Emory Undergraduate Medical Review

Fall 2021 • Volume 8 • Issue 1

Picture by Richard Lee

EMORY UNDERGRADUATE MEDICAL REVIEW

Vol. 8 | Issue 1 **Fall 2021**

MISSION STATEMENT

The Emory Undergraduate Medical Review (EUMR) publishes a semesterly journal that features faculty and student-authored articles on cutting-edge medical issues. Our interdisciplinary articles span various clinical fields and are peer reviewed by medical professionals from more than a dozen leading academic institutions, including Emory University, Yale University and the Mayo Clinic.

In addition to our publication, EUMR hosts various medically-related events on campus, including collaborations with the 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,

EUMR's fall 2021 semester was marked with adaptation and change. For the first time since spring of 2020, Emory University welcomed all students back to campus, and we obtained a hint of normalcy. As students, we were reminded of the familiar challenges with in-person learning while celebrating the beginning of face-to-face memories being made with old and new friends alike. As an editorial board, we replaced virtual meetings in different time zones with engaging on-campus events and a more interactive editing and publishing process. Thanks to our team, EUMR flourished throughout the semester as an organization that has overcome its circumstances.

We began the fall by recruiting fifteen talented new members, filling the ranks of our writer, editor, and first-year positions. An enormous debt of gratitude is owed to our editorial board for transitioning to the new setting while making yet another semester of publication a success. Together, we have produced a combined total of twenty articles across our digital and journal platforms. Interdisciplinary exploration has never been more deeply intertwined with EUMR's mission and culture, and our writers continue to find new ways to exemplify it in our eighth volume. In this issue, readers can look forward to articles ranging from an entire ethnography on healthcare culture to works that investigate the intersection between medicine and philosophy.

Outside of our journal, EUMR's events team has continued to enrich the Emory community and expand our presence across campus. With the restoration of in-person events, EUMR collaborated, for the first time, with Goizueta Business School through our Business Innovation in Healthcare Panel, which featured a number of guest speakers. Our devoted events team also revived the tradition of our EUMR Suture Lab while programming our first-ever EUMR mixer.

Most importantly, we would like to thank our dedicated advisory board who continue to serve as mentors to our editorial board. We are proud to announce the addition of two new advisory board members, Dr. Kevin Li and Dr. Sarah Caston. They will succeed Dr. Lynn O'Neill and Dr. Sarah Blanton, both of whom will be dearly missed. We wish them the absolute best in their careers moving forward.

We cannot wait to work with everyone again this spring; we have some exciting events and initiatives that will roll out soon. Stay tuned!

Cordially,
Anjanay Nangia & Richard Lee
Editors-in-Chief
EUMR 2021-2022

Bitter pills: U.S. nationalism in healthcare culture, an ethnographic analysis

SARINA ADELINE
Staff Writer

While logging clinical shadowing hours, I tumbled between the hospital lobby and patient suites, stunned by the contrast between the austere, sterile hallways and the high-stakes chaos of the operating rooms. I felt like a loose cog in a high-powered steam engine. Similar to many of the patients, I felt dazed by the bleached tiles, sterile gloves, and the near-alien medical jargon, which patients have reported to impede their healthcare experience (LeBlanc et al, 2014; Castro, et al, 2007). Even more outlandish, however, was the culture of medicine beyond physician-patient interactions. The medical personnel appeared to sort themselves according to an unspoken hierarchy (Janus, 2014). When away from patients, surgeons, and attending doctors sprawled out across the well-stocked break rooms; nurses often withdrew among themselves; and medical students gathered in frenzied clumps. While observing the medical students specifically, I detected a distinct division: the separation of domestic and international students. In the bustle of the hospital, it was easy to miss, at first. Yet as I learned more, I began to realize this social and cultural hierarchy had sobering consequences for those perceived to be at the bottom rung. 90% of American adults believe that becoming a doctor is the most prestigious occupation in the United States (Physician Foundation, 2016). However, in 2016, the Physician Foundation surveyed 20,000 practitioners, and only 44% of them characterized their morale and feelings about the state of the medical profession as positive (Physician Foundation, 2016). The stark contrast of these two figures points to the state of many clinical workspaces. The fast-paced clinical environment leaves little room for error. It is hostile toward those who fall behind. Despite an emphasis on objectivity and "capital S" Science as the higher power that governs medical practice, clinical workplaces engender a complex social structure for medical students. Within this structure, some students experience a greater level of privilege than others. This hierarchy allows some students to rise through the ranks while others slog through a battering of verbal and psychological abuses. I deepened my understanding of this troubling dynamic by conducting nine semi-structured interviews with medical students. They recounted stories of their third and fourth years in medical school, during clinical rotations, revealing the lack of protection for and systematic misconduct against international medical students. The clinical setting is not divorced from the sociopolitical climate of its country; hospital culture is deeply impacted by the surrounding cultural and political context (Butler, 2019; Ailon, 2008). Attitudes and stereotypes embedded in medical institutions help shape the script of interactions within clinicians' circles, and a holistic approach to health-

Figure 1. A physician chats with staff at the front desk of a hospital lobby. Image from Eastwood 2020.

care is needed if this is to change (Chandra et al, 2017).

Race, linguistic ethnicity, cultural presentation, gender, and disability are just a few of the variables that have been identified and studied by social scientists as risk factors for mistreatment or alterity in the medical system. It was impossible for me, as an observer without empirical data, to isolate any one of those as the cause of the social hierarchies present among medical students in the hospital setting. However, through this ethnographic analysis, I have analyzed the narratives of the medical students to begin to unpack a key attitude, one which emerged during the interviews as a possible concern in American medicine: U.S. Nationalism. Nationalism, a concept first coined by Ernest Gellner, is a shared attitude that allows individuals to come together as part of a collective state. Nationalist attitudes inherently create an "Other" by assigning belonging to some and excluding others (Gellner). It is a dominant cultural narrative that can be an early symptom of more insidious social cultural frameworks, such as anti-immigrant sentiments or racial prejudice. In an address to Black physicians at a conference, Swiss medical historian Henry E. Sigerist exclaimed, "No country is more eager to educate other nations in the principles of democracy, but when it comes to the practice of these principles at home, we are sadly deficient and tolerate discrimination against fellow citizens" (Sigerist, 1947). It seems that the medical community suffers from this irony, too, mirroring the nationalist attitudes of the surrounding country.

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All nine medical students that I interviewed attend a medical school outside of the U.S., meaning that regardless of their country of origin, these students are categorized as "foreign" medical students by their host hospitals if they choose to complete clinical rotations in the U.S. I would like to note that as an undergraduate student, I am removed from the institutions I reference, and I am writing without much personal stake. The medical students expressed to me that they felt safer speaking to me than reporting to their institutions, which is not an uncommon phenomenon (Waring, 2005). For a complete ethnography, ideally, I would have had time to immerse myself in the hospital environment to observe the students and clinicians in action. I would have also conducted dozens more interviews to gather more data. For the purposes of this paper, I relied on the participants to recount their lived experiences. If we are to agree that mitigating violence and improving health outcomes are goals of the medical field, then it is reasonable to assert that even the limited data set provided by these anecdotes is evidence enough to encourage us to reflect on the shortcomings of our current structures. While the data I collected through interviews and observations yielded clear patterns of poor treatment of international medical students, this analysis does not account for the range of experiences that exist within this medical system. The first data point collected from the medical students began at the time of recruitment. Initially, many students were reluctant to speak with me, repeatedly asking about who I was and who "sent" me. I explained my purpose: to write an article about the culture of medical student training for an undergraduate publication. I believe that my position as an undergraduate student who is unaffiliated with any of the medical students' programs helped build rapport; however, some students still declined to reveal their full names on interview transcripts. I agreed to change participant names for the purposes of the publication. Aside from one interviewee, I did not know the participants personally, but in some instances, I received their information through a mutual contact, which may have helped build rapport. The remainder of the medical student participants were located through social media searches and sites such as LinkedIn.

During clinical rotations, medical students participate in hands-on learning, seeing patients and practicing skills under the supervision of attending physicians. This arrangement necessitates that doctors provide direction and support to students. All hospitals are regulated through Medical Education Compliance laws and protocols mandated by the state. These policies

are largely intended to protect medical students by placing limitations on the students' workload and prohibiting exploitation or abuse. They also ensure that students receive adequate training to become well-equipped physicians. Marie, a fourth-year international medical student, expressed that, in her experience, these rules and regulations only seemed to apply to the domestic students. While preparing to match into a residency program, Marie has reflected back on her first clinical rotation. When Marie arrived, her peers told her that some clinical education programs recruit international medical school students and graduates so that they don't have to observe U.S. rules and regulations, which are only strictly enforced for domestic students. Marie experienced this pattern when, in her first week of clinical rotations, the attending doctor assigned her to a 72-hour shift to cover the hospital. Marie expressed frustration at her inability to change the situation, recalling the attending doctor taking her aside and saying, "If you want to practice medicine, this is what you have to do; or you'll lose your visa and never practice in this country" (emphasis added). Marie also remembers the matter-of-fact manner in which medical students talked about suicide, noting that five medical students from her program's cohort died by suicide. She recalled four of their names, choking up when she could not recall the fifth. "They didn't feel like they had another choice," Marie added, lamenting that, "There have been times when the thought came to me, too." Marie remembers receiving daily threats and warnings from doctors that failure to comply with their demands or to fall behind could mean dismissal from the hospital. If that were to happen, she would return home, unable to graduate, as successful completion of each clinical rotation is considered a prerequisite to graduate and match into residency. Marie described the panic that propelled her forward, waking up at two or three in the morning to arrive at the hospital before the other students: "I've given up years of my life for this. I paid for this education. I have hundreds of thousands of dollars invested in this education. If I got sent home empty-handed after all that, of course it would kill me." It is useful here to remember that the organization representing the nation's 125 accredited allopathic medical schools is called the Association of American Medical Colleges. International medical school graduates fall into a loophole, a liminal space, in which the most basic regulatory bodies are designed to exclude them, even in name. In a system that does not recognize you as a member of the professional community, the protections provided by policy and regulation quickly fall away, leaving international medical students in a vulnerable position. Similar to Marie, fourth-year student Hana recalls brutal hours during her rotation at Jackson Park Hospital in Chicago, IL. The first day of the rotation, the attending doctor told Hana to arrive at the hospital at 6am central time. Hana had a two-hour commute ahead of her. She could not move closer to the hospital, as the living expenses were too great for her family, which included a toddler. The hospitals closest to her (a 10-minute commute) refused to accept her, because of her status as an international medical school student. Local hospitals claimed that they had no way to prove Hana's accreditation and readiness to serve in their hospital, alluding to rules that they declined to cite in digital correspondence. Hana has passed step one and two of the United States Medical Licensing Examination (USMLE). She has also sat for three check-point exams specific to her medical school prior to starting clinical rotations. Most U.S. Medical School programs require that their students pass only USMLE step one prior to starting clinical rotations. Some domestic students have even received exemptions to this rule in the last two years due to the COVID-19 pandemic. Meanwhile, Hana notes that the limitations she's faced and hoops she's had to jump through in order to complete her rotations seem to increase nearly every semester.

..there is an art to medicine as well as science...

Hana remembers her first day in Internal Medicine at Jackson Park hospital as being an extended mind-game with her instructor, an attending doctor. Prior to her 6am arrival, her instructor, Dr. D, contacted Hana via Whatsapp, letting her know to wear comfortable shoes. Hana wore dress flats, which were


ΙΠΠΟΚΡΑΤΟΥΣ
ΟΡΚΟΣ
HIPPOCRATIS
IVSIVRANDVM

Figure 2. The Oath of Hippocrates, or Hippocratic Oath, dates back to the 5th century B.C. It is a code of ethics that outlines some guiding principles and best practices for physicians. Today, it is perhaps the most widely cited Greek text in the medical profession. Image from Kantarjian 2014.

comfortable to walk in, but still fit within the hospital's professional dress code. She remembers the hospital environment as quiet when she arrived, making it easy to locate the room where she was instructed to check in. She found the room dark and locked. While asking for Dr. D at the reception desk, she noticed a person in a white coat walk swiftly behind her. Hana called after the doctor politely. The doctor stopped, looked at her, and then turned around and started walking faster. With a scoff and chuckle, Hana reflected, "It was the rudest interaction I've ever had," remembering that "I followed him, and the closer I got, the faster he walked." Then Hana realized it was a game. She walked on her tip-toes, so that Dr. D couldn't hear her footsteps. He slowed his pace. When she caught up to Dr. D, he berated Hana about her shoes, snapping, "I told you to wear comfortable shoes. Are you stupid? Your job is to keep up. The attending doctor is not going to wait for you. I expect you to keep up if you're still going to wear those shoes" (Hana's emphasis). Throughout the day, Dr. D walked at a brisk pace, often deliberately closing doors in Hana's face. With her small stature, Hana often had to break into a jog to keep pace with Dr. D. She observed this behavior with some of her peers as well. As written in the Hippocratic Oath, there is an art to medicine as well as science, and warmth, sympathy, and understanding may outweigh the surgeon's knife or the chemist's drug. It is not far-fetched to claim that Dr. D had lost sight of the "art" of medicine to an insidious degree, but he is not alone. Medical culture demands hierarchy, and the myth of a sanitized, objective science drives that hierarchy forward. What read to me as callousness, to the doctor, was a fact of his job. For many, performing doctorhood means assuming a position of aloof expertise, and paternalistic authority is deeply embedded in the culture of medicine. While this does not entirely account for Dr. D's behavior, it is important to remember that cultural tensions in medicine persist far beyond the individual.

Hana and her peer Feliza, both of whom completed at least one rotation at Jackson Park, would often go from 6am to after 7pm without eating. When they asked Dr. D for a lunch break in the second week, he responded: "Not if you want to get into residency." Feliza recalled that this threat was frequently dangled over her head, not only by Dr. D but by nurses and physician assistants too, who seemed to revel in the fact that they had some status over the international students in the hospital hierarchy. Feliza added, "Accepting the abuse is atonement for your inadequacy. Nothing you do is enough. There's some of this [for domestic students], but all the natural abuses that are set up in the American system are exaggerated and completely overlooked for foreign [students]. For us, there's no recourse." Being an international medical student often meant going above and beyond in an already rigorous training program. A student hoping for a recommendation letter or a passing grade could expect to be the first to arrive and the last to leave, taking on grueling responsibilities, including the doctor's own paperwork. This, Feliza and Hana both noted in separate interviews, was not the worst of the abuses. Dr. D, among other physicians presiding over medical students, sometimes singled out the unmarried international medical students. Feliza remembers being called to Dr. D's office at the end of an 18-hour shift (in which Dr. D had already come, left, and then returned again). Dr. D propositioned Feliza, saying that if she was willing to engage in sexual contact with him, he would write her letter of recommendation "right then and there." Hana recalls several students, who looked up to Hana as an older peer, coming to her in tears about this type of interaction: "It was relentless." Out of fear, the students did not report. Feliza recalls that at one point, one female student did report the interaction to her school. Afterward, Dr. D's behavior became even more polarized: "sickly sweet" in mixed groups and "tyrannical when the students were alone with him."

The student who reported the incident left the program shortly after. Feliza has not heard from her since. After the individual left the program, things at the hospital went back to the way they were.

Adric, a third-year medical student, describes his experience as a Black male and international medical student as, "the hardest thing I've ever done." Although his parents emigrated to the U.S. when he was a child, Adric grew up traveling frequently back and forth between countries. When he enrolled in a medical school outside of the U.S., he did not realize how it would impact his chances of matching into a U.S.-based residency, a tradeoff which he is now reminded of daily. Adric notes that he does not know how much of the treatment he receives is because of his race and how much is because of his international status, despite having lived in the U.S. most of his life. He notes that he has overheard comments made about him in response to his ability to think quickly on his feet and recall medical information: "Yeah, but he's a Black doctor" and "Sure, but you name one patient in here who wants a doctor like that" (Adric's emphasis). It should be noted that no credible research exists to suggest that Black doctors practice medicine at a poorer standard than doctors of other races. In fact, research has found that Black infants under the care of Black doctors are more likely to survive childbirth than those delivered by white physicians, who are less likely to identify warning signs—such excruciating pain of the mother—before the complication becomes life-threatening (Greenwood, 2020). Racist attitudes documented within the medical community (Cooper and Fett, 2019) point to a deep-rooted implicit bias that impacts physicians' ability to provide care.

...all the natural abuses that are set up in the American system are exaggerated and completely overlooked for foreign [students]. For us, there's no recourse.

