient.

Ultimately, psychiatrists and other mental health care providers must ensure that they consider patient treatment from a holistic perspective to provide a unique combination of psychiatric medication, psychotherapy and wellness interventions for each individual who is experiencing mental illness. In most cases,

introducing wellness interventions into psychiatric treatment plans can only benefit the patient; options such as introducing exercise regimens or encouraging patients to get better quality sleep are both cost-effective and accessible. Therefore, these wellness interventions serve as convenient, evidence-based forms of psychiatric treatment that may be even more effective than psychiatric drugs or psychotherapy alone. With levels of mental illness increasing globally, it is essential that current models of psychiatric care be reevaluated to consider the health and well-being of individuals, thus improving the overall mental health of psychiatric patients. These wellness interventions must be introduced to the general population as preventative measures in order to ensure that our world remains as mentally healthy as possible. ❧

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Helen is a fourth year majoring in Neuroscience Behavior and Biology and Spanish. Her interests are in the public health side of medicine and feels passionately about ensuring that people of all backgrounds have access to quality healthcare, particularly with regards to mental health.

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Hero hormone: GnRH as a down syndrome treatment

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Anyone who has gone through puberty has experienced the effects of gonadotropin-releasing hormone (GnRH)—a hormone that signals the release of other hormones which trigger the maturation of gonads at the onset of adolescence ("Gonadotropin-Releasing Hormone", 2022). At its basic level, GnRH is essential for typical sexual development in humans. However, levels of GnRH are found to be significantly lower in cases of abnormal development. For those who do not have Down syndrome, this could lead to various complications in sexual development with no effect on cognitive development. In people with Down syndrome, though, abnormally low levels of GnRH have been observed in conjunction with a relative decline in cognitive and olfactory function around the onset of puberty (Makin, 2022). This observation has led to the key question of whether these two phenomena may be connected. In response, a 2022 study showed that not only are GnRH and cognition indeed correlated, but also that artificially stimulating greater production of GnRH actually reverses loss of cognitive function (Manfredi-Lozano, 2022). This groundbreaking finding holds potentially large implications in restoring cognitive function to those with Down syndrome as well as in the study and treatment of developmental and neurodegenerative diseases in general.

Milestone	Range for Children with Down Syndrome	Typical Range
GROSS MOTOR		
Sits Alone	6 – 30 Months	5 – 9 Months
Crawls	8 – 22 Months	6 – 12 Months
Stands	1 – 3.25 Years	8 – 17 Months
Walks Alone	1 – 4 Years	9 – 18 Months
LANGUAGE		
First Word	1 – 4 Years	1 – 3 Years
Two-Word Phrases	2 – 7.5 Years	15 – 32 Months
SOCIAL/SELF-HELP		
Responsive Smile	1.5 – 5 Months	1 – 3 Months
Finger Feeds	10 – 24 Months	7 – 14 Months
Drinks From Cup Unassisted	12 – 32 Months	9 – 17 Months
Uses Spoon	13 – 39 Months	12 – 20 Months
Bowel Control	2 – 7 Years	16 – 42 Months
Dresses Self Unassisted	3.5 – 8.5 Years	3.25 – 5 Years

Figure 1. Chart comparing age ranges for developmental milestones of children with Down syndrome to the ranges of children with typical development.

Down syndrome, otherwise known as Trisomy 21, is a neurodegenerative disease that occurs when a developing fetus has an extra copy of chromosome 21 due to abnormal cellular division, leading to atypical physical and mental development (Centers for Disease Control and Prevention, 2021), as shown in Figure 1. While many people with Down syndrome live long, fulfilling lives, this unusual development can pose some challenges, notably delayed and/or decreased cognition. Symptoms of Down syndrome are chronic, but there is currently a wide range of treatments and therapies people may receive that are tailored to their individual needs and strengths, including physical therapy, speech-language therapy, occupational therapy, and emotional and behavioral therapy (U.S. Department of Health and Human Services, 2017). Currently, standard care for Down syndrome revolves primarily around symptom management, as there is no proven treatment targeting its cause rather than its effects.

In people with Down syndrome, though, abnormally low levels of GnRH have been observed

A 2022 study surrounding GnRH, however, could lead to a potential new treatment that goes beyond symptom relief and may reverse the progressive cognitive decline characteristic of neurodegenerative diseases. A team led by French neuroscientist Vincent Prevot recognized a potential link between lowered GnRH levels and a decline in cognition, olfactory function, and fertility in mice engineered to mimic

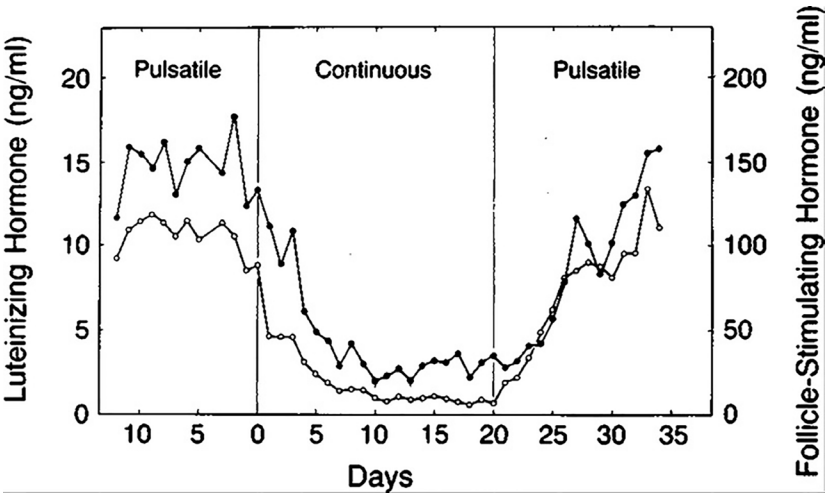

Figure 2. Graph showing levels of Follicle-Stimulating Hormone (FSH) and Lutenizing Hormone (LH) maintained with pulsating gonadoptropin-releasing hormone (GnRH) delivery and dropping with continuous delivery.

Down syndrome symptoms. Specifically, these cognitive changes were monitored through periodic cognitive tests and brain scans. It has been observed that GnRH neurons "also connect to the cortex and hippocampus, brain regions associated with learning and memory" (Makin, 2022); this connection may now be explained by a new revelation that stimulating production of GnRH imitating the natural process of GnRH release "abolished the olfactory and cognitive deficits [of the affected mice]" (Makin, 2022). With typical function, GnRH is released in pulses (also termed pulsatile release), as shown in Figure 2, that better maintain levels of subsequently released gonadotropins such as luteinizing hormone and follicle-stimulating hormone (Terasawa, 2019). Luteinizing hormone triggers the production of progesterone and testosterone, depending on sex, while follicle-stimulating hormone controls the production of ova and sperm; people with Down syndrome have decreased levels of both, which may be linked to cognitive deficits. The team used several methods of producing this pulsatile release of GnRH to ensure that this was, in fact, what caused the reversal of the cognitive deficits. Such methods included increasing levels of microRNAs that controlled GnRH production, injecting healthy cells that produced GnRH normally, harvesting brain grafts from healthy mice to replace the inactive neurons linked to stimulation of GnRH production, and chemogenetics to trigger receptors artificially placed in DNA (Makin, 2022). They found the increased GnRH production and subsequent release of gonadotropins as typical in puberty to indeed be correlated with improvement on simple cognitive tests.

Based on the results, six of the seven men showed improvement on cognitive tests, and all seven showed improved "functional connectivity…"

These findings led to a pilot study wherein seven adult men diagnosed with Down syndrome were given devices placed under their skin that pumped out GnRH in pulses over a six-month period. The pulsatile delivery of the GnRH and its effects mimicked the results seen in mice and the typical function of GnRH in humans. Based on the results, six of the seven men showed improvement on cognitive tests, and all seven showed improved "functional connectivity… in cortical areas involved in speech and 3-D orientation... verbal comprehension, temporary 'working' memory and attention but not sense of smell" (Makin, 2022). Because this is a limited study with no controls, this relationship between GnRH promotion and improved cognition is still quite theoretical. That said, these results are promising, and they open doors for a myriad of opportunities for future studies.

Further research could examine how these results may be relevant in developing treatments for other neurodegenerative diseases, such as Alzheimer's. The cognitive decline observed in Down syndrome in many ways parallels the same process in early-onset Alzheimer's (Godfrey, 2018), and Down syndrome and Alzheimer's are known comorbidities (Alzheimer's Disease & Down Syndrome). If this connection between GnRH production and cognition holds true, it could be adapted to prolong not only lifespan but also quality of life in cases of Alzheimer's or dementia. Additionally, it would be interesting to examine whether GnRH treatment could be adapt-

ed for use in treating other diseases or disorders, such as autism spectrum disorder (ASD), that present with cognitive delays. An experimental study using GnRH therapy to treat inappropriate hypersexual behaviors in people with ASD has seemingly promising results, though due to ethical and safety concerns, there is no further research on this topic (Eyuboglu, 2018). Finally, another area of interest notably absent in the above study is how biological females would respond to this treatment. For centuries, women have been excluded from clinical studies for a multitude of reasons, one of which being the confounding variable of varying hormone levels at different stages of their menstrual cycle. With comparatively little research on a demographic that makes up not only half the world's population, but also roughly half of those with Down syndrome (Moawad, 2022), it remains to be seen whether these breakthrough discoveries will hold true for women as well.

Gonadotropin-releasing hormone therapy has shown potential in reversing cognitive deficits in people with Down syndrome and opens up many possibilities for future research to affirm or refute its clinical use. Though this treatment's effectiveness remains currently unproven and the studies conducted have been limited, the insight gained from this fledgling research sparks hope for favorable treatments for Down syndrome and other neurodegenerative diseases in the future. ❧

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Chloe is a second year majoring in Comparitive Literature. She is interested in neurodegenerative diseases and and how new research can improve treatments and quality of life for those living with them.