Adric informed me of a common practice in hospitals used to test students, called "pimping." Pimping describes when doctors drill students for information, an oral test designed to end in failure. The attending doctor will ask a series of questions, and as long as the student can provide an answer, he will continue to ask increasingly complex and detailed questions. These questions are often not immediately relevant to the patient in question. As soon as the student trips up, the doctor seizes the opportunity to berate the student, yelling things like: "You're not smart enough. You can't keep up. You don't work hard enough." For example, Adric recalls a time when he encountered a patient with severe pneumonia during rounds. The doctor asked what medication he should prescribe. Adric answered easily. The doctor then asked for other possible medications, and why those would not be the first choice. Adric answered. The doctor asked for the possible side effects of those other medications. Then he asked for the mechanism of action for each drug. Unrelated to the patient, the doctor asked what other drugs shared that mechanism of action, and how that related to a rare medical condition (which Adric had not learned about, and the patient in the room did not have). Adric finally admitted he didn't know. "None of this is immediately pertinent to the patient, ever," he said, "They are just pimping you. It doesn't matter how much info

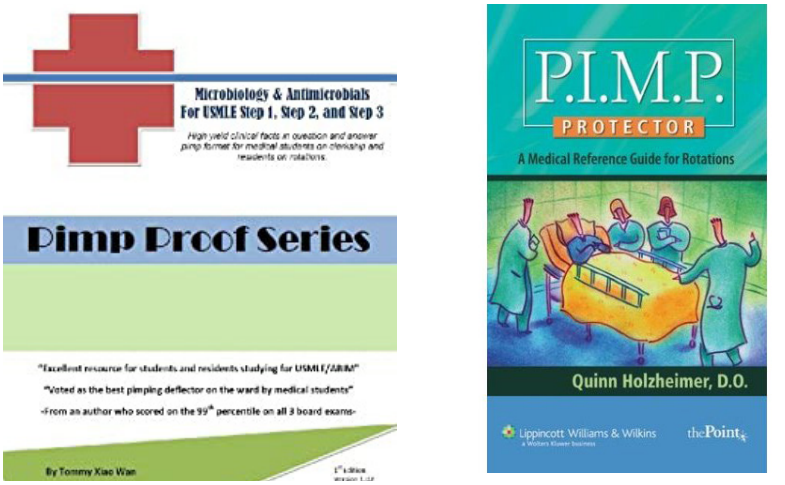

Figure 3. The practice of "pimping" in medical education is infamous among students and physicians alike. It describes when a doctor drills a student with a series of questions, often increasing in complexity and specificity until the student is unable to provide an answer. This practice is so common, that self-help style books have popped up to provide advice for students navigating medical school. Images from Amazon.com.

you have, once you get stuck, you are belittled. They want to drill in the idea that you will never get into residency because you're inadequate." Marie also reported the practice of pimping, recalling that in one instance, after the doctor walked away, a nurse told her: "You think you're going to be a doctor? You aren't worth sh*t." When Marie began to defend herself, a domestic student smirked and said, "Just shut your f*cking mouth while you're ahead. You couldn't even answer Dr. Y's question." Marie finished recalling the memory by musing, "The main takeaway is that there's a whole lot of yelling." At the time of her interview in October, Marie planned to graduate in May of the following year. Due to rising tuition costs imposed on visiting international medical students in U.S. clinical rotations and a slew of new requirements she must meet, Marie does not know if she will graduate. She is missing one elective clinical rotation to receive her MD. In 2019, approximately 20,000 students graduated from allopathic medical schools in the United States. Up to 23 percent of residents and fellows in the United States were classified as International Medical School Graduates (IMGs). Through a nationalist and overly patriotic lens, the flocking of international students to become U.S. doctors is inevitable. More than that, attracting international students is a source of pride. Rep. Buddy Carter affirmed this attitude when he declared on live television that as Americans, "We have the best healthcare system in the world." Inside teaching hospitals, however, international medical students find a starkly different experience.

Not only do international medical students have to navigate the complex and grueling system of medical education, they simultaneously find themselves confronted with an insurmountable barrier: the idea that they are the "Other," separate from—and in some ways, "less than"—domestic students. Despite having studied for and passed the same exams, performed the same tasks, and muscled through the same checkpoints, many IMGs traverse U.S. clinical rotations as total outsiders. This article illuminates the experiences of only nine of those students, all of whom feared repercussions for speaking to me. Callous treatment is not limited to international students, and I have certainly encountered stories of brutal overnight shifts and caustic doctor-trainee interactions among domestic students. Despite the limited scale of my study, every international student with whom I spoke reported instances of verbal abuse including harassment, so-called pimping, and degradation. As I analyzed the evidence, I found myself returning to a troubling question: in an initiation process designed to deliver abuse, how can doctors be expected to become compassionate caretakers? This issue deserves further study to elucidate the social and political mechanisms behind the mistreatment of international medical students. Because exposure to workplace violence and toxicity increases the risk of physician burnout (Hacer and Yasar, 2020), it is possible that hazing rituals such as those detailed in this article compromise the quality of care that physicians can provide. Biases against international medical students may also correlate with biases against patients, suggesting that correcting this sociopolitical issue requires deeper analysis and reflection on the structures within American medicine that allow such attitudes to persist. ❧

AUTHOR BIO

Sarina is a fourth year majoring in Creative Writing. Her interests are in studying the culture of medicine and she hopes to go on to study Medical Anthropology after undergrad.

Edited by Sabrina Jin, Rhea Tumminkatti, and Dr. Sarah Caston

Placed by Jocelyn Chow

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An upgrade from the condom: Novel male contraceptives

ESTHER JUNG
Staff Writer

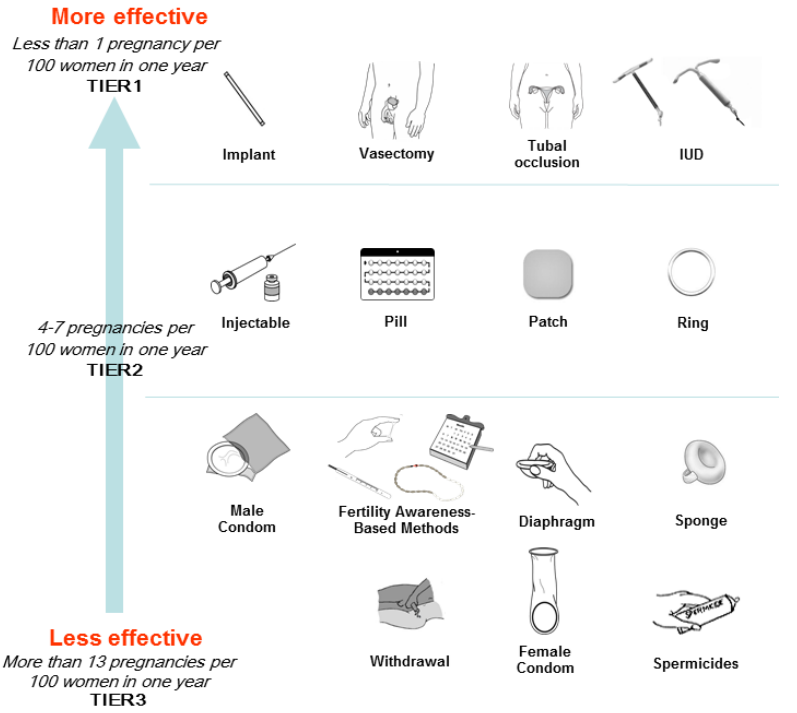

Figure 1. Comparing typical effectiveness of birth control methods. Out of the 15 birth control methods shown above, only two can be exclusively utilized by males: condoms and vasectomies. Image from Centers for Disease Control and Prevention.

For hundreds of years, humans have utilized condoms to prevent unwanted pregnancies and the spread of sexually transmitted diseases. While condoms were first crafted from animal bladders or intestines, their use of rubber became more widespread starting in the 1800s. Following the invention of latex, most condoms from the 1920s to now are made from latex. But aside from condoms, there has been a troubling lack of development for men's contraceptives. Over the past century, a wide range of female contraceptive options, such as hormonal birth control, emergency contraception, vaginal rings, and intrauterine devices (IUDs) have become easily accessible. On the other hand, vasectomies and condoms are the only contraceptives for men. Condoms remain the only truly reversible contraceptive available since vasectomies are expensive surgical procedures that can reduce fertility in men afterwards (Carbone et al., 1998). The lack of male contraceptives led scientists to investigate new alternatives, both hormonal and nonhormonal, to current contraceptive options. Condoms are the most accessible form of birth control currently available to men. However, condoms have a failure rate of about 13% a year and, with actual use, are only 83% effective (Plana, 2017). Vasectomies, while much more effective than condoms with an over 99.8% effectiveness rate of preventing pregnancies, are also much more costly (Centers for Disease Control and Prevention, 2020). About 3-5% of men who receive vasectomies eventually request a reversal; the reversal itself can be expensive, especially since repeated reversals may be necessary to fully restore fertility (Carbone et al., 1998). Despite the fact that pregnancy involves both men and women, women experience much more societal pressure to take responsibility for obtaining contraceptives. A multitude of birth control options are available for women, ranging from physical barriers, like diaphragms and female condoms, to chemical interventions, like IUDs, oral contraceptives, and spermicide, as shown in Figure 1. Hormonal contraceptives, like oral contraceptives and progestin IUDs/implants, are typically more effective than physical contraceptives by releasing small amounts of the hormones progestin and estrogen. These outcomes prevent a woman's egg from fully developing each month and cause mucus in the cervix to thicken, stopping the sperm from reaching the egg. Unfortunately, hormonal

...women experience much more societal pressure to take responsibility for obtaining contraceptives...

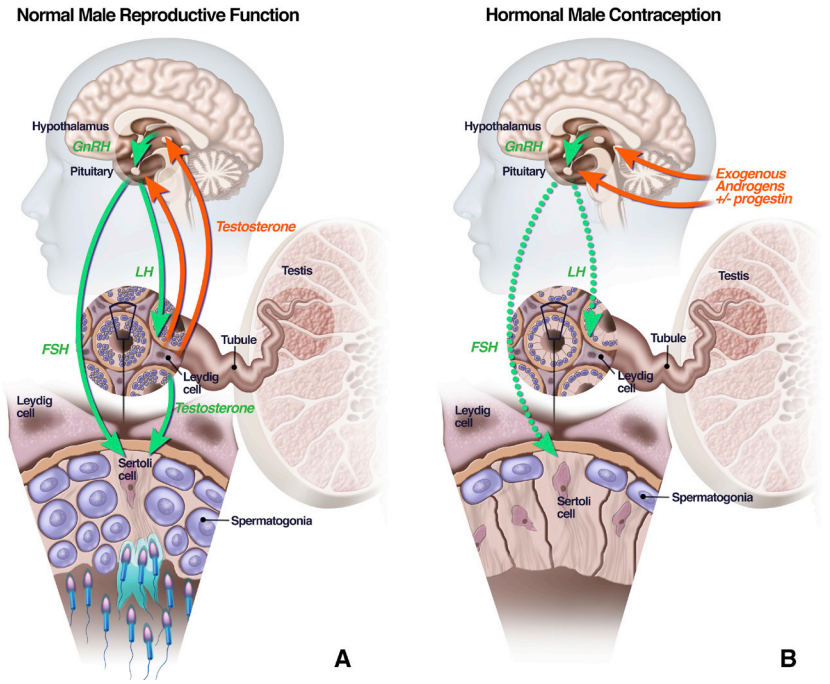

Figure 2. Normal vs. suppressed the hypothalamic-pituitary-testicular axis. Suppression of FSH and LH production from exogenously administered androgens and progestins deprive testes of the signals required for sperm production, leading to contraception. Image from Amory 2016.

contraceptives are also associated with increased health risks and unintended side effects. Birth control pills containing estrogen and progestin can increase the risk of heart attack, stroke, blood clots, and liver tumors (Zakharova et al., 2011). From 2015 to 2017, the use of birth control pills and IUDS among women decreased by 34.0% and 33.8% respectively with the leading reason being side effects (National Survey of Family Growth, 2019).

The lack of birth control alternatives available to men further contributes to the burden placed on women to be responsible for preventing unwanted pregnancies. According to the National Survey of Family Growth, from 2015 to 2017, 28.3% of men 15-49 years of age used condoms as their main method of contraception, followed by their partner's use of the pill, utilized by 20.2% of men (2019). The proportion of men who use condoms as their main method of contraception decreased significantly while the proportion of men who relied on their partner's use of the pill did not increase. The lack of this change could be attributed to increases in women utilizing other contraceptive methods like IUDs, thereby highlighting the growing dependency of men on women for providing contraception.

This study showed a promising future for the efficacy and convenience of Nes-T gel ...

Current research focuses on two forms of male birth control: hormonal and nonhormonal. Hormonal contraceptives for males, similar to their female counterparts, release hormones naturally found in the body. While female hormonal contraceptives usually contain progestin and estrogen, male hormonal contraceptives utilize progestin and testosterone. Testosterone regulates sperm production as well as regulating sexual characteristics. Hormonal contraceptives adopt testosterone to suppress sperm concentrations to levels that are insufficient to induce pregnancy. Luteinizing hormone (LH) stimulates the production of testosterone, and follicle-stimulating hormone (FSH) helps regulate production and regulation of sperm. In turn, low concentrations of LH and FSH are strongly associated with suppressed sperm counts at or below 1 million per milliliter, a threshold associated with a risk of pregnancy less than 2% (Anawalt et al., 2019), as shown in Figure 2.

Clinical trials have demonstrated hormonal male contraception's effectiveness. Nestorone® (Nes) is a transdermal gel that contains hormones to be absorbed through the skin. Nes gel with testosterone (T) gel showed effective suppression of sperm concentrations in healthy men. Anawalt and their colleagues (2019) conducted a double blind study with 44 healthy men. Participants either applied the Nes and testosterone (Nes-T) gel or just T gel to their shoulders every day over the course of 28 days, and their blood samples and seminal fluid samples were also collected regularly. The study found that at the end of 28 days of treatment, the sperm concentrations of the T gel group were unchanged, while the sperm

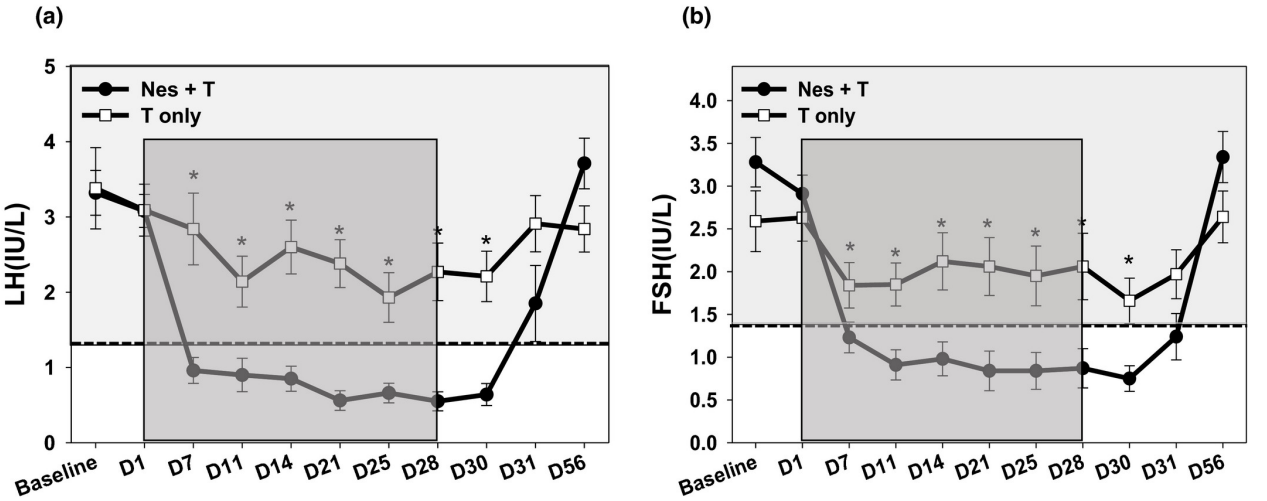

Figure 3. Hormone levels (luteinizing hormone on the left, follicle stimulating hormone on the right) of analyzed subjects from baseline, treatment and end of recovery (day 56). Serum FSH and LH concentrations were significantly more suppressed in the Nes-T gel group compared to the T gel group by treatment day 7 and remained significantly more suppressed throughout the remainder of the 28-day treatment period and through day 2 of the recovery period (day 30 of the study) ($p < 0.01$). Image from Anawalt et al. 2019.

concentrations of the Nes-T gel group decreased significantly. FSH and LH concentrations were also suppressed significantly in the Nes-T gel group by treatment day 7 and remained significantly suppressed throughout the 28 days of treatment. Although LH concentrations in the T gel group did decrease significantly on treatment days 11, 25, and 28, FSH and LH concentrations were significantly more suppressed in the Nes-T gel group than the T gel group from treatment day 7 and on. Furthermore, over 80% of the subjects reported satisfaction with gel being a potential contraceptive, and more than 50% agreed with the statement "If available today, I would use this method of contraception as my primary method". This study showed a promising future for the efficacy and convenience of Nes-T gel, should it become commercially available for use.

Enacting change within both the healthcare and education systems will drastically improve reproductive health...

From a public health perspective, the introduction of male contraceptives to the United States, especially marginalized populations, is crucial for reproductive health. In the United States, 45% of the 6.1 million pregnancies that occurred in 2011 were unintended, a significantly higher rate than that in many other western countries. Income level and educational level play significant roles in rate of unintended pregnancy, and poor and less-educated females were more likely to have unintended pregnancies while being less likely to have induced abortions to end these pregnancies (Finer & Zolna, 2016). These disparities would be greatly reduced, argues Olivia Plana, if male contraceptives were made more accessible to marginalized populations in the future (2017). One crucial issue is the disparity in health insurance, as minority and low-income men are less likely to have private health insurance or "Medicaid coverage than... their female counterparts" (Barone et al., 2004). Yet another issue is the significant gap in the awareness of contraception and sexual health resources among men based on race and ethnicity; black and Hispanic men are much less likely to have knowledge about various forms of contraception and therefore experience poorer reproductive health outcomes (Plana, 2017). Introducing male contraceptives and enacting change within both the healthcare and education systems, as a result, will drastically improve reproductive health in the United States by offering men a new alternative to outdated condoms and costly vasectomies. The introduction of a novel male contraceptive brings newfound hope, especially to communities of color and/or lower socioeconomic status disparately facing struggles in family planning and reproductive health.