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Placed by Joseph Park

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Graph showing FSH and LH levels with pulsatile and continuous GnRH administration. (1991). New England Journal of Medicine. Retrieved 2022, from https://www.nejm.org/na101/home/literatum/publisher/mms/journals/content/nejm/1991/nejm_1991.324.issue-2/nejm199101103240205/production/images/img_medium/nejm199101103240205_f2.jpeg.

Targeted exterminators: Bacteriophage therapies as a potential solution

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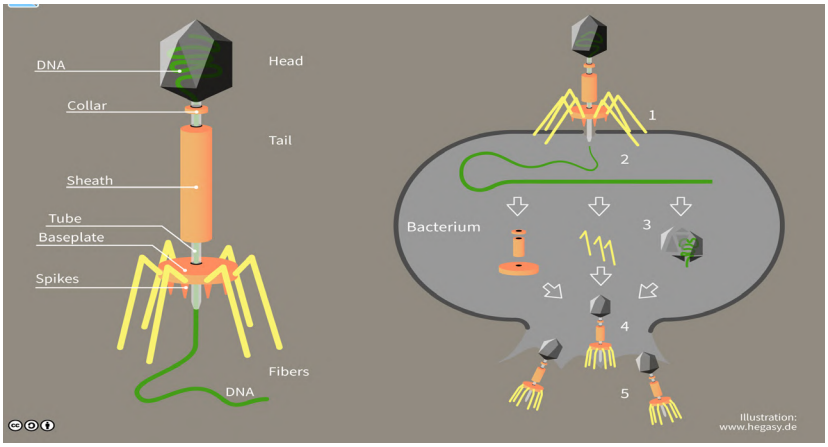

Figure 1: The basic structure of a phage and how it infects a host bacterium. (Hegasy Phage T4, 2017).

Antimicrobial resistance is responsible for over one million deaths annually and has become a leading global cause of death (Murray et al., 2022). The COVID-19 pandemic has exacerbated antimicrobial resistance, with a CDC report estimating a 15% increase in hospital-onset infections and deaths (COVID-19, 2022). Although responsible antibiotic prescribing practices and coordinated resistance rate monitoring have helped to combat the issue, the antimicrobial resistance crisis has been amplified by the lack of new methods to treat resistant infections. Antibiotics are categorized into classes by their mechanism of action for combating bacterial infections. New classes of antibiotics are extremely important in dealing with resistance, as mechanisms of resistance to one antibiotic are often effective to varying degrees against other antibiotics in the same class. However, no new class of antibiotics has been discovered since the 1980s, and the rate of development of novel compounds to treat bacterial infections has been far outpaced by rates of resistance (Miethke et al., 2021). Therefore, there is a pressing need for novel therapeutic approaches, such as bacteriophage therapies, to treat bacterial infections. Despite some barriers to their use, bacteriophage therapies represent one of the most promising and practical new approaches to treating antimicrobial-resistant infections due to their well-documented medicinal history and their potential benefits over traditional antibiotics.

Bacteriophage therapies utilize viruses that infect and reproduce only in the cells of specific bacterial species (bacteriophages or phages) and have a history that predates traditional antibiotics. Different bacteriophages have different bacterial host species that they infect, meaning that they are highly specialized in the cells they target and kill. In 1919 - nine years before the discovery of penicillin - a single round of phage therapeutics cured a young French boy suffering from severe dysentery in only a few days (Sulakvelidze et al., 2001). Many studies in humans and animals would provide more promising evidence for the efficacy of bacteriophage therapies in the following decades, and commercial production of bacteriophages began in the US in the 1940s. Despite their promise, bacteriophages soon fell out of favor in most of the world due to the broad-spectrum nature of most traditional antibiotics (Wienhold et al., 2019).

There is a pressing need for novel therapeutic approaches, such as bacteriophage therapies, to treat bacterial infections.

However, phage therapies have persisted as a treatment method in Europe - specifically Georgia, Russia, and Poland. This has meant that much of the existing research on bacteriophages is not in English, which has created barriers to its adoption in American healthcare settings. However, the Western world has seen increasing recognition of bacteriophage therapies as an important tool in combating antibiotic resistance. One famous case study involved an American man who contracted a multidrug-resistant (MDR) A. baumannii infection that would not respond to any traditional antibiotics and was eventually cured after being administered various bacteriophage "cock-

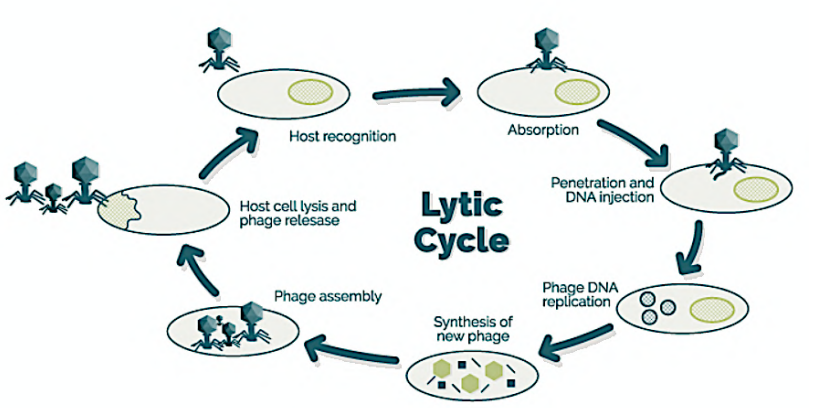

Figure 2: A step-by-step process of how a bacteriophage replicates in and kills a bacterial cell via a lytic cycle (University of Barcelona, 2019).

tails" (Lavergne et al., 2018). Since bacteriophage therapy's first use in the early 20th century, the body of evidence supporting its use has continued to grow.

There are many potential benefits to integrating bacteriophage therapies into the global healthcare system. One of the strongest arguments for bacteriophage therapies is their efficacy. A 2021 review of over 100 clinical bacteriophage studies in Poland and countries of the former Soviet Union found reported success rates (either marked clinical improvement or full recovery) of between 64-100% for different bacterial infections (Duzgunes et al., 2021). Moreover, many of these studies noted higher success rates for bacteriophage therapies than antibiotics in treating clinically important infections such as Staphylococcus, Pseudomonas, E. Coli, and Proteus. Several of the studies described specific scenarios in which the bacterial infections were not responding to traditional antibiotics, and were then successfully treated using bacteriophage therapies, which illustrates one of the strongest advantages of their use: their ability to combat MDR infections.

Bacteriophage therapies have become more and more appealing as a treatment option in the face of growing rates of antibiotic resistance. The therapy could successfully address two of the major goals of antibiotic stewardship movements by being a practical alternative to antibiotics that in turn reduces global rates of antibiotic use. Bacteriophage therapies are also theoretically much safer than many traditional antibiotics given that phages can only infect bacterial cells and have a typically narrow spectrum of action. Many antibiotics such as quinolones and amoxicillin have toxic side effects for the patient (Principi et al., 2019). Despite the high specificity shown by any given type of phage, the vast array of known bacteriophages means that, in theory, every single bacteria species should have at least one bacteriophage that can kill it. This allows the therapy to simultaneously be extremely targeted and have broad potential applications, which increases its appeal. Also, with regard to antibiotic resistance, bacteriophages have demonstrated the ability to combat biofilm infections, which occur when bacteria secrete a type of extracellular structure that allows cells to coordinate in an infection that typically decreases their susceptibility to antibiotics (Lu and Collins, 2007). Lastly, some studies have suggested that bacteriophages would reduce healthcare costs compared to traditional antibiotics, making them an even more appealing alternative to antibiotics (Miedzybrodzki et al., 2007).

Bacteriophage therapies are also theoretically much safer than many traditional antibiotics given that phages can only infect bacterial cells and have a typically narrow spectrum of action.

Despite the ever-expanding body of evidence promoting the integration of bacteriophage therapies into global healthcare systems, their use remains approved only for emergency use in the United States (Fauconnier, 2019). Much of the reasoning for this is rooted in the structure of medical regulations in the US. The current regulatory model utilizes large-scale randomized, double-blind clinical trials which are difficult for phage therapeutic developers due to both the costs and applicability. Because phage therapies are often mixtures of many different bacteriophages, it becomes difficult to fit a treatment with such case-to-case variation into the one-size-fits-all regulatory process that exists in America today. However, because there are concerns about

the return on investment and because pharmaceutical companies have not yet profited off of any bacteriophage therapies, regulators have not adapted their process to the unique characteristics of the treatment. There also exist unique concerns about the understanding of how bacteriophages behave in vivo that do not exist with traditional antibiotics, specifically with regard to the co-evolution of bacteriophages with bacterial infections and the fact that phages are self-replicating structures.

Despite these regulatory concerns, there is a real possibility that phage therapies can become the solution to the antibiotic resistance crisis the medical community needs. Belgium has been the pioneer in the West in regard to this process. As of 2018, the country approved a method of phage regulation known as "magistral preparations." Pharmacists can incorporate phages as active ingredients in these preparations that allow them to be available for patients while still requiring them to meet certain local standards of safety and regulation (Verbeken and Pirnay, 2022). Moreover, many other European nations have expressed interest in adopting a similar system, illustrating the success and potential benefits such a system can have. This provides support for the practicality and feasibility of incorporating bacteriophage therapies in national healthcare systems similar to America's.

With the mounting threat of antibiotic resistance generating a good deal of attention in medical research and development, it is becoming extremely important to investigate practical and effective alternatives to antibiotics. Having a significant history of successful and safe use in other countries, bacteriophage therapies are perhaps the most feasible and attractive of these alternatives. Specifically, it is their specific method of action, broad potential applications, and potential reduction in healthcare costs that make bacteriophages so appealing. Although there are many regulatory issues and unknowns facing their implementation in American medical systems, Belgium has proven that there are effective ways to do so while still upholding ethical standards of safety. Bacteriophage therapies, therefore, illustrate a fascinating and underexplored tool in the antimicrobial stewardship movement. ❧

Despite these regulatory concerns, there is a real possibility that phage therapies can become the solution to the antibiotic resistance crisis the medical community needs.