AUTHOR BIO

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Edited by Edward Xue, Anu Dhanashekar, and Dr. Kevin Li

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Exploration of the total artificial heart

LAURA PAULE
Staff Writer

End-stage congestive heart failure, the most severe stage of heart failure, is a condition in which the body can no longer compensate for the lack of blood that the heart pumps. End-stage congestive heart failure is a major public health concern and the leading cause of death in the United States (Morris, 2008). Despite advances in medical treatments, patients with this chronic disease exhibit pronounced symptoms following minimal physical exertion and even at rest. The majority of patients with this condition die within a year (M Botta, 2019). The standard treatment is heart transplantation; however, the lack of heart donors and the immunosuppressed conditions of patients make it difficult for many to participate in this medical procedure. In fact, there are only around 2,000 hearts available for patients annually, but more than 3,000 patients that need a transplant (Friedline & Hassinger, 2012). The total artificial heart (TAH) offers support for patients with severe biventricular failure as a bridge to orthotopic cardiac transplantation (Gharagozloo et al., 2015). Biventricular failure is the condition in which both lower chambers of the heart are not working properly to supply blood to the rest of the body. These devices can provide temporary relief as the patient awaits a donor. The aim of this paper is to look into the history of the total artificial heart, the intricacies of surgery, and the post-operative experience of patients.

...there are only around 2,000 hearts available for patients annually, but more than 3,000 patients need a transplant...

The total artificial heart is a long-term project with roots that can be traced back to the 1800s. In 1812, Cesar LeGallois hypothesized the possibility of mechanical circulatory support, but his ideas did not come to fruition until the 21st century. In the 1920s, Carrel and Lindbergh developed an in-vitro artificial heart-like device that kept organs alive even when outside the body. Later in 1937, Dr. Vladimir P. Demikhov created a TAH device made of two pumps driven by an external motor (Khan & Jehangir, 2014). Research on the TAH blossomed in the late 1950s when Akutsu and Kolff from the Cleveland Clinic implanted a TAH device into a dog which managed to survive for 90 minutes post surgery. Then, in 1969, Dr. Cooley completed the first TAH human implant at the Texas Heart Institute where the patient was sustained with the TAH device for 64 hours until he received a heart transplant (Yaung, Arabia, & Nurok, 2017). Although it did not prove to be successful and

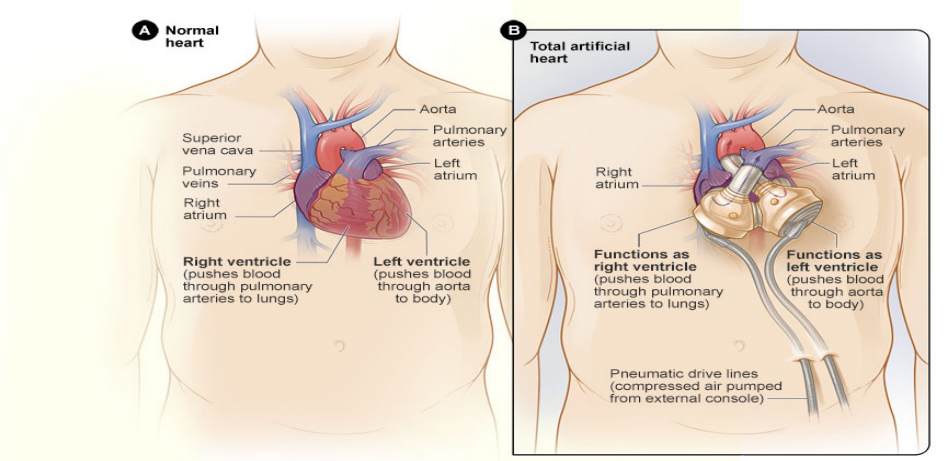

Figure 1. The location and parts of a functional heart. Figure B illustrates the location of the Total Artificial Heart (TAH), including the tubes that exit the body and connect to the device powering machine. Image from NIH n.d.

Figure 2. The Companion 2 (C2) Hospital Driver provides the power supply for the TAH while the patient is in the hospital. It may be docked into the C2 Hospital Cart or into the C2 Driver Caddy. The Freedom® portable driver allows eligible patients to be discharged home. Image from Yaung 2017.

the patient died 32 hours after, the surgery revealed the sheer potential for sustaining human circulation using a mechanical device (Cooley, 2003). In 1982, Dr. Robert Jarvik transplanted the first permanent artificial heart, which is now known as the Jarvik 7 device, into a 61-year-old patient who lived for 112 days after the surgery. Although the Jarvik 7 was able to prolong patients' survival, it required a large console that prevented patients from leaving the hospital while they waited for a donor, which substantially diminished their quality of life and incurred further costs. In 2010, SynCardia released a portable freedom driver that allowed recipients to be outpatients instead of being restricted to the hospital, giving patients a normal life even after receiving a TAH. Patients could charge the freedom driver in any electrical outlet, and even shower with this device (Jaroszewski, 2011). Currently, the SynCardia TAH is the only device of its kind to be fully approved by the FDA.

The development of a successful total artificial heart has saved the lives of many patients worldwide. The TAH replaces the ventricles of the heart, which are the two lower chambers. The TAH is connected to an external power source that pumps blood into the lungs through the pulmonary artery, and into the rest of the body through the aorta, as a normal heart would. Additionally, the TAH contains four valves that resemble the valves found in a healthy heart. These valves connect the TAH to the atria, or upper chambers, and to the major arteries. As patients prepare to receive this life-saving technology, the medical team must ensure that the patients are strong enough for surgery. The patients are admitted to the hospital one week in advance, where they continue to take their heart medications and receive nutrition through a feeding tube, if necessary. The medical provider ensures that patients and their family members are informed about the procedure, including the length of surgery, the risk and benefits, and the life post-implant. Patients go through a variety of exams to help doctors minimize complications during surgery. For example, doctors examine whether the patient's kidneys and liver are working properly, administering blood tests to determine the blood type in case a transfusion is needed during or after surgery. An electrocardiogram allows doctors to see how well the ventricles are working prior to surgery. An echocardiogram shows blood flow through the heart, including any blockages that might be present. A pulmonary function test determines whether a ventilator will be needed for a long time post-surgery. The medical team prepares all the conditions to ensure that the surgery runs smoothly (NIH, n.d.).

In 1982, Dr. Robert Jarvik transplanted the first permanent artificial heart...

Once the patient is in the operating room, the anesthesiologist will anesthetize the patient and check the blood pressure, oxygen levels, and heart rate. A ventilator machine is connected to a breathing tube and supports breathing during the surgery. Oxygen-rich blood continues to circulate through the body because of a heart-lung bypass machine, also known as cardiopulmonary bypass. The heart-lung machine takes over the role of the heart and lungs, allowing the heart to remain still for the operation. The machine carries blood from the right atrium into a reservoir called an oxygenator. The oxygenator adds oxygen to the blood just as the lungs would in a well-functioning heart. Then, the blood travels through a plastic tube to the aorta

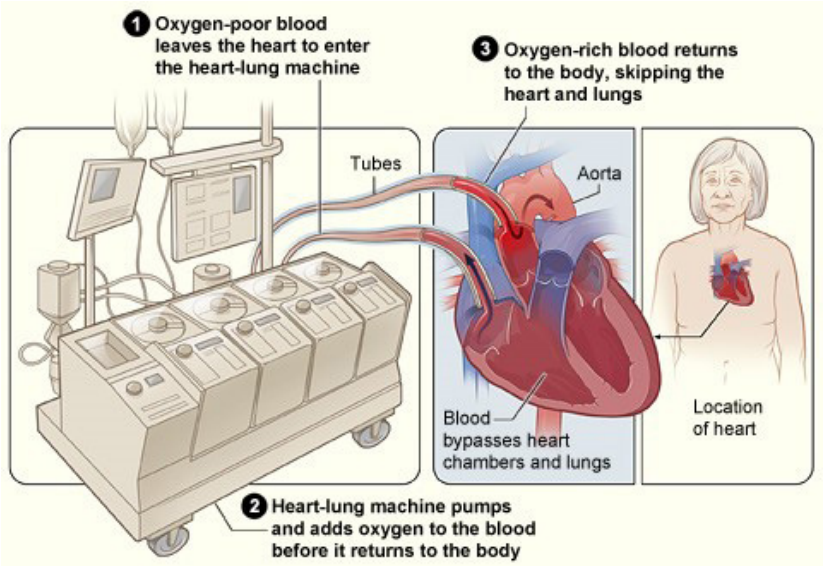

Figure 3. The heart-lung bypass machine, which is critical to ensure that the patient continues to receive oxygenated blood in the body tissues during surgery. Image from NIH n.d.

and is distributed throughout the body (Sarkar & Prabhu, 2019). For the surgery, the surgeons cut into the chest bone, open the ribcage, remove the heart ventricles, and insert the TAH, which gets attached to the atria and the primary arteries. Once the device is fully attached, the doctors can remove the bypass machine. If the TAH works properly, surgeons can close the chest again. This type of surgery can last anywhere between five to nine hours.

After surgery, patients could stay in the hospital for a month or more in the intensive care unit. They may receive fluids and nutrition through a feeding tube or IV line, and use a ventilator to help them breathe. Urine is drained through a tube inserted into the urinary tract. After several days, patients can go into a regular hospital room where nurses take care of them and slowly help them regain their strength and physical activity. Once the patients have fully recovered, they can go home, eat regular food, and go to the bathroom by themselves (NIH, n.d.).

Although the total artificial heart has increased the life expectancy of people with end-stage heart failure, the surgery can present complications. There is a possibility of patients not responding well to the anesthesia during surgery. Excessive bleeding in the chest may also occur as the device is connected to the atria. Blood clots can also develop after surgery, requiring patients to take anti-clotting medicine which could further thin the blood and lead to bleeding. Thus, a precarious balance exists between preventing clots and preventing excessive bleeding with medicine. Patients must take the medicine exactly as the doctor prescribes it to ensure the best outcomes.

The development of a successful total artificial heart has saved the lives of many patients worldwide.

The total artificial heart must continuously be researched and examined for improvements. Next generation TAHs could present increased survival benefits, lower rates of complications, and improved durability (Sunagawa, 2016). With optimization and clinical viability, TAH has the potential to transition from a heart transplantation bridge to a destination therapy. ❧

AUTHOR BIO

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Edited by Siya Malhotra, Niki Patel, and Dr. Kim Tran

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The realm of tissue-resident macrophages: Insights into ontogeny and function

ANIRUDH RAGHAVAN
Staff Writer

Macrophages are a vital component of our innate immune system and are responsible for building rapid defense against pathogens. They were first discovered by Russian zoologist and microbiologist Ilya Metchnikoff in the 19th century, and are adorned with a variety of sensing receptors to help them perform phagocytic, scavenger, and pattern-recognition functions. They are also part of a sentinel cell team, part of our body's first line of defense against tissue damage and infection. Further, their phagocytic capacity, which allows macrophages to engulf cells and large particles, aids them in performing a broad array of functions which are not only central to host defense in response to invading pathogens, but also significant for homeostatic regulation via clearance of cellular debris and dead cells (Okabe, 2018). Macrophages also have dual roles in inflammation. They can release small proteins involved in cell signaling called cytokines, which either trigger or reduce inflammation and can also secrete tissue-growth factors to stimulate tissue repair. Almost a century after Metchnikoff's pioneering contributions to immunology, the ontogeny or origin of macrophages was classified by Ralph Furth and colleagues as a mononuclear phagocyte system (MPS). This system postulated that all tissue macrophages originated from tissue localization of circulating hematopoietic stem cells (HSCs), which are bone marrow derived progenitor cells capable of differentiating into any type of human blood cell. However, recent reports suggest that a majority of tissue-resident macrophages are, in fact, sustained from birth, capable of self-renewal, and arise from progenitors separate from HSCs in the bone marrow. This has sparked novel research into their developmental pathways and tissue-specific homeostatic functions.

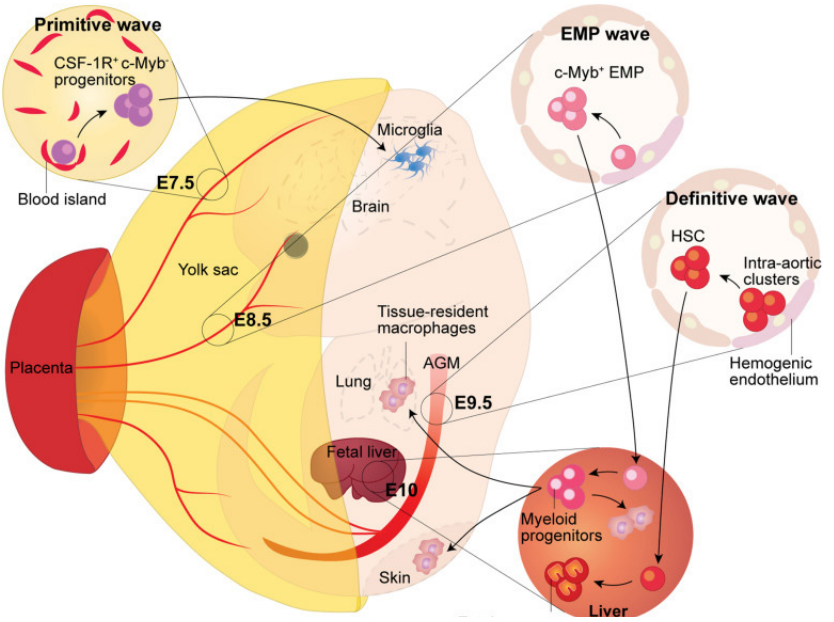

Figure 1: Fetal macrophage development occurs mainly in three successive waves of hematopoiesis. The first wave, primitive hematopoiesis, occurs in the blood islands of the extraembryonic yolk sac at E7.5. The second wave arises from the hemogenic endothelium formed at E8.5 in the yolk sac and generates erythro-myeloid precursors (EMP), so it is termed the EMP wave, also known as the transient definitive wave. The third wave, termed the definitive wave, arises from the hemogenic endothelium in the aorta-gonad-mesonephros (AGM) region, giving rise to fetal HSCs beginning at E9.5. These precursors then colonize the fetal liver and establish definitive hematopoiesis to generate adult HSCs and progenitor cells from the bone marrow. Image from Wu & Hirschi 2021.

During the process of embryogenesis in mouse models, macrophages have been shown to arise during three major waves of hematopoiesis, the process through which the cellular components of blood are formed. The first is termed primitive hematopoiesis, which initiates around embryonic day (E) 7.5 in clusters of cells within the yolk sac called blood islands (Wu & Hirschi, 2021). This process generates unipotent progenitors that can only give rise to one specific cell lineage - in this case, they give rise to the macrophage lineage. Additionally, observing for specific protein markers that are expressed on the surfaces of

progenitor cells can give hints as to which tissues they localize in: for instance, progenitors for microglia, the resident macrophages of the brain, were defined and tracked as the Colony Stimulating Factor-1 Receptor CSF-1R+ c-Myb- population in the brain and were found to originate from yolk-sac progenitors at E7.5 (Gomez Perdiguero et al., 2015). These cells lack expression of c-Myb, a proto-oncogene that encodes a transcription factor which regulates proliferation and inhibits hematopoietic differentiation, but highly express CSF-1R+, a receptor implicated in CSF-1 induced signaling that promotes the differentiation of myeloid progenitors into heterogeneous populations of macrophages (Hume & MacDonald, 2011). Primitive progenitors also gives rise to resident macrophages in the liver, epidermis, and lung as reported by similar surface protein expression analyses, but it is interesting to note that the brain is the only tissue that retains the macrophages derived from primitive hematopoiesis throughout adulthood (Ginhoux et al., 2010).

The second wave of embryonic hematopoiesis is termed the transient definitive wave and refers to macrophage generation from erythro-myeloid progenitor cells (EMPs) in the hemogenic endothelium of the yolk-sac at about E8.25 (Hoeffel et al., 2015). The hemogenic epithelium refers to a transient specialized vascular epithelium which specifically carries out hematopoiesis. Erythro-myeloid progenitors are a c-Myb+ population which seed the fetal liver at about E10.5 and are found in circulation in the embryonic bloodstream at E12.5 (McGrath et al., 2015). EMPs in the fetal liver were found to be short-term progenitors of cells including erythrocytes and macrophages. An experiment conducted by McGrath and colleagues found that transplantation of E10.5 EMP into normal adult mouse recipients produced erythrocytes. However, the production of myeloid cells, which are capable of differentiating into macrophages as well as granulocytes, monocytes, and dendritic cells, was limited (McGrath et al., 2015). This perceived lack of long-term potential of the EMP wave of hematopoiesis in adults has led to this wave being termed as the transient definitive wave (Hoeffel & Ginhoux, 2018).

The hemogenic epithelium refers to a transient specialized vascular epithelium which specifically carries out hematopoiesis.