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Unintentional but not inconsequential: Iatrogenic harm in pyschotherapy

ADVAITA KRISHNAN
Staff Writer

Table 3. Therapeutic interactions in anorexia nervosa which may cause iatrogenic harm

Intervention	Clinical examples
Overprotection	Over zealous uses of inpatient/high intensity care
	Excluding or disempowering the family from treatment
Criticism or confrontation-coercive treatments	Coercive treatment under the Mental Health Act
	Use of loss-of-privilege systems to motivate change
Accommodation	Providing therapy with no or insufficient nutritional direction
	Engaging in bargaining of treatment goals with the persuasive patient
Enabling	Services palliating loneliness and isolation
	Providing the opportunity for further striving competing and calibrating against others.

Figure 1. Therapeutic Interactions and consequent iatrogenic harm.

"First, do no harm". The Hippocratic oath is more than just the oldest documentation of a medical ethical doctrine, its primary principle has been forged into the very essence of what it means to be a physician. And yet despite beneficent intentions, unintentional harm, better known as iatrogenic harm, is still an unavoidable consequence of being a healthcare provider. More than just a bitter pill that's hard to swallow, the ramifications of iatrogenic harm can be disastrous if left unchecked.

Iatrogenic harm, as defined by the American Psychiatry Association, is "a disorder precipitated, aggravated, or induced by the physician's attitude, examination, comments, or treatment". Ensuring truly safe and effective treatment requires immense attention to detail and personalization of care (Rees, 2011). This conundrum is even more pronounced when it comes to psychotherapy. Psychotherapy is an "effective psychological intervention for a multitude of psychological, behavioral, and somatic problems, symptoms, and disorders and thus rightfully considered as the main approach in mental and somatic health care management" (Locher et al., 2019).

The ramifications of iatrognic harm can be disastrous if left unchecked.

The connotation of iatrogenic harm is geared towards medication, however, a conservative estimate of over 5% of patients reporting negative long-lasting feelings after therapy shows that psychotherapy is not removed from the consequences of mistreatment despite the best of intentions (Lambert & Bergin, 1994).

To expect the eradication of all negative outcomes arising from psychotherapy is a lofty goal according to Boisvert and Faust. Psychotherapy, unlike other treatments that are pharmaceutical, is influenced by a variety of external factors that one must consider. It is impossible to eliminate the nuanced variables that exist in everyone's life, and clinicians cannot isolate patients to treat a fixed set of conditions. The field requires constant adaptation to the individual's circumstances, making it harder to account for and eliminate negative effects.

The only way to eliminate all negative effects that arise from psychotherapy would be to abolish the practice which would, needless to say, cause more harm than good. The aim is to ameliorate the frequency of bad outcomes, shifting the scale more towards positive outcomes.

To address how to mitigate undesired outcomes, it is crucial to understand the existing barriers of care that affect the discernment of iatrogenic harm in psychotherapy treatment in the current system of care. After dissecting the standards of psychiatric care, Linden highlights that psychotherapy care is heavily influenced by the decision-making of the therapist and the therapist alone. This is unlike most other fields as any harm that ensues is thus always a direct consequence of the physician's decision-making, not due to the pathology of a drug as is normally the case with iatrogenic harm. Given that therapists often have trouble deciding the course of treatment and predicting the outcomes, it is a strenuous task to be able to discern the side effects of the decision-making. Additionally, mental health is not quantifiable, making it arduous to differentiate between the negative effects of treatment or the development

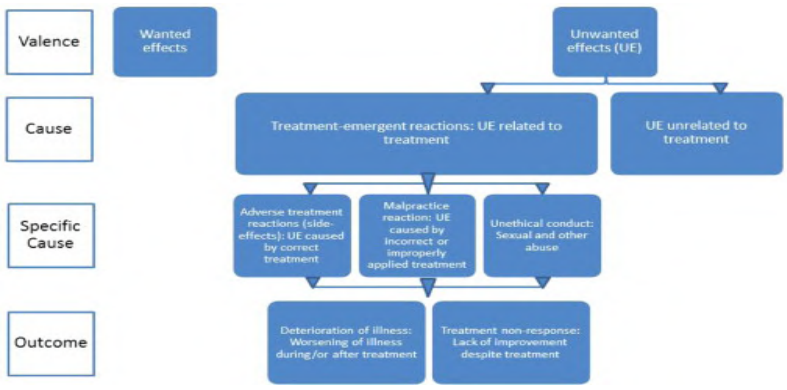

Figure 2. Unwanted events are negative events that occur during or after tretment, that may or may not be iatrogenic nature.

of additional circumstances in the life of the patient. It is also increasingly challenging to have to assign 'positive' and 'negative' labels to emotions arising from treatment. For example, an impending divorce can fall into both categories depending on the person and situation.

A study conducted by Rozental et. al. in 2018 about the negative effects of psychotherapy showed that there has been an increase in the awareness of the iatrogenic harm caused during psychotherapy. The results showed that on the whole clinicians were mindful of the risk of decline of the patients, and by adding a preventive measure of monitoring the patient in between sessions, the risk of deterioration was reduced from 23.2% to 15.2%. Additionally, the study showed that clinicians have difficulty in determining if a patient has declined due to the nature of the field, and that introducing a robust form of progress monitoring would help further reduce the risk of deterioration. By introducing progress monitoring, it would also be possible to identify the factors that contribute to the decline of the patient.

To aid in the qualitative assessment of iatrogenic harm, several metrics have been proposed such as the Negative Effects Questionnaire and patient-centered self-interviews.

There is a need to redesign the way data about psychotherapy and iatrogenic harm is collected, to be able to truly evaluate the extent of the harm being caused and how to ameliorate the effects for the patient. At present, there is a need to evaluate the data collected by a routine recording of the number needed to treat versus the number needed to harm. The Number Needed to Treat (NNT) is the number of patients who would receive treatment to prevent one additional bad outcome (Center for Evidence-Based Medicine, 2020), whereas the Number Needed to Harm would be the number of patients who must receive treatment for one patient to experience an adverse outcome (Suchmacher & Geller, 2021). Adverse outcomes include but are not limited to suicide, regression, exacerbation of symptoms, or new forms of distress (Rozental et al., 2018). By mimicking other specialties and routinely evaluating this data set, it would allow for the creation of a feedback loop that would help physicians to assess the relative risk of the psychotherapeutic intervention. (McKay & Doss, 2021)

However, the study conducted by Rozental highlighted certain conundrums that are yet to be resolved. For instance, the nature of psychotherapy makes it difficult to define its symptoms and side effects, and without terminology, it is difficult to develop a metric and analyze data. Additionally, negative results often do not get reported making it hard for clinicians to garner a holistic understanding of the gravity of the situation. Without this standardization, the perception of 'negative' consequences is determined by the perspective of the clinicians and oftentimes iatrogenic consequences are chalked up to developments in the patients' lives; while a complex issue to resolve through research that accounts for different perspectives and factors such as physician ratings and patient self-reports.

This is unlike most other fields as any harm that ensues is thus aways a direct consequence of the physician's decision-making, not due to the pathology of a drug as is normally the case with iatrogenic harm.

Nonetheless, immense strides have been made in the field of psychotherapy, especially in terms of the mitigation of iatrogenic consequences. And while there are numerous hurdles to be

tackled, the awareness of the existence of these problems is sure to drive change. No physician wants to harm their patient- even if done so unintentionally. ❧

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Cataract sugery: A seriously needed yet widely inaccesible operation

ALYSSA CHEN
Staff Writer

Losing the ability to see is a concept that is both a terrifying concept and a brutal reality for all who live long lives. As the leading cause of blindness in the world, cataracts, a natural opacification of the lens over time, is a condition half of all Americans will experience by age 80 (Desai, 2013). In 2015, they affected more than 24 million Americans (Kauh, 2016), and are projected to affect over 30 million by 2028 (Nvision, 2022). If allowed to progress, cataracts can cause visual impairment and, if left untreated, blindness. Its inevitable onset has led to a widely established treatment method: cataract surgery, an operation involving the extraction of cataracts and the placement of an intraocular lens, which can reverse visual impairment (Kohnen, 2009). Although cataract surgery is a widely established method to remove cataracts and improve visual impairment, it is widely inaccessible for many. Out of the millions suffering from cataracts, only about 6.1 million Americans have undergone cataract surgery and replacement lens implantation (NVision, 2022). Many factors, notably geographical location, socioeconomic status, gender, and race, as well as the operation's classification as an elective rather than an urgent procedure, impact disparities in cataract surgery.