The third wave of embryonic hematopoiesis is termed the definitive wave. It refers to macrophage generation from hematopoietic stem cells (HSCs) derived at about E9.5 (Medvinsky & Dzierzak, 1996). They arise from the endothelial lining of the aortic wall in the aorta-gonad-mesonephros (AGM) region and is an intra-embryonic mesodermal layer unlike the previously discussed extra-embryonic hemogenic epithelium. HSCs then migrate into the developing fetal liver where they rapidly proliferate and mature. By E16.5, these HSCs migrate to and colonize the developing fetal bone marrow (BM), where they remain throughout adulthood to generate all required blood cell lineages (Coskun et al., 2014). An additional interesting distinction between extra-embryonic yolk-sac derived macrophages and intra-embryonic AGM derived macrophages is that while they coexist within the same tissue in the steady state, in an inflammatory state large numbers of HSC-derived macrophages invade tissues such as the heart and liver (Yap et al., 2019; Blériot et al., 2020). Before investigating the consequent functions of tissue-resident macrophages next, it should be noted that in some disease settings it can be difficult to ascertain functional differences between tissue-resident macrophages and macrophages recruited from circulation. A broad overview of the waves of embryonic hematopoiesis, accompanying progenitor circulation paths, and eventual macrophage tissue localizations are presented in Figure 1.

Moving from ontogeny to function, one of the primary functions of tissue-resident macrophages postnatally is immune-surveillance, a process through which the immune system monitors the body for the presence of invading pathogens, infected host cells and neoplastic cells. Cells that have been neoplastically transformed have altered genotypes or phenotypes due to the effects of carcinogenic chemicals, oncogenic viruses, or radiation, and thus often express tumor-associated proteins on their cell surface (Drew, 1979). To help accomplish this, macrophages exhibit sensitivity to

pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) through receptors such as toll-like receptors and RIG-I-like receptors. PAMPs are detectable small molecular motifs conserved within specific classes of microbes whereas DAMPs are endogenous danger molecules that are released from damaged/dying cells, and thus recognition of DAMPS is essential for a rapid immune response to an infiltrating pathogen. Upon the initial recognition of a foreign particle or pathogen, resident macrophages are responsible for initiating inflammatory responses by stimulating the influx of inflammatory leukocytes and recruiting circulating monocytes (Cailhier et al. 2005). Macrophages derived from these monocytes then rapidly dominate inflammatory lesions and constitute the majority of all macrophages present in the region (Davies et al., 2013). Such effects were elucidated by selectively depleting tissue-resident macrophages, mostly through administration of clodronate "suicide" liposomes to specific tissues, inducing apoptosis of resident-macrophage and inducing a state of experimental inflammation. "In such cases of tissue-resident macrophage depletion, multiple consequences, such as reduced host protection to infection due to impaired inflammatory cell recruitment and loss of inflammatory signal mediators were observed" (Cailhier et al.. 2005; Ajuebor et al., 1999; Kolaczkowska et al., 2007).

...cardiac tissue macrophages have been implicated in functions varying from regulation of gap junction conduction...

Conversely, tissue-resident macrophages are also responsible for resolving inflammation and promoting homeostasis. While they accomplish this via removal of apoptotic cells and cell debris, tissue-resident macrophages also directly contribute to tissue repair. Depletion of resident macrophages in specific tissues in a time-dependent manner showed that in the early inflammatory phase, these macrophages were responsible for "formation of vascularized granulation tissue, epithelialization and minimizing scar formation" (Davies et al., 2013), whereas in the tissue-repair/inflammation resolution stage they are implicated in wound closure and prevention of trauma-associated hemorrhage. An increasingly distinct role of tissue-resident macrophages in tissue repair mechanisms is emerging as important contributors to apoptotic cell clearance, especially in the context of inflammation resolution during the resolution of inflammation (Gordon & Plüddemann, 2018). The return to homeostasis can be exemplified by iron recycling from hemoglobin by resident macrophages called Kupffer cells in the spleen and liver (Scott & Guilliams, 2018). Damaged or senescent erythrocytes which display altered cell-surface markers are recognized, phagocytosed, and subsequently degraded by proteolysis within these macrophages, which then release hemoglobin, and ultimately, iron that can be stored or exported. Another role of tissue-resident macrophages, specifically in adipose tissue, is energy homeostasis. This has been studied using mice deficient in the gene Trib1. Trib1 is an adaptor protein which is vital for adipose tissue maintenance as well as regulating differentiation of tissue-resident macrophages. Experiments which selectively depleted tissue-resident macrophages adipose in Trib1-deficient mice led to decreased insulin

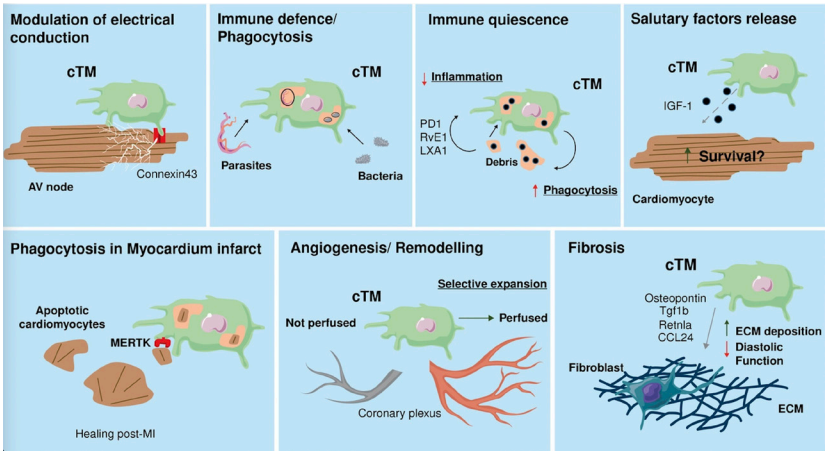

Figure 2: Broad functions of cardiac tissue macrophages (cTMs). Roles include regulation of electrical conduction at the atrioventricular (AV) node via coupling to cardiomyocytes, immune defense & quiescence via removal of debris and apoptotic cells, phagocytosis post myocardial infarction (MI) and subsequent healing, regulation of cardiomyocyte metabolism and survival, angiogenesis & vascular remodeling, and profibrotic activity directly affecting the heart's diastolic function. Image from Nicolás-Ávila et al. 2018.

sensitivity (insulin resistance) and increased activation of proinflammatory cytokine genes when the mice were fed a high-fat diet (Xie et al., 2020). Tissue-resident macrophages also perform highly specialized functions within their specific organ system. For instance, "cardiac tissue macrophages have been implicated in functions varying from regulation of gap junction conduction, cardiomyocyte metabolism, angiogenesis, and even development of fibrous connective tissue structures (fibrosis)" (Nicolás-Ávila et al., 2018). These circulatory system-specific functions are encapsulated in Figure 2.

With the initial discussion on unraveling the embryonic origin of hematopoiesis, it is quite evident that the three successive waves are indeed complicated and not fully understood. However, recent advances in single-cell RNA-sequencing, such as the modified scRNA-sq technique called single-cell tagged reverse transcription and sequencing (STRT–seq), and transcriptome profiling assist in more accurately detailing early macrophage development in both mouse and human embryogenesis (Bian et al., 2020). Additionally, it is significant to note that the local microenvironment can strongly influence the phenotypes and behavior of tissue macrophages in conjunction with ontogenic factors: a burning question is how lineage-specific genetically-coded differentiation can interplay with influences of the local tissue microenvironment to lead to differentiation. In line with this, it would be interesting to analyze how tissue macrophage ontogeny, either derived extra-embryonically or intra-embryonically, can specifically influence function as well. A recent paper published by the American Association for Cancer Research posits that "the embryonic lineage of macrophage may have adverse effects and are implicated in increased proliferation of tumor cells and immune evasion at the onset of tumorigenesis in early-stage lung cancer" (AACR, 2021), amongst other cancer types. The ways in which these macrophages can in fact promote tumor growth, proliferation, and invasiveness are briefly illustrated in Figure 3. Hopefully, such studies and future related work will enable therapeutic avenues in terms of in vivo manipulation and regulation of specific tissue-resident macrophage populations. ❧

...the embryonic lineage of macrophage may have adverse effects and are implicated in increased proliferation of tumor cells...

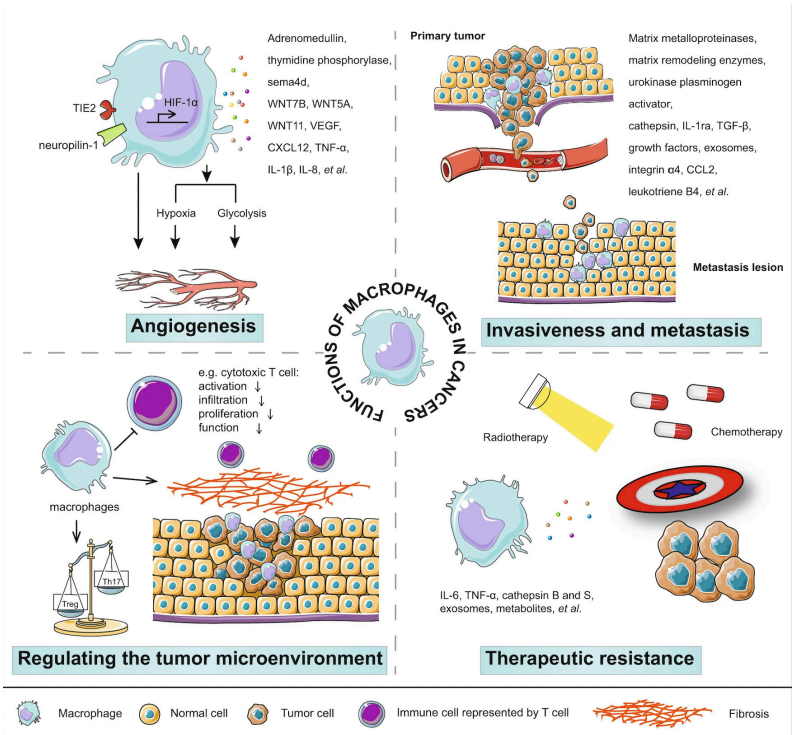

Figure 3: Tissue-resident macrophages as key drivers of cancer progression & metastasis. Four broad mechanisms are catalogued here. (1) Angiogenesis increases general density of blood vessels supplying tumor cells, increasing tumor growth and enhancing tumor cell glycolysis; (2) tissue-resident macrophages can dissolve the extracellular matrix and increase ease of tumor cell escape, increasing their metastatic capacity; (3) macrophages can prevent infiltration of CD8+ T cells into the tumor microenvironment by inducing fibrosis, preventing cytotoxicity against tumor cells; (4) macrophages can activate STAT3 in tumor cells via signaling factors such as IL-6 and TNF-α, resulting in enhanced proliferation and survival of tumor cells under several chemotherapeutic regimens. Image from Duan & Luo 2021.

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Edited by Rhea Tumminkatti, Lizzy Wagman, and Dr. Gregg Orloff

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Engineered synthetases: Ancient machine, new proteins

YUNA LEE
Staff Writer

Arguably the most important molecule that can join with other molecules are amino acids, the building blocks of life. They make up proteins responsible for a wide range of functions — from catalyzing the vast range of chemical reactions within a cell to providing the structural elements of a cell, life cannot function without amino acids. There are 20 common natural amino acids that make up proteins in all biological systems. What if, however, it is possible to encode any kind of amino acid into proteins, ones that can be manipulated in the lab to carry any desired chemical and physical properties?

Because the 20 amino acids limit the types of proteins that can be made, scientists have been searching for a way to synthesize proteins with unique and novel functions. One such way is through engineering pyrrolysyl-tRNA synthetase, an enzyme involved in the translation of proteins in the ribosome. By utilizing 4-billion-year-old protein producing architecture, scientists can create new proteins with implications spanning from powerful vaccines and cell-based therapies for cancer to new advancements in protein medicinal chemistry.

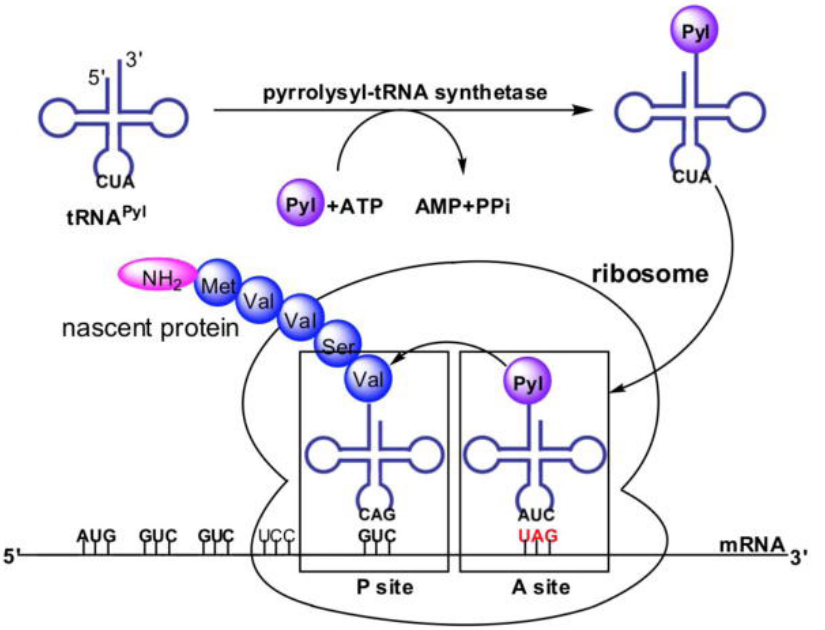

Figure 1. The essential four components of the Pyl incorporation machinery: PylRS, Pyl tRNA, Pyl, and amber codon. (Wan et al., 2014) Image from Wan et al. 2014.

The discovery of pyrrolysyl-tRNA synthetase happened after the identification of the amino acid pyrrolysine itself. Identified as the 22nd proteinogenic amino acid in the early 2000s, pyrrolysine is a rare and highly specialized amino acid found in a small amount of methylamine metabolizing archaea called methanosarcinales (Zhang et al., 2005). Methanosarcinales convert methylamines to methane through methanogenesis, and Krzycki and colleagues found a single UAF stop codon in the genes corresponding with methanogenesis. However, the UAF nucleotides, commonly identified as the stop codon, did not prevent translation (Burke et al., 1998). Because the truncated protein with premature termination is rare, Burke and colleagues reasoned that there must be another reason for re-coding the amber stop codon. The in-frame amber codon, instead of coding to stop, codes for an amino acid that does not match any of the 20 canonical amino acids or selenocysteine, the 21st proteinogenic amino acid. The product amino acid instead resulted in a lysine with a modification at its side-chain amine. This new amino acid was identified as pyrrolysine (Pyl, O). Similar to the 20 canonical amino acids, an aminoacyl tRNA synthetase (AARS), tRNA, a codon, and amino acid, as seen in Figure 1, are required for pyrrolysine to be incorporated into a protein, which is where Pyrrolysyl-tRNA synthetase (PyIRS) comes in.

...it is possible to encode any kind of amino acid into proteins, ones that can be manipulated in the lab...

PylRS differs itself from most aminoacyl-tRNA synthetases due to its three unique features: high substrate side chain promiscuity, low selectivity toward alpha amines, and low selectivity toward the tRNA an-

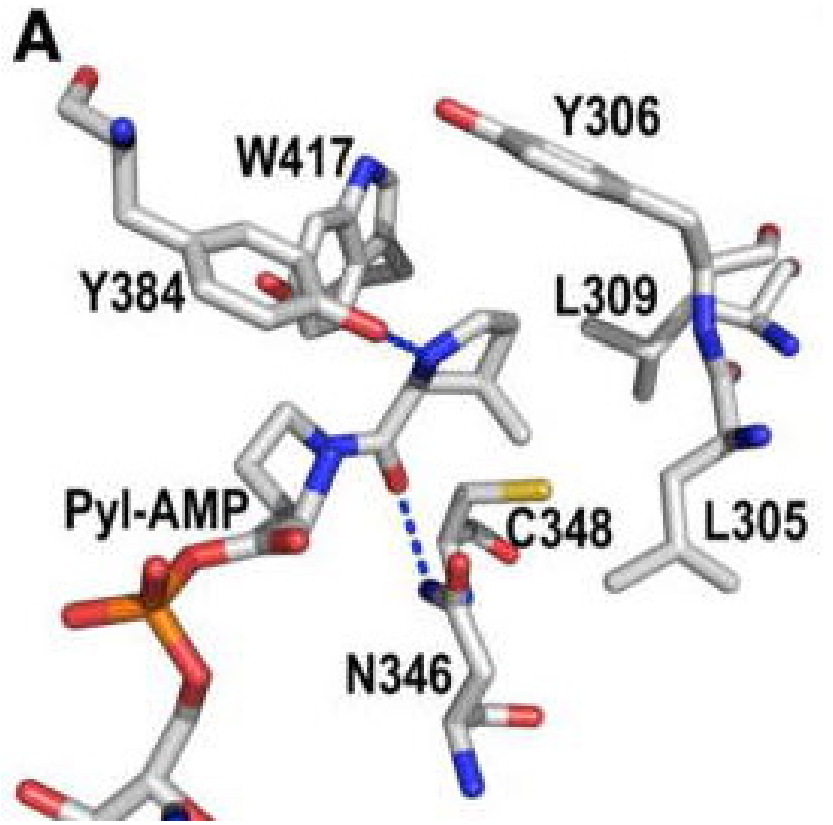

Figure 2. The active site of PylRS. (Wan et al., 2014) Image from Wan et al. 2014.

ticodon (Wan et al., 2014); these characteristics allow for easy engineering of unnatural amino acid incorporation into proteins. High substrate side chain promiscuity, which measures a molecule's ability to interact with other molecules, is the result of PylRS' high tolerance towards variations of the substrate side chain, a unique property many AARSs do not have due to evolutionary pressure to specifically interact with their amino acid substrates (Woese et al., 2000). Many AARSs have high fidelity to the point where their editing domains detect and reject even slight variations of the specific amino acid substrate, demonstrating how picky natural AARSs are. This highlights PylRS's unique ability to accept a variety of non-canonical amino acids (NCAAs), which are amino acids that are usually chemically synthesized, and not among the 20 common amino acids. PylRS's recognition of alpha amines also increases the variety of NCAAs available for protein synthesis. Again, in contrast to other AARSs, PylRS has a rather loose recognition of alpha amines while most AARSs are strict in recognizing most alpha amine features (Wan et al., 2014). Lastly, PylRS' low selectivity towards the tRNA anticodon allows the identification of nonspecific anticodon sequences. PylRS has a unique tRNA-binding domain, as seen in Figure 2, special C-terminal tail, loop region, and bulge domain involved in the specific recognition of the anticodon (Nozawa et al., 2008). Because Pyrrolysine has only one corresponding codon, one tRNA, and one synthetase, it is not clear why PylRS has not evolved to directly interact with the anticodon of tRNA for strictly pairing Pyrrolysine with the amber codon. The non-selective recognition of the tRNA anticodon could be rationalized considering that the pyrrolysine gene cluster can be highly regulated and only turned on in the presence of methylamine. Its non-continuous and rare expression would leave PylRS with no constant evolution pressure for evolving a more optimized feature.