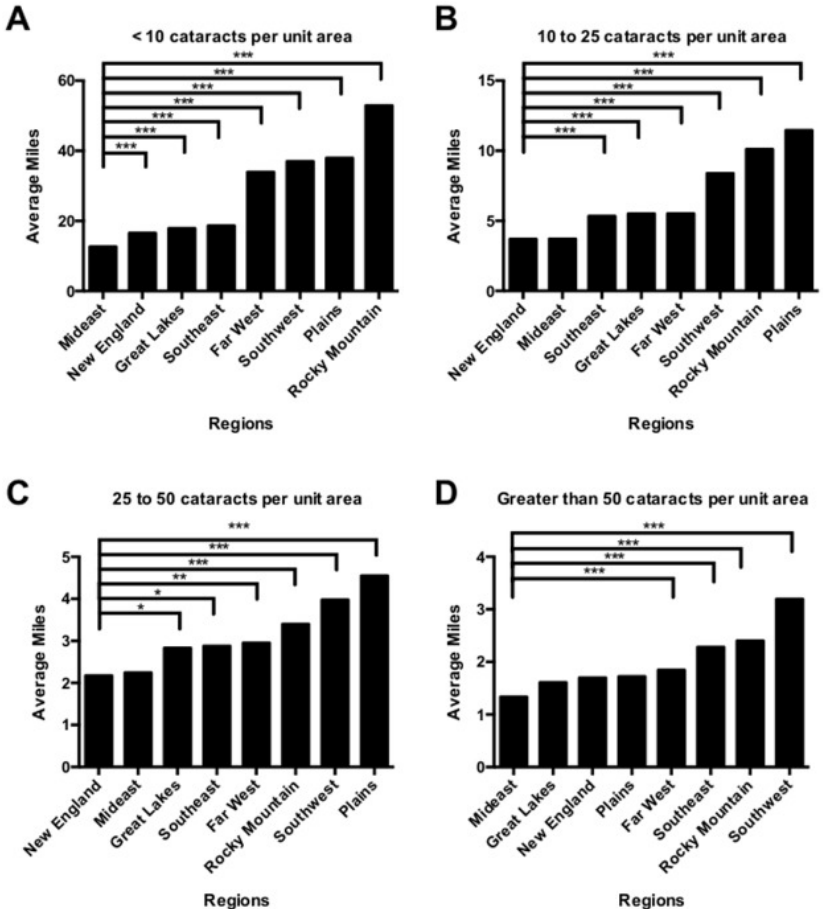

*Figure 1: Bar graphs showing average distance to nearest eye care provider by region. Distance was divided by expected number of cataracts per normalized geographic unit (NGU). Average distance for each region for <10 cataracts per NGU (A), 10 to 25 cataracts per unit area (B), 25 to 50 cataracts per unit area (C), and greater than 50 cataracts per unit area (D). * adjusted p value < 0.05, ** adjusted p value 0.01 to 0.05, adjusted p value < 0.001.*

Out of the millions suffering from cataracts, only about 6.1 million Americans have undergone cataract surgery.

Perhaps one of the most influential factors affecting access to cataract surgery involves socioeconomic status. Like most surgeries, it is expensive, costing anywhere from $3,500-7,000 per eye for patients without private insurance or medicare (Hill, 2022). This varies based on a patient's choice of facility, surgery, and intraocular lens type and includes pre- and post-operative fees. Medicare or private insurance can cover 80% or more of all costs (Hill, 2022). The role of health insurance is important in minimizing barriers to the operation; in 2014, cataract surgery was the most commonly performed surgery on Medicare beneficiaries, and

80% of all cataract surgery recipients in the US were Medicare beneficiaries (Lee, 2017). Research shows that patients of lower socioeconomic status face higher disparities in accessing care and subsequently are left to seek less or lower quality eye care (Zhang, 2013). Patients with incomes of less than $30,000 have increased hazards for surgery; that is, they are more likely to opt-in and pay for it despite their low-income earnings. Research suggests that less-affluent patients are more likely to need cataract surgery as a result of the nature of their jobs, where they may experience environmental influences such as sunlight and pollutants which would accelerate cataract onset and density (Kauh, 2016). Regardless of whether they are covered by insurance, patients of lower socioeconomic status may also face barriers in costs of transportation or follow-up care.

Even for those with insurance coverage, patients are challenged by their geographical location relative to eye care facilities. Specifically, Medicare beneficiaries living in rural areas who are farther away from facilities face significant difficulties in accessing cataract surgery, even if their lifestyle makes the surgery more necessary, as discussed previously (Lee, 2017). As of 2012, 1,901 Medicare beneficiaries in need of cataract surgeries were expected to travel more than 100 miles to their location of cataract surgery in states including South Dakota, Texas, Nevada, Wyoming, Nebraska, and Montana, where patients travel 324.82 miles on average to reach their destination. (Lee, 2017). Residing in areas without eye care facilities majorly discourages patients from undergoing cataract surgery, even if needed. Generally, NE and Mideast regions showed a 1:1 ratio in expected versus observed cataract surgeries, the far west showed more expected than observed surgeries, while the Great Lakes. Southeast, and Plains regions showed more observed surgeries than expected (Lee, 2017). This correlates with findings showing that age-standardized cataract surgery rates were highest in Lake Charles, Louisiana at 37.3%, and lowest in Honolulu, Hawaii at 7.5%. (Kauh, 2016). This places a significant travel burden onto patients living in regions without proximate access to ophthalmologists, and presents a socioeconomic hardship for those without the financial means of engaging in such travels. Indeed, studies have found that residents of more rural areas often have fewer clinical visits and visit fewer medical specialists than residents in less rural areas. When elderly patients are closer to medical facilities, the rate at which they both visit and comply with their physicians increases (Nemet, 2000). Studies like these demonstrate the importance of a high availability of optometrists and ophthalmologists to ensure faith in and drive to receive care (Kauh, 2016)

Research shows that patients of lower socioeconomic status face higher disparities in accessing care and subsequently are left to seek less or lower quality eye care.

On the basis of sex, females have a higher proportation of cataracts, yet, they face higher rates in unmet needs for surgery (Richter, 2009). Research on these gender disparities on a global scale have shown that women have a lower coverage rate of cataract surgery (Zhi, 2021), suggesting that a contributor to these unmet needs may be socioeconomically related. Interestingly, the proportion of female ophthalmologic surgeons is less than males, who usually perform (Cai, 2022). Addressing this gender disparity directly from the source of cataract surgery - by increasing the proportion of female ophthalmologic surgeons and the proportion surgeries they operate compared to males - may also aid in increasing access and improving gender

FIGURE 1.

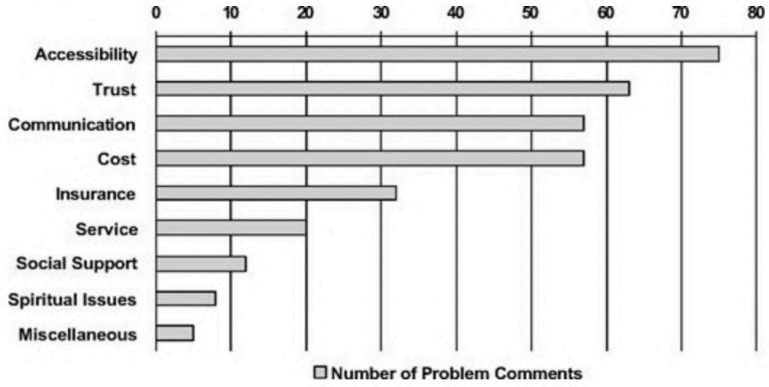

Figure 2: Frequency of comments on barriers to eye care made by older African American focus groups. Data stratified by topic of comment.

equality overall.

Racial disparities also highlight a large proponent of unequal access to cataract surgery. African-Americans have less prevalence of cataracts compared to White Americans, yet are also less likely to receive necessary cataract surgery (Shahbazi, 2015). A study by Shabazi et al. studied a population in need of utilizing cataract surgery and found that the utilization rate of African-Americans, regardless of gender, was lower than that of whites (African-American males, 7.92%, African-American females, 6.17%, white males, 12.08%, and white females, 10.54%.). A source of this lower utilization rate may stem from distance to facility and mistrust and miscommunication with doctors: in a research study by Owsley et. al, the most significant barrier to accessing cataract surgery most cited by older black patients included lack of transportation and accessibility to offices, as well as trust issues (Owsley, 2006). Given that cataracts are the leading cause of blindness for the African American population (Tielsch, 1990), there is significant need to address racial disparities in increasing access to surgery that would reverse visual impairment. In comparison to white patients, Latinos and Asian Americans had greater greater hazards to surgery (Kauh, 2016). It is important to note that racial disparities in accessing cataract surgery include races in addition to the ones above; the variation in utilization of cataract surgery among even the few races this review discusses alone demonstrates the need to increase access to cataract surgery to patients nationwide, regardless of their race.

Racial disparities also highlight a large proponent of unequal access to cataract surgery.

While this article focuses on commonly studied factors contributing to the wide inaccessibility of cataract surgery - namely, geographical location, socioeconomic status, sex, and race - it is important to recognize that many other factors exist. These include patient education and awareness about cataracts and cataract surgery, as well as the number of ophthalmologists nationwide. Researchers also study the correlation between latitude of residence and likelihood of needing cataract surgery; however, while certain results have shown an association it is still overall in contention (Lee, 2017). Moreover, studies have found that certain lifestyle choices, such as multivitamin use or reducing smoking, can prevent or delay cataract onset (Chang, 2011).

With a seemingly countless number of factors affecting access, there is much to be addressed. A variety of efforts in different areas may help alleviate these disparities to increase access, including 1) Address the gender gap in surgeons performing cataract surgery (as males perform more surgeries more than females) (Cai, 2022); 2) Increase patient education and awareness, especially regarding the important role of cataract surgery in reversing visual impairment, because even if patients are aware of cataract surgery, they may not choose to receive it because of its elective

form of care; 3) Assess currently available resources in areas with high racial disparity (Shahbazi, 2015); 4) Establish more practicing ophthalmologists and facilities in rural areas. In decades past, various state health departments have also suggested the establishment of a standard preventing residents from traveling more than 30 minutes to see a physician (Bosanac, 1976); 5) Find ways to lower cataract surgery costs; and 6) Continue to examine progress (or lack thereof) in advancing access to cataract surgery in the U.S. following the emergence of studies in this article and future studies to come.

Efforts towards improving access may take many years of implementation before seeing results; however, maintaining steady flow and sharing of research efforts can help track progress. Moreover, based on the intersections of different scientific, socioeconomic, and political factors that together contribute to access (or lack thereof) to cataract surgery, it will take the collaboration of patients, doctors, insurance companies, politicians, educational institutions, and many more to see change. It may not be an easy path, but doing it together and towards a shared purpose will aid in improving access for all. ❧

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Alyssa is a second year majoring in Neuroscience Behavior and Biology. Her interests are in neurodegenerative diseases, vaccine hesitancy, and healthcare access.

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Women in prison: The importance of trauma-informed care

ANKITHA KUMAR
Staff Writer

Figure 1: Incarcerated women are much more likely to have a diagnosed history of mental illness compared to their male counterparts. A woman with bipolar disorder sings "Mary had a Little Lamb" to herself at the Bexar County Jail (Villa, 2017).

Feet shackled and hands cuffed, Sophia Casias lay curled up on the cement floor of the Bexter County adult detention center. Seven months pregnant, she could not balance her body weight. "Get up!" a voice bellowed. A guard grabbed her by the hair as she sobbed, unable to breathe. After reflecting on this event years later, Sophia Casias realized that these events triggered memories of being sexually assaulted by her family members as a child (Yearwood, 2020). Ms. Casias's experience is not a one-off event. Rather, her story reflects the plight of most incarcerated women. Incarcerated women face disproportionate amounts of trauma that are exacerbated by U.S. prison conditions. Evidence shows that Women-centered Trauma-Informed Care and Practice (TICP) can improve the physical and mental well-being of incarcerated women.

Women in prison face disproportionate amounts of trauma and mental health challenges compared to their male counterparts. Incarcerated women are often overlooked—only 7% of the incarcerated population is female, leading to fewer housing options (Villa, 2017). Because of the lack of detention centers for women, women tend to be placed further from their families than men, negatively impacting their mental health. The statistics back up these claims: 32.2% of women reported serious distress in the past 30 days compared to 25.5% of men (Villa, 2017). Additionally, 67.9% of women in prison reported a diagnosed history of mental illness compared to 40.8% of men in prison. The 27.1% difference in the history of mental illness means that incarcerated women possess a greater amount of pre-existing trauma and triggers than do incarcerated men (Villa, 2017). Indeed, incarcerated women have significantly higher rates of trauma exposure, victimization, post-traumatic stress disorder, and interpersonal trauma (Bilyeau, 2020). 57% of women in prison are survivors of domestic violence. Furthermore, 53% of incarcerated women were subject to emotional, physical, and/or sexual abuse as a child (Jewkes, 2019). Women report trauma exposure as a key reason for their crime. Many women are victims of more violent crimes—rape and assault—than what they are convicted for: non-violent drug charges (Jewkes, 2019).

Incarcerated women face disproportionate amounts of trauma that are exacerbated by U.S. prison conditions.

An inmate's trauma has extensive psychological and physiological effects that determine their experience with incarceration. Generally, after a threat, the brain and body work together to respond (Benedict, 2014). The brain cues the sympathetic nervous system, which triggers a fight-or-flight response. This response leads to alert senses, tense muscles, and shut-down of the digestive system. Once the threat is no longer active, the brain cues the parasympathetic nervous system which triggers relaxation in the body (Benedict, 2014). Brain scan data has shown that many trauma survivors are permanently "stuck" in a fight or flight response. These survivors unconsciously scan the environment for threats and experience

Image 2: Incarcerated pregnant women in 23 states are subject to shackling of their legs, arms, and stomach (Urell, 2022). Policy in all 23 of these states requires shackling after labor, with some states requiring shackling during labor and childbirth (Walshe, 2012).

difficulty relaxing.

In addition to prior traumatic experiences, incarcerated women are subject to further trauma in prison. Female inmates experience initial trauma at arrival with many psychological assaults along with unresolved problems from outside of prison. Female inmates who are subjected to strip searches at arrival report that this lack of autonomy reminds them of past sexual abuse and assault. Traumatic events continue throughout a woman's time in prison. Female inmates are continuously forced into hospital visits where all escorts are male, resulting in these women feeling unsafe. Additionally, male correctional officers frequently "monitor" female inmates as they shower, use the toilet, or change clothes. The lack of privacy causes incarcerated women to feel terrified and threatened, leading to a continuously activated fight-or-flight response (Scott, 2014).

An unspoken source of trauma for female inmates is shackling them during childbirth (Urell, 2022). Cora Fletcher, a 17-year-old girl charged with retail theft, was 8 months pregnant when she was detained at the Cook County Jail in Illinois. After complications at her prenatal check-up, Ms. Fletcher was rushed to the county hospital. As the medical team worked to induce her, her hands and feet were shackled to both sides of the bed. Three days later, when Ms. Fletcher went into labor, the escorts accompanying her to visit agreed to release one hand and one foot. Ms. Fletcher gave birth with one hand and one foot shackled to the bed and received no acknowledgment for the humiliation and trauma she endured.

To create a safer environment for incarcerated women, prison policy should focus on limiting opposite-sex supervisors, strip searches, pat-downs, and restraints.

Ms. Fletcher's experience mirrors that of most pregnant women who give birth while incarcerated. A 2018 study (n = 690) found that 83% of perinatal nurses who cared for pregnant and postpartum inmates reported the use of shackles on their patients (Goshin, 2018). This statistic includes shackling during and immediately after labor and delivery but doesn't account for shackling during transportation to the hospital (Urel, 2022). Shackling during childbirth and pregnancy leads to trauma for a plethora of reasons. The most well-known reason is that shackling causes trauma due to physical pain. Shackling poses physical risks such as the reduced ability to administer epidural, hip dislocation due to restraints, permanent deformities, stomach muscle tears, and umbilical Hernia (Urel, 2022). Additionally, shackling leads to post-traumatic stress disorder as it is a dehumanizing experience that violates personal dignity. Female inmates who were subject to shackling reported that this experience caused further depression and mental health challenges (Urell, 2022). Finally, shackling can be a re-traumatizing event for many women. Incarcerated women are highly likely to have suffered childhood trauma such as sexual, physical, and emotional abuse. Shackling is a re-traumatizing experience that brings back memories of awful childhood experiences from the past (Urel 2022).

Prison policy research has shown that women-centered Trauma-Informed Care and Practice (TICP) is key to protecting incarcerated women's physical

and mental health. Implementation of TICP at Massachusetts Correctional Institution-Framlingham resulted in a 62% decrease in prisoner-on-staff violence (Jewkes, 2019). Trauma-informed care is centered around three key principles. First, inmates must feel safe, connected, valued, and hopeful of recovery. Female inmates with traumatic pasts tend to defend themselves through violent measures when they feel unsafe (Jewkes, 2019). To create a safer environment for incarcerated women, prison policy should focus on limiting opposite-sex supervisors, strip searches, pat-downs, and restraints. Second, all staff including correctional officers, counselors, and mentors must understand each woman's trauma and how it relates to her adult psychopathology. Third, staff must work with the woman's support system in order to promote her autonomy (Jewkes, 2019). According to Mayer Spivack's 1984 publication of "Institutional Settings: An Environmental Design Approach," providing facilities to cook food and the ability to take on a hobby of choice are effective ways to provide inmates with autonomy (Jewkes, 2019).

Solving the pregnancy shackling problem is part of Women-centered Trauma-Informed Care and Practice (TICP). Tennessee is the most recent state to limit restraints on pregnant inmates. Tennessee state law allows pregnant inmates to be handcuffed in front of their bodies during transportation outside the facility. However, the law prohibits inmates from being shackled around their ankles, legs, and waist (Hernandez, 2022). It is necessary for future policy to extend beyond Tennessee's measures in protecting pregnant inmates. Future prison policy should center around prohibiting shackling during labor and delivery. Lawmakers cite the purpose of shackling as "to prevent women from escaping from the hospital" (Clark, 2013). However, shackling is not necessary as it is highly unlikely for women to escape during the stress of labor and delivery, especially when accompanied by armed correctional officers (Clark, 2013). At the least, shackling should not be a uniform policy and should consider a woman's history of violence and physical state. Most female inmates are serving time for nonviolent crimes and have zero escape attempts. As mothers who are hours away from giving birth, these women do not have the physical strength to escape (Clark, 2013).

U.S prison conditions such as shackling and lack of autonomy result in disproportionate trauma for incarcerated women and affect their psychological and physiological state.

Ms. Sophia Cass and Ms. Cora Fletcher experienced traumatic events that no woman should ever have to face. Their stories represent the horrific conditions that many incarcerated women endure. U.S prison conditions such as shackling and lack of autonomy result in disproportionate trauma for incarcerated women and affect their psychological and physiological state. Women-centered Trauma-Informed Care and Practice (TICP) has the potential to increase the physical and mental well-being of incarcerated women. Adopting evidence based-policy will allow female inmates to resolve previous trauma and minimize future trauma. ❧

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Evolution of emotions

NEHA BAJAJ
Staff Writer

Upon hearing the words evolution, adaptation, or natural selection, one may automatically consider the physical characteristics of populations and how they have evolved over time. However, these terms are not limited to just physical attributes; they also extend to the mind as they determine psychological characteristics. Many processes of the mind and brain are a product of the accumulation of small changes over time that have manifested into emotions and behaviors. This article explores the history, origination, and evolution of emotions from our ancestors, how emotions evolved to serve an adaptive role, and how the specific emotions of pride and shame arose and are expressed physiologically.

In 1859, naturalist Charles Darwin published the book On the Origin of Species, which revealed his discoveries throughout his travels of the Galapagos Islands as he characterized the different sizes and shapes of the island's finches. In his book, Darwin highlighted the terms adaptation and natural selection that led to the idea of evolution. Adaptations are defined as the change or process of change by which an organism becomes better suited for its environment, thus allowing them to thrive. Relatedly, natural selection is the process through which organisms better adapted to their environment are more likely to survive and produce living offspring. The coupling of adaptation and natural selection leads to the evolution of populations over time. At first, Darwin's book solely focused on the physical characteristics of finch beaks on the Galapagos Islands and how varying beak structures impacted the diet and foods that a finch could consume. Later on, these ideas were translated to humans and were used to explain the structure and function of anatomical features in the body. Shifting this train of thought to humans catalyzed the emergence of questions surrounding emotions: How did emotions arise? Have emotions been present for centuries? What causes emotions to emerge in response to a specific stimulus? To answer these questions, Darwin treated emotions as "separate discrete entities, or modules, such as anger, fear, disgust, etc." while focusing on the "visible but temporary changes in appearance" that accompany these different emotions (Ekman, 2009). These observations were critical since "facial expressions have been shown to reveal the most amount of information and detail about an individual's emotions" (Ekman, 2009). As a result, Darwin devised an experiment to test his hypothesis in order to understand the movement of the human face. The experiment involved showing 23 English men, women, and children of different age groups a set of photographs of human faces and asking them to name the emotion they believed the photographs were displaying. Through his experiment, he found that several "shades of expression are instantly recognized without any conscious process of analysis" and that some "facial expressions convey a particular emotion more convincingly than others" (Cambridge, 2015). For example, Darwin noted that simple emotions shown in the photographs,

Many processes of the mind and brain are a product of the accumulation of small changes over time that have manifested into emotions and behaviors.