Due to PylRS' unique properties, this system has been applied to bacteria, yeast, and mammalian cells for protein synthesis involving more than 100 non-canonical amino acids or alpha-hydroxy acids (Srinivasan et al., 2002). In the synthesis of protein shown in Figure 3, NCAAs 15, 16, and 17 are lysine derivatives that are incorporated using PylRS. This allows for the synthesis of ubiquitinated proteins, also known as the "kiss of death", a quality control process where enzymes destroy proteins that are no longer neexded (Li et al., 2009). NCAAs 14 and 28-32 can activate fluorescent protein by labels reacting with tetrazine, which results in broad implications for the imaging of site-specific proteins (Lang et

...scientists can create new proteins with implications spanning from powerful vaccines...to new advancements in protein medicinal chemistry.

al., 2012). Non-canonical amino acids and alpha-hydroxy acids contain many unique reactive groups that permit the integration of biochemical and biophysical probes for protein function investigation and biotechnological development. The pyrrolysine system allows the in-vitro and in-vivo synthesis of proteins with multiple post-translational modifications of lysine. This may address epigenetic challenges such as protein function regulation through modifications, enzyme activities, and nucleosome interactions with transcription factors (Wan et al., 2014).

As more studies have explored the uses of engineered synthetases, genetically encoded noncanonical amino acids may significantly enhance the capacity of therapeutic and medical interventions. As biomedical technologies have evolved in the last decade, the tendency to treat clinical diseases such as cancer, autoimmune disease, and genetic disorders have increased (Kang et al., 2018). Much research and efforts have been contributed towards the chemical modification of protein therapeutics through traditional conjugation (a chemical strategy that links two molecules together) methods. Yet the results are often suboptimal due to the large number of ineffective products being mixed with the target pharmacological property (Kang et al., 2018). However, engineered synthetases with NCAAs allow us to modify proteins with fine-tuned precision. NCAAs can link proteins to cytotoxic compounds, polymers, and additional classes of molecules while minimally interrupting the native chemical processes in living systems. Compared to conventional strategies such as antibody-drug conjugates and bispecific antibodies, the efficacy using engineered synthetases is higher at low concentrations due to fast kinetics; engineered synthetases' site-specific properties also results in longer therapeutic windows with improved stability (Rezhdo et al., 2019).

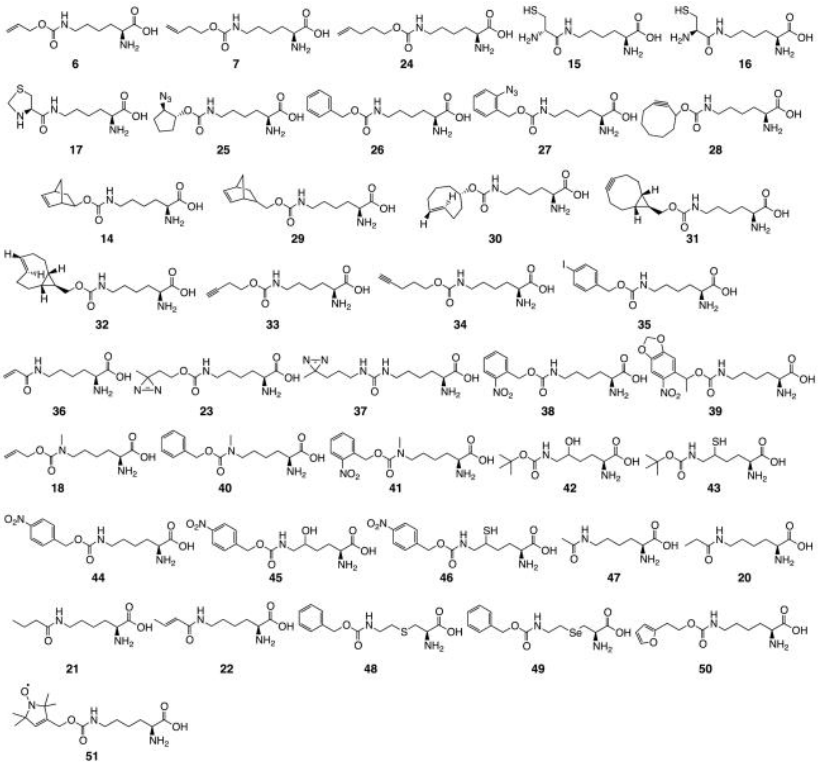

Figure 3. Lysine derivatives that have been genetically incorporated into proteins using engineered PylRS mutants in coordination with Pyl tRNA. (Wan et al., 2014) Image from Wan et al. 2014.

...engineered synthetases' site-specific properties also results in longer therapeutic windows...

Bispecific therapeutics is one biomedical avenue where engineered synthetases have the potential to improve treatment efficiencies. Before the use of engineered synthetases, the traditional route for producing bispecific antibodies was through genetic fusion, which, although are effective against some cancers with upregulated drug pumps, create complications such as poor "pharmacokinetic and physical properties, immunogenicity, or manufacturing challenges" (Kularatne et al., 2013). With NCAAs, however, its orthogonal chemical reactivity can create site-specific conjugation, hence producing bispecific antibodies with well defined orientations and distances between binding domains. One example of such bispecific antibodies is bispecific molecules that redirect T cells to cancer cells; by conjugating small-molecule ligands such as DUPA (which targets receptors on the surface of cancer cells), there is greatly improved selectivity and cytotoxicity against cancer cells (Kim et al., 2013).

Pyrrolysyl tRNA synthetase

engineering takes advantage of a highly complex, natural system to create new and novel proteins. Engineered synthetases have shown promising results, hence demonstrating genetically encoded NCAAs' huge potential in medical and pharmaceutical fields. ❧

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The morality and philosophies of medicine: Questioning scientific assumptions

ANUSHA TANNERU
Staff Writer

The pertinence of a philosophical framework in medicine has long been debated. Philosophy is often characterized—or rather, mischaracterized—for indulging in abstract concepts, whereas science is typically defined by its evidence-based and rational explorations. The two seem like distinct opposites, but are rather a perfect pair. If the medical community examines its ethical dilemmas using philosophical thinking, then medicine will benefit tremendously. After all, progress occurs when fundamental scientific assumptions are questioned and criticized. Philosophy is a useful framework and analytical tool to examine ethical issues in medicine while those novel medical situations can assist philosophy in gaining more knowledge in its own subject. This is where the field of bioethics itself emerges.

Philosophy has multiple distinct sub-disciplines, such as metaphysics, epistemology, logic, political philosophy, and ethics (Hassan et al., 2018). Furthermore, some of these sub-disciplines, like epistemology, focus on obtaining knowledge through logical reasoning processes, even going so far as to incorporate empirical evidence.

However, it is important to note that what medicine incorporates from philosophy is only a small component of the discipline itself. Philosophy and medicine are already intertwined. Western medical ethics are based on the teachings of Greek physician Hippocrates, whose 'Hippocratic Oath' articulates four core principles that remain significant today: respect for autonomy, nonmaleficence, beneficence, and justice (Lakhan et al., 2009). Furthermore, Western medical schools insist that these values be taught to aspiring doctors, all of which have philosophical origins (Beauchamp & Childress, 2008).

...progress occurs when fundamental scientific assumptions are questioned and criticized...

According to prominent philosophers such as Immanuel Kant, respect for autonomy refers to the unmodifiable intrinsic value within all individuals (Varkey, 2021). To respect this, all medical professionals must acknowledge an individual's power to voluntarily make their own rational decisions about their health (Varkey, 2021). Beyond medicine, autonomy has also influenced common perceptions of free will that individuals have.

With regards to nonmaleficence, medical professionals must promise to 'do no harm' to their patients. This means that they are obligated to thoroughly investigate possible treatments and assess risks and benefits before helping patients come to a decision (Varkey, 2021). Nonmaleficence is closely related to beneficence, which dictates that medical professionals act for the benefit of their patients.

Justice is most prevalent in politics and public policy. This principle is primarily based on 'distributive justice,' which is about the fair and equitable distribution of resources. This is based on the person, the need, the effort given, the contribution

Table

Medical ethics during COVID-19: Two paradigms

Ordinary medical practice The Individual (Deontological)	Disaster medical practice The Collective (Utilitarian)
Thorough assessment	Quick assessment
First come, first served	Sickest first served
Maximal treatment	Minimal adequate treatment
Careful follow-up	Limited follow-up
Relatively unlimited resources	Limited and depleting resources
Capacity distensible	Capacity saturated
Facility sufficient	Need for nontraditional extensions (firehouses, hotels, schools)
Remain open to new cases	Shut down for new cases
Healthy staff	Incipient staff illness/danger
Grateful patients and families	Angry crowds that may be turned away

Figure 1. The benefits and costs of treating patients during normal and crisis situations with two separate methods. Image from Komrad 2020.

Medical Principle		Most Important		Least Important	
	$\bar{X}$(SD)	N	%	N	%
Non-maleficence	.25 (.12)	54	57.4	9	9.5
Justice	.16 (.09)	47	50.0	10	10.6
Autonomy	.16 (.10)	21	22.3	28	29.8
Beneficence	.15 (.10)	23	24.4	33	35.1
Truth Telling	.12 (.10)	16	17.0	46	48.9
Confidentiality	.16 (.11)	15	15.9	58	51.1

N = 92.

Figure 2. Study on Australian Psychology students where rankings of medical principles were compared against each other to determine a hypothetical ranking of most important to least. *Image from Page 2012.*

given, the merit of an individual, or according to the free market (Varkey, 2021).

Balancing justice with the other core principles adequately is difficult when the patient is supposed to be first priority, as per beneficence. For example, in disasters, triage can complicate the delicate balance as seen in Figure 1. In these situations, the principles of justice and autonomy are drawn into conflict with each other (Komrad, 2020). Justice and beneficence are not the only two potentially conflicting principles. For example, if a minor is vulnerable, nonmaleficence and beneficence override autonomy because the child's parents must act on their behalf (McCormick, 2008). Similarly, if a patient prioritizes religious convictions over medical treatment—such as in cases with Jehovah's witnesses and blood transfusions—medical professionals must respect their autonomy, so long as the patients are properly informed of risks (McCormick, 2018).

The ranking of these principles is controversial, however, and there are different rankings across individuals. For example, as seen in Figure 2, a study was conducted among first-year Australian psychology students in 2012 that asked them to rank in importance the four medical principles and two additional principles listed, confidentiality and truth-telling. Confidentiality regards a non-disclosure of patient information unless specifically asked, while truth-telling describes the duty of a medical professional to report honest and factual information to their patients. They reported that nonmaleficence and justice are the most important, while confidentiality and truth-telling were found to be the least important (Page, 2012). Yet, an argument can be made that a lack of confidentiality and truth-telling could violate patients' autonomy, as one must assume that they will make rational decisions after being informed. This one example already highlights challenges in this hierarchical model.

...medical professionals must promise to 'do no harm' to their patients.

Aside from this example, there are many other 'ethical gray areas' in modern medicine that can benefit from a philosophical mindset. For example, voluntary euthanasia presents a conflict between autonomy and nonmaleficience: although denying the means to ending one's life is a violation of autonomy, this prohibition can still be justified because knowingly allowing a patient to die would inflict harm on them (Fenton, 2018).

The debate on voluntary euthanasia is a prime example of philosophy and medicine intersecting. Proponents of active euthanasia— killing a patient by active means—state that there is no moral distinction between letting a patient die knowingly or actively aiding that patient in dying other than a percieved burden of moral responsibility on the medical professional (Fenton, 2018). This is like saying that an adult watching a child drown is as morally wrong as pushing a child into the water. Regardless, the main argument against euthanasia arises from the practicality of introducing this into a complex medical system. In this case, it requires using philosophical arguments to appropriately inform public policy.

Another avenue where philosophy could enhance the practice of medicine is mental health and psychiatry. Compared to other diseases, psychological disorders are outliers within the medical model as there is less of an understanding regarding what these disorders are (Fenton, 2018). The medical model can be understood as the assumption

that there is a physical problem in brain structures and biological systems that result in psychological disorders. For example, this model assumes that clear, observable symptoms of diseases like Alzeheimer's can act as a window into the 'physical' nature of a disease. This model can then be extrapolated and applied to psychological disorders like depression. In order to do this, it prioritizes empirical evidence which allows the medical model to serve as a guide for diagnosis.

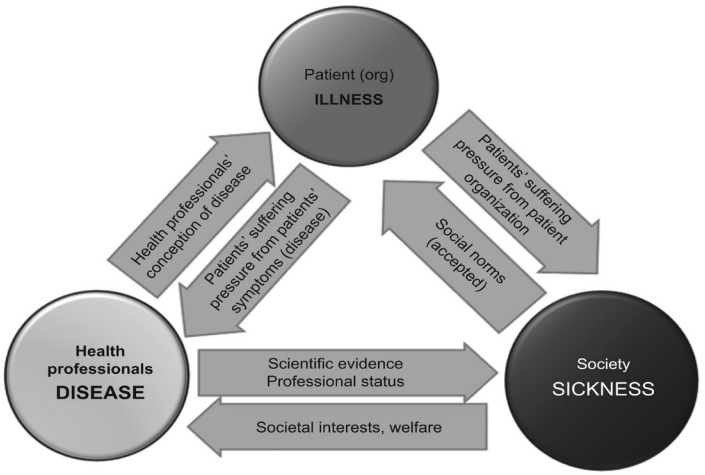

Figure 3. Hypothetical model of healthcare and the myraid of factors affecting it, as well as relationships and influences between each of these factors. *Image from Hoffmann 2012.*

Central to this model is the concept of disease and injury, which are defined as some deviation from 'normal' functioning or reduction of an individual's well-being and health. Yet, this framework is complicated by the multiple analyses used to assess the efficacy of healthcare. For example, the concept of 'well-being' is understood to be how individuals live a healthy lifestyle, while health is a simple state of being (Stoewen, 2015). Instead of understanding these two concepts separately, there should be an intersection between the two to assess the efficacy of healthcare.

...medicine is a science in the service of human beings.

Another significant issue in this medical model is how it directs treatment of mental disorders. Since this model assumes that abnormalities in normal functioning stem from biological markers, the model concludes implicitly that these mental disorders result from abnormal brain functioning. Therefore, any other external factors like social and psychological factors are seemingly given less attention even if they are influential on the abnormal behavior (Farre & Rapley, 2017).

Yet, for instance, in order to diagnose disorders like schizophrenia, patients must demonstrate significant deviation from 'normal' thinking — a construct that is largely determined by rationality, a philosophical concept, where individuals are seen as agreeable to reason. While we can find empirical evidence for behavioral reasons behind this rationality, there are no clear biological markers that encompass what this 'normal' thinking is. Schizophrenia has biological abnormalities, but it also has environmental and social stressers, such as discrimination and economic adversity, that play a role in its development (Patel et al., 2014). However, we still implement these standards to categorize individuals as 'normal' and 'abnormal' on a biological basis (Fenton, 2018). Therefore, the current examination of mental health in the medical model must be expanded. Medical professionals must account for behavior and experience in their treatment, because mental disorders are not simply physical diseases, but rather deviation from some established norms that stem from some moral rationale. This concept is presented in Figure 3, which shows the multiple dimensions present in how we define diseases, illnesses, and illnesses and how these definitions can impact treatment and outcomes for not just mental health, but for all health (Hoffman, 2016).

Philosophy is important to and interconnected with medicine in many ways. If medicine is the product of a desire to reduce pain and suffering, then philosophy is the path to understanding why humans suffer and for what and how. For example, there was the understanding in Ancient China that form and spirit were two sides of the same coin, just as mind and matter are (He & Lang, 2017). This idea resulted in a people-focused practice of medicine, which was superseded by the Western value-based and empirical model (He & Lang, 2017). Medicine must return to a

model that incorporates not just physical symptoms, but lived experiences and behavior. Most importantly, we must understand that medicine is a science in the service of human beings. It is an evolving, inclusive system maintained by critical human concepts such as thought, emotion, and will, all things philosophy explores (He & Lang, 2017). Just as Hippocrates himself emphasized, philosophy is as embedded in medicine as medicine is embedded in philosophy. ❧

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Propargylamines: A single compound with a multitude of uses and applications

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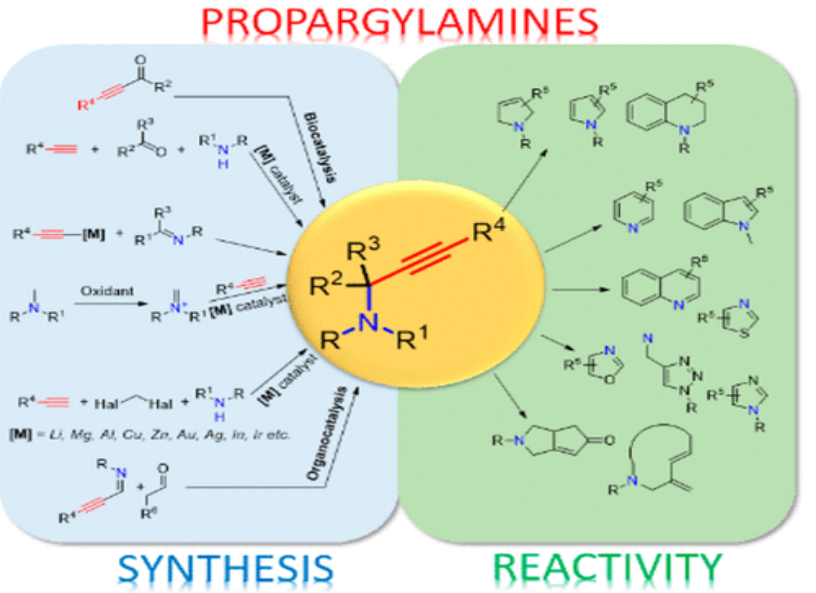

Figure 1. General structure of a propargylamine compound with various methods of how to synthesize compound and its chemical uses. *Image from Lauder et al. 2017.*

Inventions, especially new discoveries in medicine, are celebrated for what they contribute to society. People focus on how the future can be shaped due to the development overlooking the equally exciting process of how the breakthrough came into existence. A medicinal compound is often synthesized from multiple smaller compounds to combat a certain problem and act as a therapeutic agent. More recently, significant investments have been made into developing chemical compounds that not only have medicinal properties themselves, but also act as a precursor for synthesizing many medicinal compounds. Propargylamine is one such compound. Propargylamines are not only versatile in their uses for the synthesis of a variety of medications, particularly anti apoptotic drugs for Parkinson's disease, but are also produced and used sustainably, First identified in 1963, propargylamines are composed of an alkyne group with an amine group in the beta position. Initially, propargylamines were used to synthesize oxazolidines, a five membered ring compound with an oxygen in the first position and a nitrogen in the third position commonly used in paints, as well as other nitrogen containing heterocycles (R. Easton et al., 2002; Shachat & J. Bagnell, 2002). As research on heterocycles increased and their varied medicinal applications were discovered, propargylamines began to be intensely studied to find how they could be used to synthesize these heterocycles. Later, it was discovered that the alkyl groups on propargylamines are phenomenal at acting as both an electrophile and a nucleophile (electron accepting or electron donating), providing them with a plethora of reactions that are not possible among the vast majority of functional groups. The amine group is a particularly good nucleophile, giving propargylamines much more variety in the reactions they partake in (Lauder et al., 2017). The combination of these two functional groups in conjunction with any other moiety present in the two open bonding sites of the central carbon, lead to endless possibilities for combination, and thus functionality.

...propargylamines are not only versatile in their uses...but are also produced and used sustainably...

Furthermore, propargylamines are sustainably synthesized with an A3 coupling reaction. A3 coupling reactions are when a metal-catalyzed reaction between an aldehyde, alkyne, and amine occurs to synthesize a singular compound like a propargylamine. Copper catalysts are especially prominent in synthesizing propargylamines, with over 93% yield with a 1.5% catalyst loading, or the percent weight of catalyst used in the reaction, at room temperature (Sampani et al., 2021). These reaction conditions make this process sustainable due to the low catalyst loading and the reaction transpiring at room temperature without the need to heat the environment. Propargylamines are versatile in

their synthesis because numerous metal catalysts could be used besides copper, such as silver and palladium. These alternative metal salt catalysts are not as environmentally friendly as the copper salts, particularly in price, but more importantly, allow for synthesis pathways for hundreds, if not thousands, of propargylamines, all with different functionalities (Brissy et al., n.d.; Li et al., 2021).

Propargylamines have been extensively researched as products, but also as reactants. The most prominent nitrogen heterocycle propargylamines synthesize is pyrroles: chemical compounds with a secondary amine on an aromatic five-membered ring. These rings are excellent for receiving electrophilic attacks ending in a substitution reaction but poor at undergoing nucleophilic attacks on the rings. This limited variability of chemical reactions allows pyrroles to excel in electrophilic attacks by being easier to control (Katritzky et al., 2010). Propargylamines are used to synthesize pyrroles with the assistance of many metal salt catalysts, even with non-copper metal salts, which are comparable in sustainability to traditional propargylamine synthesis despite being more expensive. With gold salts, for example, the catalyst loading is increased to 5% but the reaction only needs one hour to complete, which is another essential component in sustainability as time is another valuable resource that must be conserved (Saito et al., 2009). Propargylamines synthesize pyrroles significantly more efficiently than other comparable methods such as the Paal-Knorr pyrrole synthesis reaction which require expensive metal salt catalysts, namely palladium, and energetically unfavorable microwaves (Rao et al., 2004). Pyrrole synthesis is an especially noteworthy application of propargylamines. For example, pyrroles are a structural component that are seen throughout the landscape of several crucial drugs and medicines, including antipsychotics, anxiolytics, anticancers, antibacterials, antifungals, antimalarials, and much more. Some specific pyrrole-containing medicines include calcimycin, ageliferin, aloracetam, atorvastatin, and obatoclax (Bhardwsaj et al., 2015). Thus, pyrroles are undoubtedly useful in not only the treatment of, but also the cure of a large percentage of diseases that exist. As a direct precursor, propargylamines serve an essential role in the synthesis of this vital compound.

Propargylamines synthesize pyrroles significantly more efficiently than other comparable methods....

Another chemical compound with many medicinal applications that can be synthesized using propargylamines are thiazoles. Thiazoles, also known as 1,3-thiazole, are a five-membered heterocyclic compound containing a sulfur in the first position and a nitrogen in the third position. After decades of research into synthesizing thiazoles with propargylamines, a gold-catalyzed method was discovered. These reactions have a catalyst loading as low as 1% at 20 degrees Celsius for three hours or less, all respectfully sustainable conditions (A Heugebaert et al., 2011). These conditions are very close to standard conditions as these synthesis reactions occur at room temperature with only the introduction of a small quantity of catalysts, which are significantly more environmentally conscious when compared to historical approaches to thiazole synthesis. Thiazoles can be found in several drugs, including anti-cancers, anti-HIVs, anti-inflammatories, and antibiotics. Each application requires a specific thiazole derivative with propargylamines being heavily relied upon to synthesize specific thiazole derivatives in a cheap and efficient manner leading to propargylamines being invaluable to the medicinal industry (Arshadi et al., 2017).

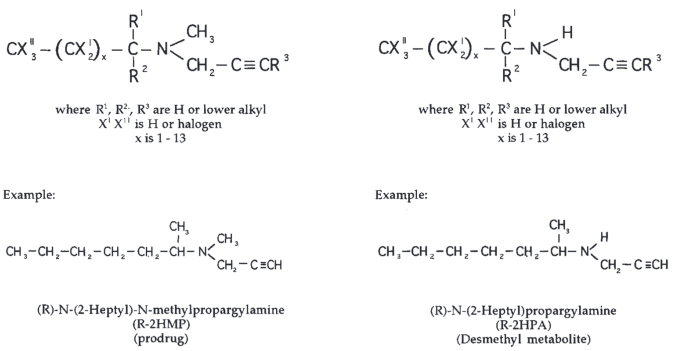

Figure 2. Examples of N-methylpropargylamines used in anti apoptotic drugs. *Image from Boulton et al. 1997.*

One specific drug that utilizes thiazoles is Riluzole. Riluzole is the primary drug in treating amyotrophic lateral sclerosis, ALS, a disease that results in the death of motor neurons in the brain which inevitably leads to death. While Riluzole, or any other drug, cannot cure ALS, usage allows the patient to live for over a year longer. Riluzole are believed to have the capabilities to be modified to have stronger potential in longer treatment of ALS as well as the possibilities to expand into the treatment related neurodegenerative diseases, provided that future research can support this belief (Aksinenko et al., 2021). Beyond ALS, propargylamine-synthesized thiazoles are heavily involved in cancer therapy. Thiazole is present in compounds found in a multitude of anticancer drugs including tiazofurin, dasatinib, dabrafenib, ixabepilone, and epothilone. In these drugs and more, thiazoles fight cancer by inhibiting enzymes, proteins, cell functions, and more with some examples being EGFR kinase, B-RAF, tubulin polymerization, CDC7, and topoisomerase (Sharma et al., 2020). Without propargylamines, thiazoles would not be as readily accessible for research and use in combating a plethora of ailments.

Finally, one of the most well-known uses of propargylamines compounds is in the antiapoptotic drug used for Parkinson's disease. Aliphatic propargylamines, which differ from traditional propargylamines by their open carbon chain, are used to treat Parkinson's disease specifically due to their ability to act as monoamine oxidase B inhibitors (Boulton et al., 1997). Monoamine oxidase B is an enzyme found in the brain that catalyzes the removal of an amine leading to the compounds being irreversibly inhibited in its function. These propargylamines are found in various drugs, such as Selegiline, which treats Parkinson's disease and other neurodegenerative disorders caused by excessive MAO-B protein apoptosis (Finberg & Rabey, 2016). When enough MAO-B proteins are killed it has the negative consequence known as the "cheese" reaction, or acute attack hypertension resulting from eating cheese and other similar food products while taking a MAO inhibitor (Cheese Effect - Oxford Reference, n.d.). Although there are other compounds that compete with propargylamines to act as irreversible MAO-B inhibitors, especially in the context of neurodegenerative diseases (Finberg & Rabey, 2016).

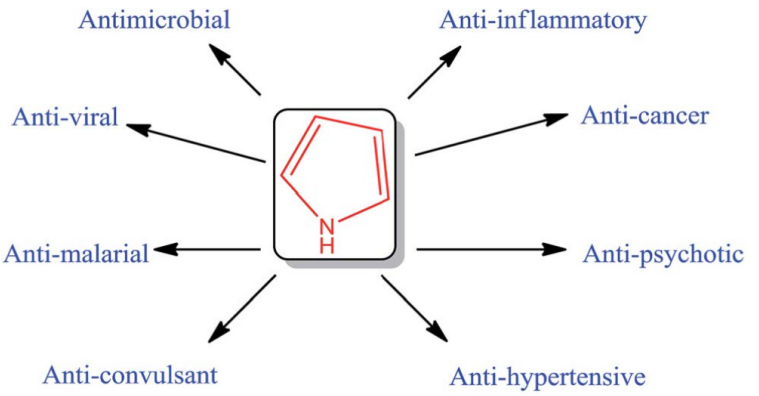

Figure 3. The many medicinal uses of pyrroles. *Image from Bhardwaj et al. 2015.*

Aliphatic propargylamines... are used to treat Parkinson's...

Propargylamines are also present in Rasagiline, another anti apoptotic drug to treat Parkinson's disease. Rasagiline, while having a very high potential to effectively treat Parkinson's disease, also acts similar to Selegiline in that it is extremely successful at avoiding undesirable effects of the "cheese" reaction (Teo & Ho, 2013). While many Parkinson's disease treatments have noticeable side effects, multiple propagarylmaine drugs avoid this as well as being more viable.

Propargylamines have a history of being a reliable option for drug synthesis. Either with directly being involved in the drug or acting as a precursor, propargylamines have demonstrated much promise in its applications, especially due to its flexibility and sustainability as a product and a starting point in drug development. However, much of its potential is undiscovered. Fortunately, there has been a recent boom in research of propargylamine synthesis and usage. Each year more and more progress is made in unlocking propargylamine's

full potential. While unlikely to become a household name due to its background functionalities, propargylamines are on the verge of becoming mainstream in the pharmaceutical field. ❧

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The price of factory farming: Farmed animals' contribution to antibiotic resistance in humans

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As one of the most pressing current medical dilemmas across the globe, antibiotic resistance consistently receives widespread attention from medical professionals and public health experts as its severity increases. While addressing antibiotic resistance and its implications, many tend to focus on reducing human consumption of antibiotics, yet the majority of its use arises from a less obvious and often overlooked source: livestock. The overuse of antibiotics in the animal agriculture industry leads to increased antibiotic resistance in both animals and humans. Reducing antibiotic use in animal agriculture through a combination of political and individual actions may be the first step in addressing this global crisis and ensuring that antibiotics can continue to effectively treat life-threatening infections in humans.

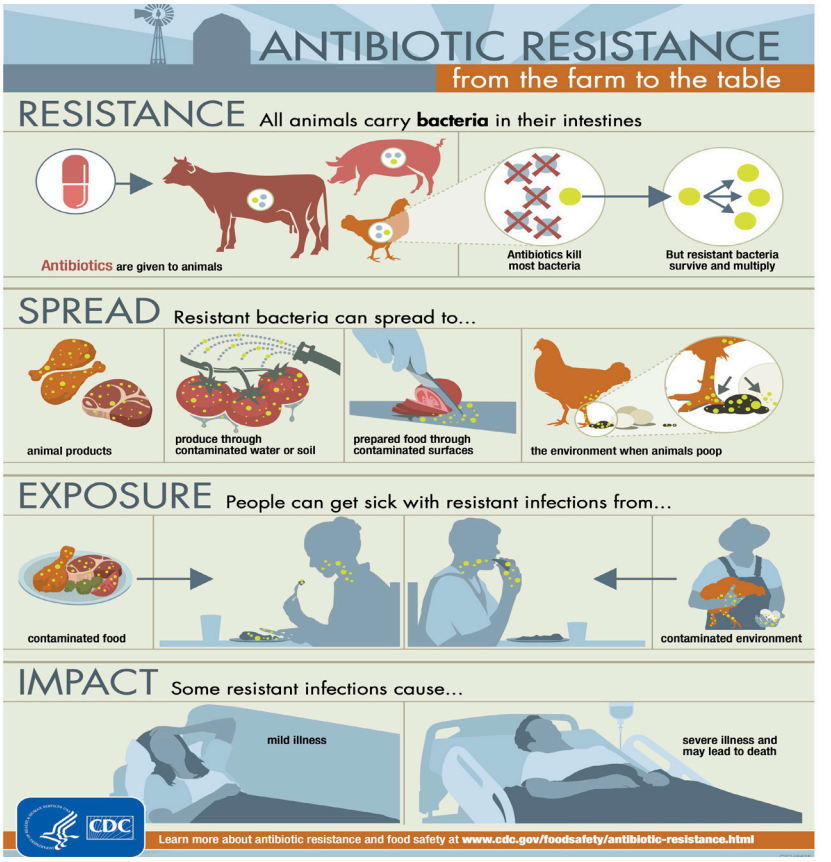

Figure 1. Antibiotic resistance: from the farm to the table. Image from Redfield 2019.

In order to fully understand how the cattle and poultry industries contribute to antibiotic resistance, it is important to first establish what antibiotic resistance is, how it arises, and why it is important. Antibiotics are used to kill or stop the growth of harmful bacteria and can be taken in the form of tablets, creams, sprays, and injections. In humans, antibiotics are used to treat a wide range of bacterial infections, like strep throat, whooping cough, urinary tract infections, as well as more serious conditions such as sepsis (CDC, 2021).

...antibiotic use in animals as the leading cause of rising antibiotic resistance in 2016...

Antibiotic resistance impacts a diverse cohort of patients by decreasing the efficacy of antibiotics to fight infection. Antibiotic resistance is a result of natural selection in bacteria populations, as random genetic variation gives some bacteria the ability to resist antibiotic treatment, which increases their fitness and allows them to survive and reproduce. These mutations can also be transferred through plasmid exchange. Plasmid exchange involves one bacterium passing plasmid, a circular double stranded DNA molecule, to a recipient, which further multiplies populations of resistant bacteria (Landers, 2012). Given that antibiotic use inherently increases the likelihood of antibiotic resistance, healthcare providers are often presented with difficult ethical dilemmas because they must balance limiting antibiotic use to preserve its efficacy with their responsibility to give patients the best care possible (Landers, 2012). Most public health

experts agree that human use of antibiotics must be used wisely and conservatively so that they can remain effective for serious infections.

An often missed piece of the antibiotic resistance puzzle is antibiotic use in farmed animals, which plays a pivotal role in propagating the crisis. The use of antibiotics in livestock leads to increased antibiotic resistance in both animals and humans. The United Nations General Assembly listed antibiotic use in animals as the leading cause of rising antibiotic resistance in 2016 (Boeckel et al., 2017). The scope of this issue is immense. Compared to the three million pounds of antibiotics used on humans, scientists estimate that between 17 to 24 million pounds per year are given to chicken, cattle, and swine for non-therapeutic purposes (Landers, 2012). To exacerbate the issue, new mutations that lead to antibiotic resistance are more likely to arise in animals given that their biomass exceeds that of humans (Boeckel et al., 2017).