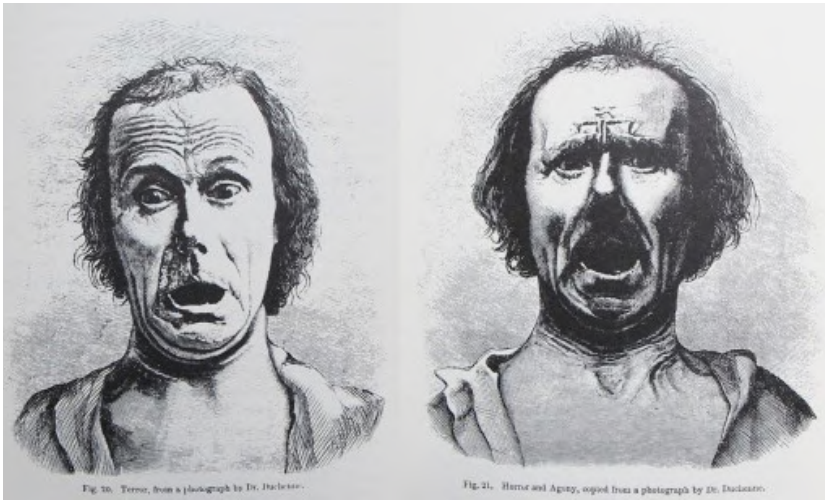

Figure 1. Photograph shown to the participants of Darwin's experiment to recognize the emotion of fear. Image from Cambridge, 2015.

such as surprise, terror, grief, and happiness, were easily identified among the participants. Contrastingly, compound emotions such as a half-crying face or crying specifically from grief took the longest time on average to recognize.

Simple emotions were more easily understood since human nature is predisposed to see and recognize them, whereas more complex and combined emotions are a more recent development in evolutionary history and thus take a longer amount of time to identify. Overall, these results spearheaded the conversations and scientific discoveries of the evolution of emotions.

Over time, our emotions have served an adaptive role in aiding our ancestors and enabling them to react appropriately to a multitude of situations, such as escaping in times of fear. As a result, our ancestors were primed to certain actions through their fight for survival which dictated distinct physiological responses. Thus, emotions responding to such scenarios, such as fear, evolved first. A sense of fear was needed to identify sources of danger, including fighting, escaping predators, death, etc., that repeatedly occurred throughout history. This continual encounter with life-threatening stimuli allowed the environment to naturally select for the emotion of fear and led to its presence in future generations. Through this process of adaptation and selection, the limbic system developed. The limbic system is a collection of structures within the cerebrum of the brain responsible for processing emotions. As our ancestors evolved, the limbic system evolved as well as they became more attuned to processing these acute emotions. As a result, our ancestors' responses to certain stimuli throughout their lives have yielded emotions that serve distinct adaptive roles.

Shifting this train of thought to humans catalyzed the emergence of questions surrounding emotions: How did emotions arise? Have emotions been present for centuries? What causes emotions to emerge in response to a specific stimulus?

Diving deeper, two emotions emerged in evolutionary history at relatively similar times: pride and shame. Both pride and shame are considered "self-conscious emotions as they are heavily focused on the individual that is experiencing them" (Cosmides, 1997). These emotions arose due to the large packs of animals living and sharing resources together as having more resources enabled an individual animal to gain a greater sense of superiority and dominance. Over time, this response was passed down from generation to generation and became a greater part of humans' physiological response to certain stimuli. Furthermore, pride enhances an individual's social status that "generates proud feelings, boosts self esteem, and communicates to the individual that she or he merits increased status" (Roth, 2020). Physiologically, pride is expressed in a way that activates certain portions of the brain such as the "emotion-processing circuits including the amygdala and other brain regions such as the bilateral dorsomedial prefrontal cortex," which are brain structures responsible for

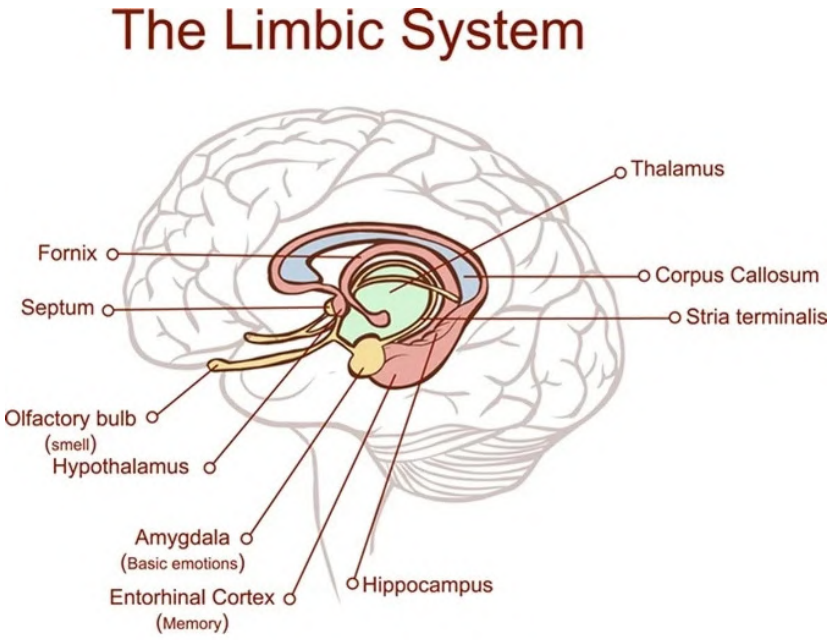

Figure 2. Diagram shows the limbic system and the several different components of this brain feature responsible for controlling and developing an individual's emotions. Image from Medical Net, 2021.

acting as an intermediate between cognitive control areas and generating and regulating emotions (Roth, 2020). The amygdala and bilateral dorsomedial prefrontal cortex are linked and work in tandem to create and process emotions. Shame is another emotion that has developed over time and is characterized as a response to a situation in which an individual "violates social norms or puts themselves in a non-ideal situation" resulting in a change in physical and physiological characteristics such as "blushing, sweating, and an increased heart rate" (Kämmerer, 2019). Shame arose in response to self-criticism and judgment of oneself in an effort to live up to certain social standards. Overall, emotions of shame and pride have evolved to serve evolutionary purposes in individuals.

Darwin noted that simple emotions shown in the photographs, such as surprise, terror, grief, and happiness, were easily identified among the participants. Contrastingly, compound emotions such as a half-crying face or crying specifically from grief took the longest time on average to recognize.

In conclusion, over time, our ancestors developed particular emotions, such as fear, pride, and shame, which were selected due to their relevance and importance in responding to stimuli and thus have subsequently been seen in successive generations. As a result, the information presented in this article is pivotal in order to deepen the understanding of our evolutionary history from the perspective of our emotions. ❧

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Not so free: Insulin accessibility in the United States

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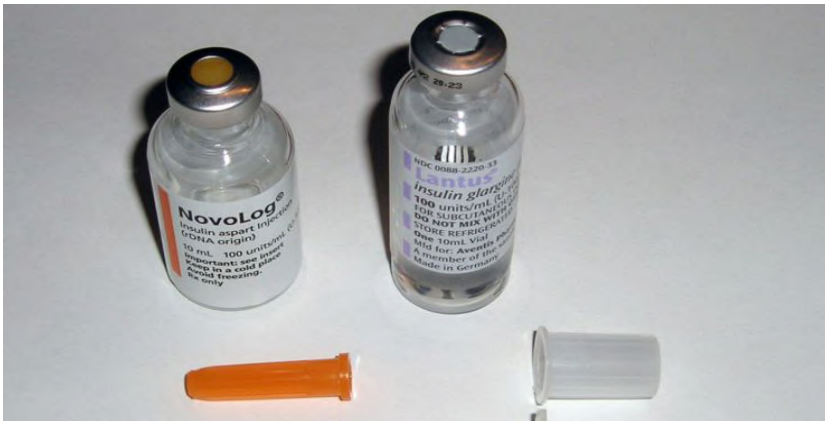

Figure 1. The price of insulin, generally taken through injection as shown above, has rapidly risen over the past few decades (Bradford 2006).

"I don't know how I've been able to make it out alive after so many years of [rationing insulin]" (The Register's editorial, 2019). For Roxanne Strike and the 7 million other Americans who require daily insulin to manage their diabetes, uncertainty is the norm. In fact, average insulin prices have doubled over the past decade, and up to 14% of insulin users spend at least 40% of their post subsistence income, which is money left over after food and housing costs, on the crucial drug (Locklear, 2022). Given the inaccessibility of insulin despite a dire need for it, it is important for policymakers to investigate the factors making this drug inaccessible and the strategies that might make it less so.

"I don't know how I've been able to make it out alive after so many years of [rationing insulin]" (The Register's editorial, 2019).