If antibiotic use in livestock has such detrimental effects, why is it used to such a large extent? Evidently, there is a large incentive for farmers to use antibiotics on their livestock and it can be attributed to the two main functions of antibiotics in animals: growth promotion and hygiene. Antibiotics can help animals gain mass to produce more meat and replace hygiene regulations by preventing disease while overcrowding the animals to produce large quantities of animal products at little cost (National Research Council Committee on Drug Use in Food Animals, 2017).

Not all antibiotic use in farming is harmful to humans. Ionophore, for example, is a type of antibiotic commonly used in calves but has never been used in humans. Mutations, therefore, do not affect human health and are unable to transfer to other forms of antibiotics (Landers, 2012). Despite the fact that antibiotic use in livestock does not universally harm human health, there is nevertheless strong evidence that links antibiotic resistance in animals with antibiotic resistance in humans. Importantly, the antibiotics most commonly used in livestock are tetracyclines, making up 67% of all antibiotic sales for animals in 2019 (Dall, 2020). Tetracyclines are used routinely to treat humans for conditions such as severe acne and several sexually transmitted infections, so their use in animal agriculture contributes to their decreasing efficacy in humans (Chopra, 2021).

...minimizing the number of antibiotics we use on animals and minimizing the number of animals we raise for food.

Antibiotic-resistant bacteria in farmed animals have both direct and indirect consequences on human health. Humans can be directly affected by coming into contact with these bacteria in their food or indirectly affected by coming into contact with resistant bacteria that have spread to other areas of their environment, such as air, soil, and water. Antibiotic resistance in animals has worsened in scope in recent years. Researchers from the Princeton Environmental Institute, ETH Zurich, and the Free University of Brussels mapped antibiotic resistance around the world and found that rates of resistance have increased dramatically in the past two decades (Boeckel et al., 2019). Princeton researcher Ramanan Laxminarayan asserted that although they want "higher-protein diets for many people, if this comes at the cost of failing antibiotics, then we need to evaluate our priorities" (ScienceDaily, 2019). Laxminarayan's comment encapsulates the sad truth about this global issue: there is no perfect solution. However, there are several strategies that can be employed to lessen the rate of increase in resistance.

The solutions to farmed animals' contribution to antibiotic resistance in humans can be characterized into two main types: minimizing the number of antibiotics we use on animals and minimizing the number of animals we raise for food. The former approach might involve increased farming regulations; for example, the World Bank supported the proposal of a "user fee" paid by those purchasing antibiotics for non-human use. A 50% user fee on antibiotics used on animals could decrease global antibiotic consumption by 31% (Boeckel et al., 2017). A 50% user fee is projected to produce between $1.7 and $4.6 billion per year, and the proceeds from these fees could be allocated towards research and discovery of new antibiotics. Given that the estimated cost of developing a new antibiotic is $1 billion, this

strategy may not produce enough revenue to be effective (Boeckel et al., 2017).

Other farming regulations, such as enforcing quotas for antibiotic usage per year, could also significantly reduce antibiotic consumption. A limit of 50mg of antibiotics per population correlation unit (PCU) per year, for example, could lower consumption by 60% (Boeckel et al., 2017). This method could be implemented in high-income countries to help alleviate the burden on farmers in developing countries that depend heavily on livestock. Regulations that improve the conditions for animals on farms would also be beneficial as they can decrease the risk of diseases and therefore the need for antibiotics. Variables such as temperature, humidity, social stressors, and nutrition all contribute to animals' susceptibility to disease, and targeted regulations s can ensure that livestock can remain disease-free without necessitating the overuse of antibiotics (National Research Council Committee on Drug Use in Food Animals, 2017). However, given the large demand for animal products, creating these conditions in factory farms is difficult and costly.

The second type of solution aims to decrease the number of animals raised for food by switching to alternative forms of protein. This method would not only limit the number of animals raised for food due to lower demands for meat but would also address the issue of overcrowding on factory farms. Animals raised for food are often competing for space, food, and water, and these unhygienic conditions make the animals more prone to disease, which is one of the reasons why livestock are treated with antibiotics (National Research Council Committee on Drug Use in Food Animals, 2017). Global antibiotic consumption could be reduced by 66% if individuals limited their meat consumption to 40 grams – the equivalent of one hamburger a day (Boeckel et al., 2017). Given that an average American currently consumes 260 grams of meat per day, this solution may be difficult to achieve and would require strong incentives for individuals to lower their meat intake (Boeckel et al., 2017).

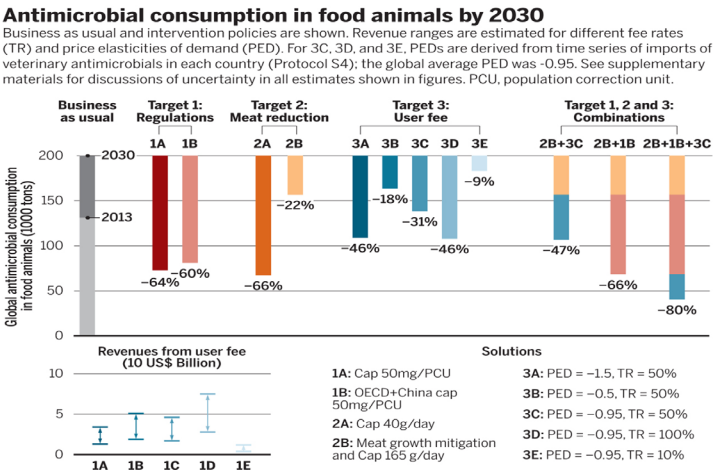

Figure 2. Antimicrobial consumption in food animals by 2030. Image from Van Boeckel 2017.

Ultimately, these potential solutions can be implemented together, and their added benefits could reduce antibiotic consumption in animals by around 80% (Boeckel et al., 2017). Antibiotic resistance is a pressing and concerning issue, yet it is not hopeless; by spreading awareness of why antibiotics are used on animals and how it contributes to resistance in humans, individuals can mobilize to safeguard life-saving antibiotics for human use.

Antibiotic resistance is a pressing and concerning issue, yet it is not hopeless...

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Virtual reality may improve memory in the elderly

AASTHA BANSAL
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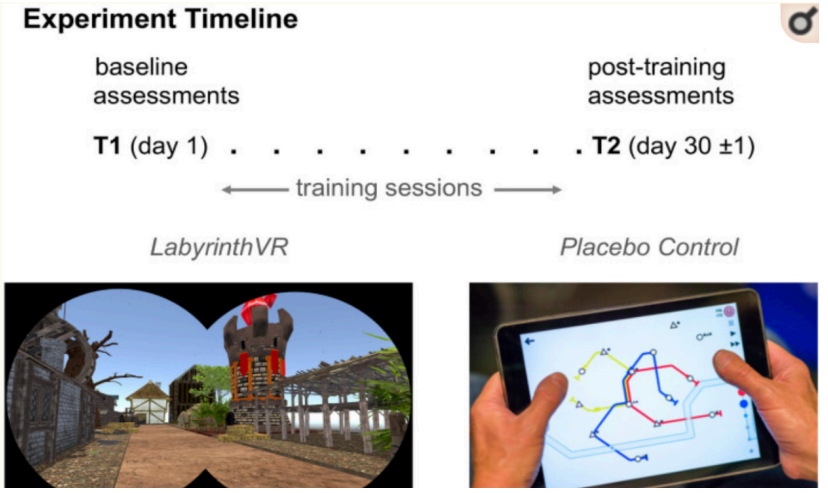

Figure 1. Participants were randomized to training regimens that included 12 h on task playing either the Labyrinth-VR or the Placebo Control games over 30 days. Image from Wais 2021.

Dementia and memory impairment affect about 3.4 million Americans; approximately 14% of these are 71 years or older, and this number is projected to increase as the US population continues to age (One in 7..., 2007). Right now, there is no cure for aging-related memory decline, although there is much historical and ongoing research into interventions to slow or arrest it. Among these, growing evidence suggests that virtual reality (VR) can serve as a potentially viable means to increase memory retention in the elderly.

A common side-effect of aging is a decline in sharp and long-term memory recall. When this is severe and classifiable as a disease, seniors face dementia. Dementia is an inability to remember and process important information that impedes daily activities (CDC, 2019). The World Health Organization (WHO) estimates that there were about 35.6 million people living with dementia in 2010, and this number is expected to double nearly every 20 years (García-Betances, 2015). This indicates not only how common dementia is in the world today, but also how urgently this issue must be addressed with its exacerbation in future generations. Individuals affected by dementia experience impairments in many domains of adult life, including but not limited to facial recognition, financial management, and household safety. More specifically, dementia compromises individual autonomy for complex activities, emotional control, social behavior, and motivation (García-Betances, 2015). According to the Mayo Clinic, dementia occurs when nerve cells and neural circuits in the brain are damaged (Mayo Clinic, 2021). Damaged brain cells impair neural communication by altering cognition and emotion, and ultimately change an individual's behavior compared to their previous baseline. There are several types of dementia associated with specific parts of the brain, but the most common type is Alzheimer's disease (AD). AD damages neurons and impairs interneuronal communication in the hippocampus, the region of the brain responsible for learning and memory (Lindberg, 2012). When this region is damaged, memory loss typically occurs. The prodromal stage (the period between early signs and diagnosable conditions) of dementia, mild cognitive impairment (MCI), seems to be the ideal time to implement preventative measures, as some MCI patients are able to eventually return to a normal state, or at least remain in a stable condition half-way to complete dementia (Thapa, 2020). Scientists believe this could even be the key to curing dementia; as such, VR interventions primarily target MCI patients.

...about 35.6 million people living with dementia in 2010, and this number is expected to double nearly every 20 years.

VR is a computer-generated interface that immerses participants in realistic three-dimensional environments, usually through wearable electronic equipment such as a headset (Zheng, 1998). The VR head-mounted display

(HMD VR) functions to immerse participants in new and creative environments providing the opportunity of improving or restoring memory abilities. A recent study examined the use of VR as a cognitive intervention to improve long-term memory (LTM) in the healthy elderly population. Scientists found that *Labyrinth-VR*—a VR spatial wayfinding game—can improve high-fidelity long-term memory (process of recalling diverse information in detailed attributes) while increasing cognitive and physical functionality in patients with average cognition (Wais, 2021). Participants were randomly selected either to play 12 hours of *Labyrinth-VR* or receive a Placebo Control over the course of 30 days, as shown in Figure 1 (Wais, 2021). The Placebo Control arm included four commercial video games that did not require users to remember detailed information to succeed. Afterward, researchers compared participants' baseline and post-training performance on high-fidelity LTM measures. *Labyrinth-VR* synchronizes the gaze of participants with their walking motion as they navigated urban and village neighborhoods, completing errands as challenges arise, as shown in Figure 2. *Labyrinth-VR* also measured participants' ability to walk between destinations in relation to goal-orientated tasks in the video game, as shown in Figure 3. The VR game increases the immersive aspects of the wayfinding experience and triggers the peripheral nervous system (the nervous system outside the brain and spinal cord). This allows motor commands to be conveyed to muscles in the body and relays sensory information. This experiment found that older adults in the *Labyrinth-VR* treatment group with average baseline cognitive performance showed significant increases and remediated age-related deficits in high-fidelity LTM retrieval relative to the placebo group (Wais, 2021). These suggest that randomized VR cognitive interventions have the potential to improve LTM abilities in older adults but further study is needed.

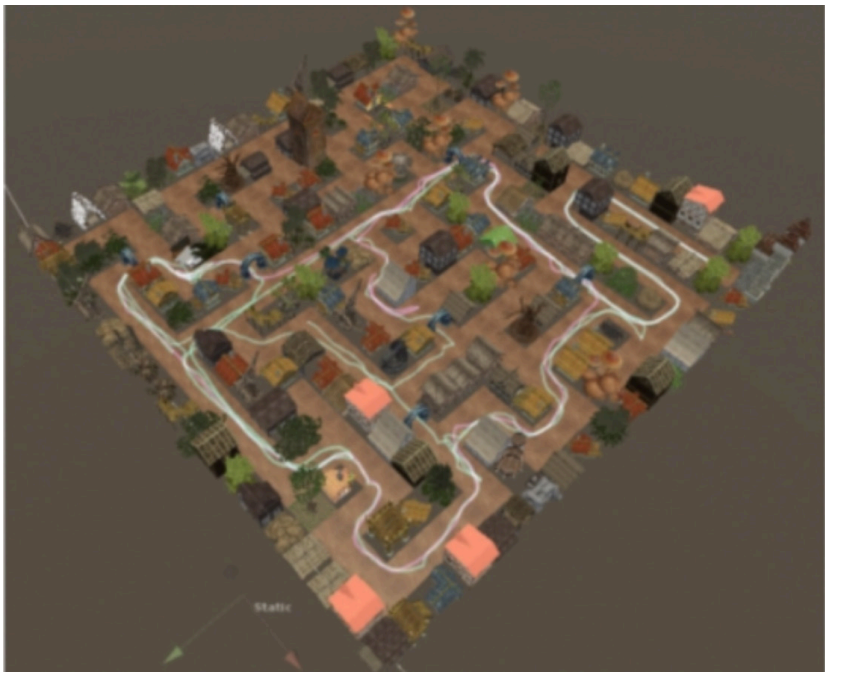

Figure 2. The virtual reality display of wayfinding trails in a village neighborhood that participants navigated through. Image from Wais 2021.

Labyrinth-VR—a VR spatial wayfinding game—can improve high-fidelity long-term memory...

As opposed to traditional computer games, VR plays a special role in improving memory capabilities in the elderly. Due to the three-dimensional and detail-orientated nature of VR, it is much more immersive and realistic than computerized training. VR intensifies the legitimacy of external surroundings and allows individuals to experience extreme sensory stimulation (Thapa, 2020). In VR, most participants feel comfortable in a safe, immersive environment, improving their functional learning and their transfer of learned functions (Kim, 2019). Individuals participating in VR activities feel engaged in an alternate dimension but are still aware of their real-world surroundings, which comforts them and allows their mind and body to relax and produce the best learning outcomes. Nonetheless, seniors may be more susceptible to vertigo and dizziness as a side-effect of VR, thus it is important to monitor their functioning consistently. VR also allows scientists to study specific brain-stimulating activities in targeted regions of the brain in relation to the rate of neuroplasticity in demen-

Figure 3. Participants were attached to ankle-mounted tracking sensors which recorded game movement based on their ambulation. Image from Wais 2021.

tia patients (Garcia, 2012). It allows for the deconstruction and modification of typically robust environments through the reorganization of synaptic connections between neurons (Garcia, 2012). VR can also improve episodic memory in dementia patients. Episodic memory involves the conscious recollection of personal experiences in an individual's life, including information on what, where, and when it happened (Pause, 2013). VR allows participants to engage in situations from a first-person point of view by observing actions as well as executing them. In the process, cortical excitability (strength of response of cortical neurons to stimulation) is modified and associated with activity changes in the hippocampus (Repetto, 2016). This boosts encoding and retrieval of episodic memory in individuals (Repetto, 2016). VR also facilitates active navigation through the virtual environments and enhances object recognition. As participants semantically execute actions related to the words, the enactment effect takes place (Repetto, 2016). The enactment effect occurs when memorization of information is enhanced as a result of physically acting out the information (Zhang, 2020). This feature, along with the fact that VR is three-dimensional, stimulates the hippocampus and improves memory recall and recognition in relation to locomotion. For these reasons, VR methods may potentially serve as effective preventative interventions for dementia in older adults.

In VR, most participants feel comfortable in a safe, immersive environment, improving their functional learning...

All in all, dementia is a serious problem that many of the elderly population face today, and it is only expected to worsen in the upcoming years. Although there is no cure for dementia, researchers are seeking methods to lessen memory impairment and VR may serve as an effective avenue. VR has not only been shown to improve high-fidelity LTM abilities, but also episodic memory recall and recognition in the elderly, making the technology worth further exploring to treat dementia. ❧

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The medical marvels of 3D printing

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Staff Writer

3D-printing, a technique which makes three-dimensional creations using computer models, is a technology we use in everyday life without even noticing. It has versatile applications ranging from constructing small-scale architectural models to printing clothes or constructing missing pieces of ancient artifacts. Recently, however, 3D-printing has become essential to the practice of modern medicine. It can be utilized to create models for surgeons to practice with, build personalized prosthetics for patients, and make organs from scratch. The applications of this technology are nearly limitless, especially in trauma and high-stress medical situations.

The basics of 3D-printing requires a series of steps, starting with the computer-aided design (CAD) model, to reach a final product. The CAD software takes cross-sections of the model, which are then sent to a machine. The file contains information on how much material is needed at various locations in order to recreate a digital image into a tangible object (Monroe Engineering 2020). The printer is then able to print the model, layer-by-layer, using the cross sections generated in the initial CAD scan (Campbell 2021).