Many Americans are uninsured or underinsured, limiting their access to insulin. Even after the 2010 passage of the Affordable Care Act, which dramatically expanded health insurance coverage and benefits, up to 1.5 million diabetic Americans are currently uninsured (Wampler, 2019). These patients are unlikely to be able to afford insulin without insurance, as 82.6% of uninsured Americans are in families earning incomes less than 400% of the federal poverty line, or $54,360 for a single-person household (Tolbert and Damico, 2020). Therefore, a considerable proportion of diabetes patients do not have insurance and are unlikely to have access to insulin. Even insured patients may have difficulty affording insulin; up to 25% of users with private coverage from small businesses paid more than $420 per year on the drug (Amin et al., 2022). In addition, many insulin users require additional devices, such as insulin pumps and continuous glucose monitors, to take their medication. Because these devices are seldom fully covered by insurance plans, the mean out-of-pocket spending for all care among type 1 diabetes patients is around $2,500 per year (Chua et al., 2020). An alarming number of Americans lack coverage for insulin and associated devices, independent of their insurance status, which places a significant financial burden upon them. Considering these exorbitant costs, it is unsurprising that up to 25% of insulin users report skipping insulin doses due to cost; this underuse is associated with poor glycemic control, which is the strongest determinant of diabetes-related complications and death (Herkert et al., 2019).

Fortunately, policy-makers are currently discussing bipartisan proposals intended to increase insurance coverage for insulin. Among these proposals are efforts by Senators Susan Collins and Jeanne Shaheen to cap out-of-pocket costs while lowering insulin list prices (Amin et al., 2022). The proposal also requires private group or individual plans to cover each type of insulin, including rapid-acting, short-acting, intermediate-acting, ultra long-acting, and premixed, which gives patients more choice and leads to even lower insulin costs (Amin et al., 2022). These various insulin types enter the bloodstream at different points after injection or intake, accommodating various comorbidities and lifestyles. Such a proposal is ideal for increasing insulin accessibility because it lowers

list prices, therefore making insulin affordable for the uninsured while also increasing coverage for those who have insurance.

While a lack of insurance accessibility increases the actual price of insulin for American patients, market factors are a root cause of this drug's high price. In fact, the companies Novo Nordisk, Sanofi-Aventis, and Eli Lilly control the vast majority of the American insulin market, and this lack of competition combined with the fact that consumers are willing to pay any cost necessary for the drug results in artificially high prices (Rajkumar, 2020). Consequently, diabetes patients are in a bind—they can choose to forgo their insulin prescriptions and suffer the potentially deadly consequences or pay eye-watering amounts of their post-subsistence income to survive. New companies that could potentially offer cheaper insulin in the United States face significant deterrence from the American triopoly. In India, for example, Novo Nordisk beat out competitors by artificially lowering prices and making market entry for other insulin-producing companies financially unfeasible, eventually gaining market control and subsequently raising prices (Knox, 2020). In many other pharmaceutical markets, companies can compete with the insulin giants by developing significantly cheaper generic versions of patent-expired insulin products. However, generic insulin development is difficult in the United States. Novo Nordisk, Sanofi-Aventis, and Eli Lilly engage in a practice called "evergreening", wherein they make small incremental improvements to their insulin products, resulting in the extension of their patents (Mayor, 2015). This process leaves behind a trail of old versions of insulin, which provide formulas for generic alternatives. However, generic drug companies refrain from manufacturing generic versions of insulin because many doctors and patients consider them obsolete, disincentivizing the production of the drug (Mayor, 2015).

Considering these exorbitant costs, it is unsurprising that up to 25% of insulin users report skipping insulin doses due to cost; this underuse is associated with poor glycemic control, which is the strongest determinant of diabetes-related complications and death (Herkert et al., 2019).

Beyond private sector forces, government regulations have historically kept insulin prices high. Because producing generic versions of insulin is difficult in the United States, companies may turn to producing biosimilars, which are analogs for biologically-derived materials such as insulin that only have small differences in clinically inactive components (Knox, 2020). The government tends to give generics interchangeability status with the original versions of drugs due to their identical formula, allowing them to be prescribed freely and lowering prices by at least 50 percent (Knox, 2020). Historically, the government did not allow any biosimilars interchangeability status, limiting their use in treatment (Knox, 2020). Fortunately, these trends are changing, as the United States government recently approved Semglee, the first interchangeable biosimilar insulin product (Cohen, 2021). The further introduction of automatically interchangeable insulin analogs at pharmaceutical counters will increase competition, in turn lowering prices.

In fact, the price of insulin in the United States is more than 10 times higher than the average of 32 other industrialized countries (Irving, 2021).

Finally, the United States government has yet to implement meaningful price controls on insulin. While the triopoly of Novo Nordisk, Sanofi-Aventis, and Eli Lilly reigns in much of the world, blatantly high insulin prices are uniquely an American problem. In fact, the price of insulin in the United States is more than 10 times higher than the average of 32 other industrialized countries (Irving, 2021). Though the United States has high insulin prices for a multitude of reasons including those aforementioned, the lack of government intervention in negotiating with manufacturers is perhaps the largest culprit. Governments of peer nations such as France set maximum prices for new pharmaceuticals that reflect their added therapeutic value and lower prices after a designated period of time

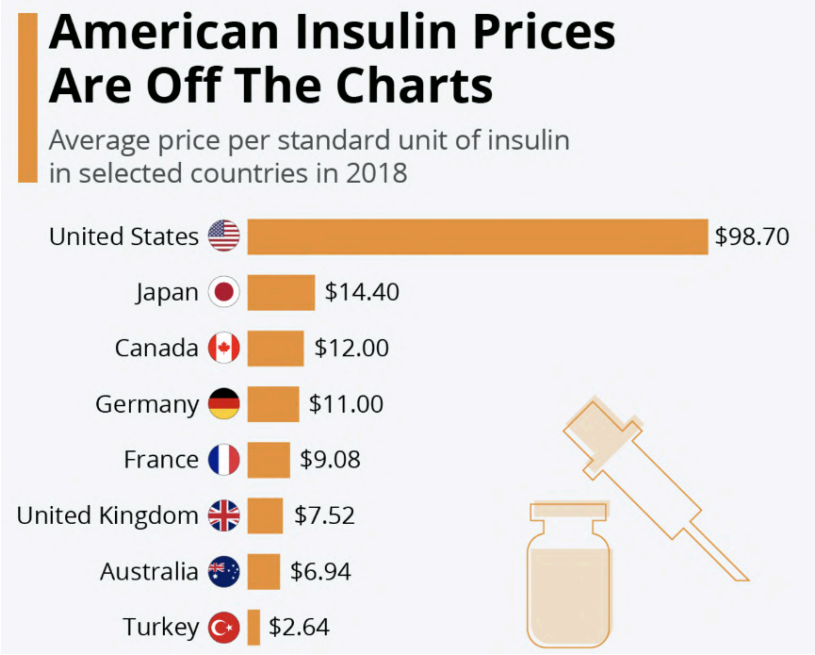

Figure 2. Insulin prices are significantly higher in the United States than in other developed countries (McCarthy 2020).

(Rodwin, 2019). These measures stand in stark contrast to those in the United States, where insulin prices largely fall under market influence.

Negotiating prices with manufacturers using the French model would solve many problems that the United States currently faces with insulin accessibility. First, pharmaceutical companies must negotiate with the government or risk losing access to an entire market, incentivizing them to lower prices. Furthermore, because the French model mandates that companies lower the prices of their older pharmaceuticals while keeping them on the market, the United States government could circumvent its lack of generic alternatives by keeping older-but-still-effective versions of insulin on the market while allowing patients to access updated versions of the drug. On the topic of innovation, the French model's rewarding of higher prices to companies that produce more innovative pharmaceuticals allows for the maintenance of research and development along with more affordable drugs through price controls. French patients have the same access to new drugs that other European Union patients do (Rodwin, 2019). By adopting price controls that involve strict negotiations with companies while continuing to reward true innovation, the United States government could help lower the price of insulin and increase accessibility for the life-saving drug.

In order to increase the accessibility of insulin, policymakers and voters need to understand the factors contributing to the high price of this drug in the United States. While many of these factors, particularly those involving a lack of governmental action, can seem daunting to overcome, the truth is that actors including the United States government and private companies are working to make insulin more accessible through policy and innovation. Though many have previously suffered from the inaccessibility of insulin, the future is bright for those who need the drug to survive. ❧

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Krishna is a second year majoring in Anthropology and Human Biology. He is interested in the cross-section of public policy and health outcomes, and the potential role of new technologies in healthcare.

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Second-hand heartbeat: Cardiac pacing infrastructure in developing ountries

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Figure 1. A depiction of a standard cardiac operating room.

Common parlance in developing countries omits the term cardiac pacing. Eight of thirty-one countries surveyed in Africa do not consistently offer cardiac pacing, and there was less than one pacing center per million citizens in these 31 nations in 2013. The rate of permanent pacemaker (PPM) implantations was 19 per million in 2014 (Bonny et al., 2018). In comparison, the rate of PPM implantation in the United States was 616 per million in 2009 (Greenspon et al., 2012). A lack of "skilled physicians" and a "scarcity of resources" has produced this disparate environment (Jouven et al., 2019). Despite a large absence of access, one must examine the plight of cardiac patients actually able to receive care under the pacemaking infrastructure in place.

Africa-Pace began conducting missions in sub-Saharan Africa in 1996, training local physicians and implanting PPMs to assuage the absence of care opportunities. As care deliverance was constrained by the arrival of mission personnel, only 542 of 1,077 "listed" patients received PPM implantations. The "majority" of the other patients died before they could be reached by mission personnel, nevertheless experiencing better fortune than most; connectivity with the western organization enabled the faint prospect of entering the operating room (Jouven et al., 2019).

Local pacemaking infrastructure exists in some developing nations, but the idealistic notion that these hospitals can rectify deadly waiting periods must be checked. At a hospital in Peshawar, Pakistan, insufficient "expertise" and a "shortage of PPM devices" resulted in an average wait of 8.7 days before PPM implantation, and Irfan et al. (2020) ascertained a correlation between adverse events and waiting period duration. The patients received a temporary transvenous pacemaker (TTvP) during this period, a practice "common in developing countries" (Irfan et al., 2020).

Connectivity with the western organization enabled the faint prospect of entering the operating room.

TTvP utilization as a "bridge" to PPMs, or more accurately an endless causeway, is problematic in its own right, and this practice occurs in nine of fifteen surveyed African nations (Bonny et al., 2018). The TTvPs typically have "no or passive fixation" (Suarez & Banchs, 2019), a mechanism best described as a prong hooking onto cardiac muscle. Dislodgement occurs when the prong becomes disengaged (University of Minnesota). TTvPs include an external pulse generator and transvenous leads reaching the myocardial tissue (Figure 2).

A meta-analysis by McCann (2007) discovered complications with TTvPs in 26.5% of patients on average, including a dislodgement rate of 15%. Hildick-Smith and Petch (1998) argue that TTvP use should entirely cease, as the devices result in a "sixfold increased risk of infection" of the eventual PPM. A mortality rate of "up to 50% [occurs] if infected leads are not removed" through a risky procedure (Hildick-Smith & Petch, 1998). Granted, in developing nations, there are

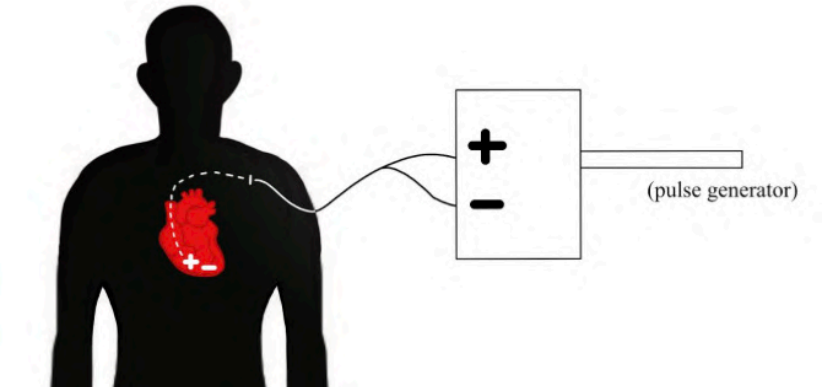

Figure 2. The anatomy of a jugular TTvP with external components.

few alternatives to TTvPs under current infrastructure, as PPM implantation cannot be hastened.

The complication-ridden nature of TTvP use warrants addressing the established lack of cardiological expertise in developing nations. A study in the Wessex region of the United Kingdom found that "immediate complications" like "arterial puncture" were less likely to occur when physicians placing the TTvP had extensive experience (Betts, 2003). Comprehensive literature concerning TTvP complication rates in developing countries does not circulate, which necessitates utilizing statistics from western hospitals to establish risk. One must therefore infer the inflated perils when TTvPs are employed in facilities lacking properly trained physicians and surgical protocol aligning with western standards. The established danger of TTvPs in western countries portends the unmitigated peril cardiac pacing patients face in less-regulated zones.

To fully apprehend patient risk, one must return to the duration of the TTvP "bridge." In the Wessex study, 19.8% of patients with TTvP placement greater than 48 hours experienced "local or systemic infection," as opposed to a 3.6% infection rate for placement less than 48 hours; TTvPs were intact for a median of two days (Betts, 2003). In a Dakar, Senegal hospital, TTvPs were placed in 60% of patients for a mean duration of 5.1 days, and longer TTvP duration correlated with increased complications (Kane et al., 2019). The two-day TTvP use in Wessex (Betts, 2003), when juxtaposed with waiting periods of longer than five days in Dakar (Kane et al., 2019) and Peshawar (Irfan et al., 2020), empirically exemplifies an unequal reality: long waits with increasing adverse events.

Even for pacemakers with at least 70% battery life, demand exceeds supply.

Although the FDA bans the reuse of pacemakers in the U.S., many developing countries are forced to turn to this practice. To be reused, the device should be sterilized and have at least 70% battery life (Aragam et al., 2011). Usually, the process comprises immersion in Lysetol for 12 hours, wiping with 70% ethanol, air-drying, and placement in ethylene oxide (Linde et al., 1998). Device crevices and the "possibility of body fluids entering the terminal leads of the pacemaker" add challenge to proper sterilization (Kirkpatrick et al., 2010). The particularities of the procedure limit the feasibility of developing countries to properly clean all reused PPMs.

Infection is a concern, especially when considering the possibility of transmitting viruses and prion diseases. Thus, most medical device manufacturers intend for their devices to be single-use (Kirkpatrick et al., 2010). The risk is further elevated considering that in developing countries, "thousands of used devices…have been sterilized and reimplanted without regulation" (Tandon et al., 2017). The reuse of PPMs only exacerbates the infection risks already threatening cardiac patients.

Even for pacemakers with at least 70% battery life, demand exceeds supply (Aragam et al., 2011). From January to July of 2008, 50 PPMs were donated from funeral homes to World Medical Relief, a nonprofit charity. Yet among the 50 PPMs, only 18 (36%) had at least 70% battery life, and one had defects in the pacemaker lead terminals, rendering the PPM useless (Baman et al., 2009). More donations do not necessarily translate to an improvement in the healthcare of developing nations.

Medical complications associated with PPM reuse include cardiac tamponade, refractory arrhythmias, and cardiac arrest (Baloch et al., 2020). Reused devices may also malfunction and require more frequent generator

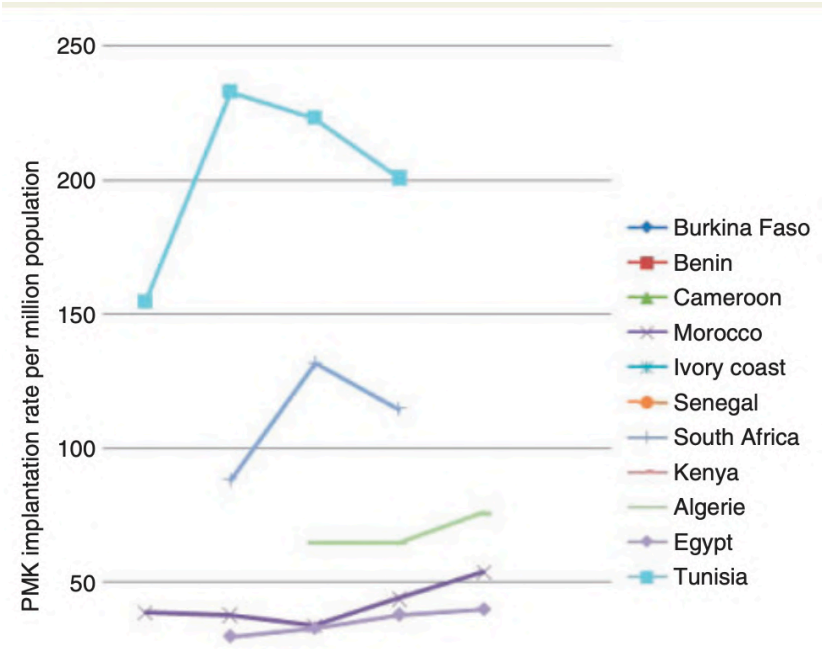

Figure 3. Compiled graph of PPM implantation rates, from Bonny et al. (2020). A "postive" trend in implantations is present for most but not all African populations.

replacements, augmenting surgical complication risks (Aragam et al., 2011). The two main risk factors for surgical complications include an age over 60 years and congenital heart disease (Dalgaard et al., 2020). However, many articles omit the higher surgical risk factors in developing countries. For example, the highest congenital heart disease rates occur in locations such as the Central African Republic, Somalia, and Burundi, with the lowest rates in developed countries (Wu et al., 2020). Elevated surgical risks combined with the medical complications from PPM reuse exacerbate inherent dangers associated with arrhythmia care.

Some studies find pacemaker reuse failure rates negligible. In a 2008 case study, 12 patients received reused PPMs at the Philippines General Hospital using "guidelines for standard of care," and no complications were reported after follow-up periods (Baman et al., 2009). However, the data frequently comes from studies either conducted in developed countries or run by groups from developed countries with ideal standards. One cannot infer that routine, unregulated pacemaker reuse in developing countries has the same rate of success.

The FDA implicitly undermines the equal standing of citizens in less wealthy countries.

Donating resterilized pacemakers below ethical standards repudiates the integral biomedical principle of justice, or equal care deliverance. By approving exportation of reused PPMs to other countries but restricting the practice in the US, the FDA implicitly undermines the equal standing of citizens in less wealthy countries (Tandon et al., 2017). PPM reuse, often patients' sole recourse, usurps autonomy to seek low-risk care. The upshot is the subversion of community trust in the healthcare system. To provide adequate care, focus must shift to increasing the quantity of available new PPMs and not merely increasing supply of reused PPMs. The importance of a balance between care quality and simply maximizing accessibility cannot be understated.

TTvPs are necessary for patient subsistence, but increases to supply of new PPMs can limit bridge periods of TTvP use and enable a reduction in TTvP reliance altogether. New PPM access limits waiting period and TTvP risk while allowing a transition away from pacemaker reuse.

Physician education, a prevailing deficiency, also determines care access. In many developing countries, the medical specialty of cardiology is underdeveloped or even nonexistent. Lower rates of PPM insertion failure, shorter surgery time, and lower complication rates could be achieved when cardiology residents are better trained (Baloch et al., 2020). A lack of skilled cardiologists is also directly related to longer waiting times and TTvP bridge periods (Irfan et al., 2020).

A few nonprofit organizations have begun to take these required steps to rectify the plight of patients. The Africa-Pace missions, which are "based on training local healthcare teams," epitomize the types of initiatives necessary to build local pacemaking capacity (Jouven et al., 2019). Improvements in local infrastructure have produced modest increases in PPM implantation in some developing

nations (Figure 3). However, as pacemaking access continues to lag far behind the western world and avoidable deaths mount, one must ponder whether coordinated efforts will progress beyond using developing countries as a dumping ground for a handful of pacemakers extracted from the deceased.

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Dr. Eisen aims to engage undergraduate students in the exploration of science and its applications in broad contexts. He has led the Emory-Tibet Science Initiative since 2005, which works with the Dalai Lama to provide a scientific education for Tibetan monks and nuns. He has published a wide variety of academic articles in science, science education, and bioethics

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