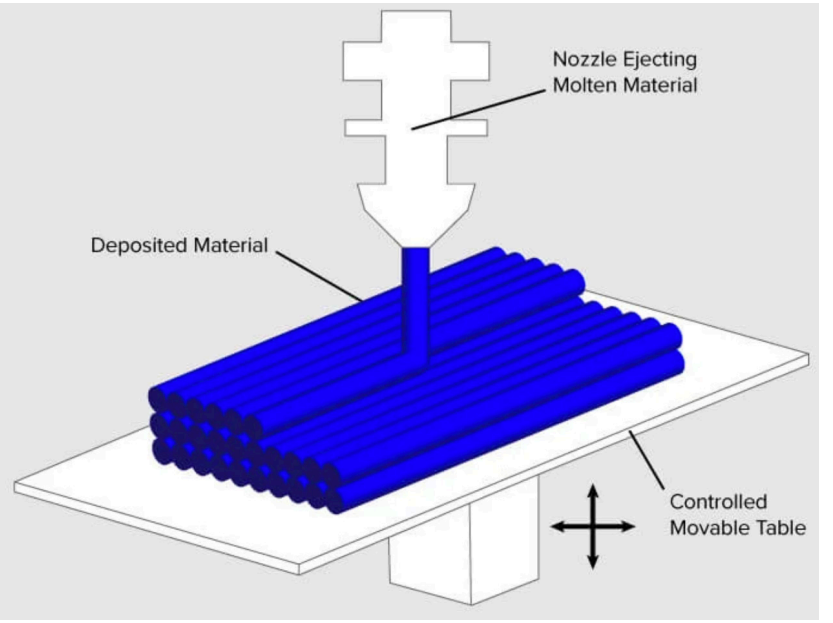

Figure 1. A basic depiction of the 3D Printing structure. Image from 3DPrinting.com

In clinical settings, physicians utilize 3D-printing to create models of organs and practice surgical procedures before conducting them on patients. Especially in high-risk surgery cases, a 3D-printed model would allow doctors to gain a better understanding of the surgical area without having to operate on the patient beforehand (Nawrat 2018). For example, neurosurgeons at Boston Children's Hospital printed a detailed human brain model to practice on before performing high-risk, life-saving surgeries (McCluskey 2015). At Texas Children Hospital, physicians created heart, lung, and kidney models of conjoined twins before successfully separating them (Hornicks 2016, Moulitch-Hou 2015). In general, 3D-printing will become essential to the future of medicine to help train future physicians in practicing complex procedures with low-cost materials, therefore decreasing the risk of complications (Lichtenberger 2018). Previously risky surgeries can see an increase in effectiveness and work environment safety.

...neurosurgeons at Boston Children's Hospital printed a detailed human brain model to practice on before performing high-risk, life-saving surgeries.

Another common use of 3D-printing in the medical field is to create custom prosthetics. With the help of 3D-printing, these prosthetics can be personalized to what the wearer wants - including specific colors, tattoos, materials they are comfortable with, and so much more. These customized prosthetics can be produced in a day, compared to a few weeks or months for traditional prosthetics, making them more cost and waste effective than buying mass-produced prosthetics (Dodziuk 2016). This is especially important for young children as they quickly outgrow their prosthetic limbs.

A special type of 3D-printing called Bioprinting can also be

used to create organs for patients. With Bioprinting, physicians use bioink - which is an ink created from specific cells and cell nutrients - to create organs layer-by-layer that function in a similar manner to those found within the body (Murphy et al 2014). These printed organs are useful in research when seeing how certain organs would potentially respond to novel environmental conditions or treatments (Nawrat 2018). This technology is currently being tested to become a cheaper and more reliable source of organs for organ donation. Though there have been only a few successful cases at the moment, doctors were able to 3D-print a bioresorbable airway splint to save the life of an infant with a collapsed airway (Zopf 2013).

Figure 2. The application of 3D Printing to body parts and systems. Image from OEM Update.

While bioprinting organs is a promising technique in the medical field, it is not the only novel application of 3D printing: another prominent use is to print medications. It is easy for researchers and physicians to create specific dosages of certain medicines or make personalized medications for their patients (Dodziuk 2016). 3D-printing can create highly specified structures and unique 3D molecule configurations that cannot be achieved manually (Hsiao 2017). This means pharmacists can create drugs of different unique structures, textures, and functions in a precise fashion.

As described, 3D-printing has many incredible and promising applications in the medical field as a whole, but the beneficial features of 3D-printing are highlighted especially in trauma and high-stress medical situations. In these environments, it is extremely helpful to have the ability to create specialized tools, prosthetics, and cellular tissue at a few seconds' notice. At the Walter Reed Army hospital, doctors were able to print titanium implants and replace the jaw of a woman who had seriously injured herself and couldn't move her face (3D Printing and the Future of Manufacturing 2012, Hornick 2016). In war-torn nations like in Sudan and Uganda, 3D printers are used to create low-cost prosthetics for injured individuals. In Sudan alone, 50,000 amputees were given 3D-printed prosthetic limbs (Heater 2014, Hornick 2016). In other complex medical cases, trauma surgeons create models of the patient before operating which helps them prepare treatment plans. Looking specifically at orthopedic trauma patients, surgeons who used a 3D-printed model beforehand to see the fracture and damage pattern had a deeper understanding of their patient's ailment than if they had not looked at the model (Kim et al 2018). A study done by physicians at Lok Nayak Hospital in New Delhi found

... the beneficial features of 3D-printing are highlighted especially in trauma and high-stress medical situations.

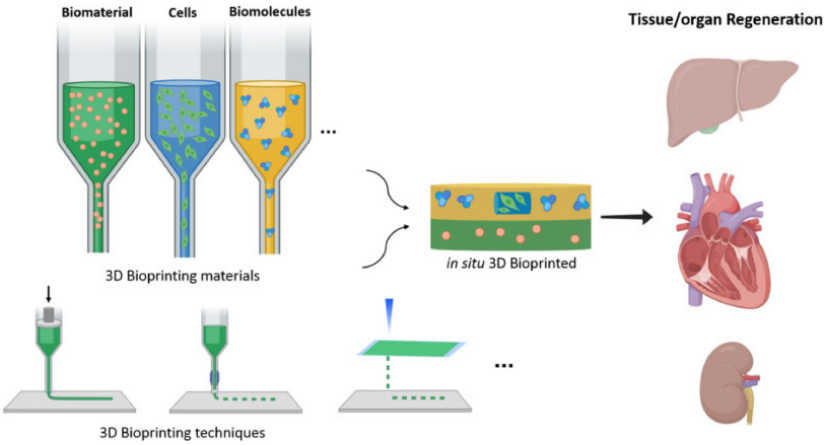

Figure 3. The construction process of 3D-printed organs for human use. Image from Vanaei et al. 2021.

that when surgeons used a model to study what was ailing their patient in trauma cases, they felt more confident operating during and after the surgery. They also reduced the time their procedures took and generally had better outcomes (Mishra 2019). Overall, 3D printing helps improve patient care and increases the doctors' understanding of the medical ailment in front of them.

3D printing has many different uses in the medical field that improve the quality of care patients receive and helps the physicians better aid their patients, especially in high stress situations. While the mechanism used to create 3D printed objects is relatively simple, it has many different uses throughout the medical field. These versatile usages will only continue to expand with time, going beyond the horizon of what we imagine possible now. ❧

AUTHOR BIO

Uma is a second year majoring in Biology. Her interests are in cell-cell interactions and their impact on overall body function. She hopes to use her knowledge to help people feel better and to ease their pain.

Edited by Anu Dhanashekar, Luisa Taverna, and Dr. Muhammad Azeem

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A bias more than skin deep: The neurology of implicit racial bias

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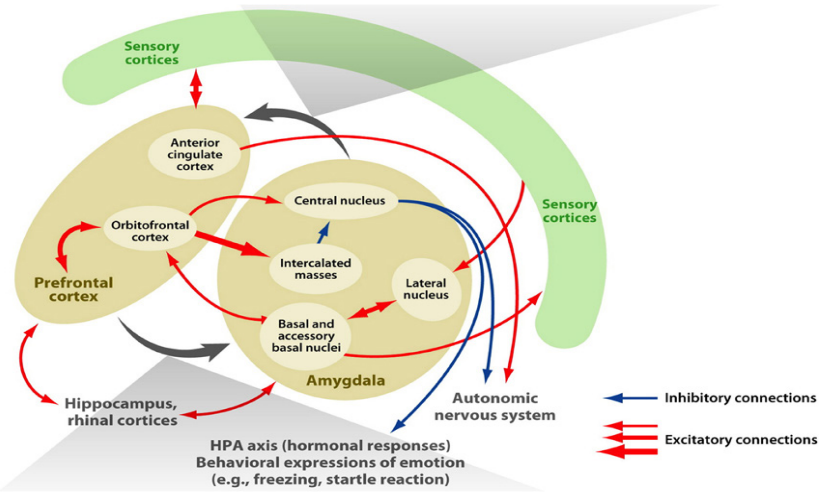

Figure 1. Diagram of Amygdala. The amygdala interacts with different parts of the brain to generate emotional responses to stimuli and create memories of emotional experiences. Image from Chekroud et al. 2014.

Recently, discussions surrounding racism have become more prevalent than ever. In a country considered to be built on slavery, inequity, and systemic structures of oppression, racism in America is an issue that permeates every aspect of modern society. However, racism is more than just prejudice against skin color. Instead, it can be viewed as a deep-rooted societal mindset that can be detected in neural pathways. Research shows that implicit biases about race correlate with neural activity in the amygdala, an area of the brain involved in modified mild threat responses to particular stimuli. When these stimuli relate to race, the responses underlie implicit bias. Therefore by studying these pathways, researchers can uncover the relationship between neural mechanisms in the amygdala and implicit racial bias. While the amygdala itself does not generate racist thoughts per se, understanding its role in reaction processing can allow us to discover better behavioral and environmental solutions for implicit racism. Although racist behavior can sometimes be performed subconsciously, research suggests that such racial prejudice can be unlearned and prevented through childhood exposure to racial diversity and other behavioral solutions.

Research shows that implicit biases about race correlate with neural activity in the amygdala ...

The amygdala is central to the "nonconscious processing of stimuli that have an acquired emotional significance based on previous experience" (Telzer et al., 2012). In other words, it is the portion of the brain responsible for generating emotional responses and memories, and it plays a role in learned and innate fears. Given its functionality concerning emotional recall and environmental sensitivity, the amygdala plays a role in both explicit (conscious) and implicit (subconscious) biases. Implicit bias is a bias that one has towards specific ideas or objects without recognizing it. It may be caused by past experiences or even subconsciously internalized social norms. When considering the role of implicit bias regarding race, many studies have found that "racial outgroups," or races that do not align with the race that a subject identifies with, are associated with feelings of hostility and untrustworthiness (Telzer et al., 2012). These feelings are implicit emotional responses that can be linked back to the amygdala. This type of response is known as the "universal outgroup stereotype," which describes an emotional response activated by the amygdala where individuals tend to feel hostility and distrust toward people who don't share traits.

During the past two decades, extensive research on the amygdala has been conducted to better understand its role in learned implicit bias. In one study, Phelps et al. (2000) discovered a significant activation of the amygdala in white American subjects when asked to view

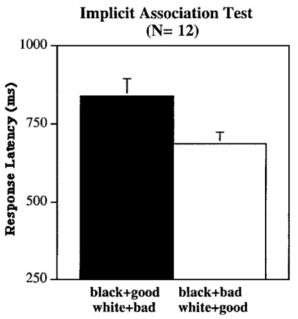

Figure 2. Results from IAT test. Slower response times define greater implicit racial bias. Image from Phelps et al., 2000.

black versus white faces, and this activation was then correlated with implicit measures of racial evaluation. Participants were asked to participate in an Implicit Association Test (IAT), which measured subconscious biases, as well as the Modern Racism Test (MRT), which measured conscious biases. Results from the IAT showed widespread anti-black bias amongst participants, whereas the MRT actually revealed conscious "pro-black" behavior. It is important to note that the sample size in this study was on the smaller side with 12 participants, so a follow-up with a larger sample size would be required to confirm the accuracy of these results. This data indicates that amygdala and behavioral responses to race in white subjects reflect cultural evaluations of race and individual experiences that modify these beliefs. The discrepancy between implicit and reported explicit racial bias in white American subjects provides evidence that implicit racism is likely more widespread than conscious racism. Admittedly, trying to identify the implicit racial motivations that are by definition unconscious seems like an impossible task. However, although certain behaviors may be motivated by biases that were developed unconsciously, the behaviors themselves are actions that can be consciously addressed.

While previous research has focused on the neuroscience behind prejudices between white and black Americans, more recent studies have aimed to examine the intergroup prejudices between other races that have not been as thoroughly researched. In 2019, a study was conducted to compare the racial responses to visual images associated with Japan and South Korea (Izuma et al., 2019). The study consisted of 70 Japanese students, aged 18-22. Subjects were placed in an fMRI to measure the reaction of their amygdala when the subjects were presented with images pertinent to their own nation, Japan (Japanese citizens, flags, etc.) compared to ones pertinent to another nation, South Korea. The subjects were then presented four behavioral tasks, including a trust game, two single-category implicit association tests (SC-IAT) which compared implicit biases towards Japan relative to South Korea, and finally an explicit measure of bias towards Japan and South Korea. Overall, the behavioral tests reflected more positive attitudes associated with Japan and negative ones associated with South Korea. After performing an analysis on the fMRI brain scans, it was inferred that neural activity in the left amygdala indicated an implicit bias

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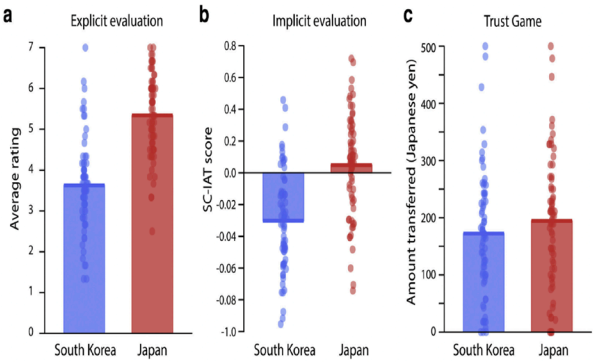

Figure 3. Results of behavioral tasks. Higher scores reflect more positive implicit attitudes towards respective racial groups. Average scores for Japanese racial groups were higher than for South Korean racial groups. Image from Izuma et al. 2019.

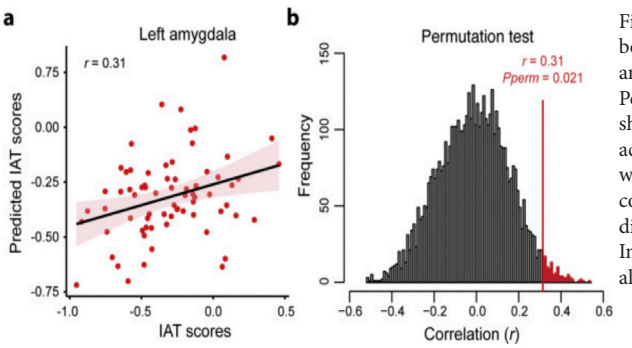

Figure 4. Correlation between implicit bias and amygdala activity. Positive correlation shows that amygdala activity was associated with implicit bias and could be used to predict bias scores in IAT. Image from Izuma et al. 2019.

towards South Korea. This neural activity was found to also predict implicit measures of bias in the behavioral tests. The correlation between the behavioral tests and neural activity in the left amygdala gave evidence that amygdala activity could predict racial biases. In particular, this study suggests that responses in the amygdala correlate with hostile and distrustful racial perceptions. The study emphasized that this racial hostility was likely fueled by more than just skin color- it also stemmed from cultural and political animosity between the two nationalities. From examining the relationship between implicit bias in the amygdala and hostile sentiments towards racial outgroups, it is clear that the amygdala contributes to biases that extend beyond a concept of skin color and include hostilities fueled by political and cultural tensions.

Such racial biases do not simply appear in adulthood. Rather, they are typically formed during early adolescence due to external influences. The amygdala plays a central role in the early learning and processing of socially constructed systems of hierarchy and social groups, such as race. A study by Telzer et al. (2012) compared amygdala reactivity towards African-American and European-American faces in children ranging from 4-16 years. Results showed that amygdala activity was largely equal towards the two facial groups until age 14, at which point amygdalic activity was greater in the presence of images of African American faces. These results suggest that while objective awareness of racial differences emerges well before adolescence, the ability to analyze and assess these differences with bias (as assessed through responses in the amygdala) does not emerge until adolescence, although it would be useful to test the generality of this conclusion with other paradigms. Furthermore, the study found that greater peer and neighborhood diversity was associated with lower levels of right amygdala response to African American faces. Because amygdala activity is a reflection of racial bias, these results suggest that a more diverse childhood environment could help decrease implicit racial bias. Living in a diverse environment may essentially dampen the reactivity of the amygdala towards different races by acclimating the amygdala to a variety of racial groups. So, while implicit racial bias may largely evolve during adolescence, there are environmental mechanisms that can be implemented to prevent these implicit biases from developing.

...these results suggest that a more diverse childhood environment could help decrease implicit racial bias.

Just as stereotypes and biased behaviors are typically learned during childhood they can also be actively unlearned to promote an unprejudiced mindset. Richeson and Nussbaum. (2004) found that a multiculturalist approach to anti-racism was more successful at promoting racially unbiased attitudes than was a color-blind approach. These claims parallel the findings of a brain imaging study of race in children. Cloutier et al. (2014) measured neuroimaging responses in the amygdala in children to pictures of faces that varied independently in both race (Black, White) and in their familiarity (familiar, unfamiliar). The results showed that although there was no significant individual effect of race or familiarity in either the right or left amygdala, a combined condition of race and familiarity was associated with strong activity in the left amygdala. The presence of a significant response only at the intersection between familiarity and race suggests that increasing racial familiarity at a young age

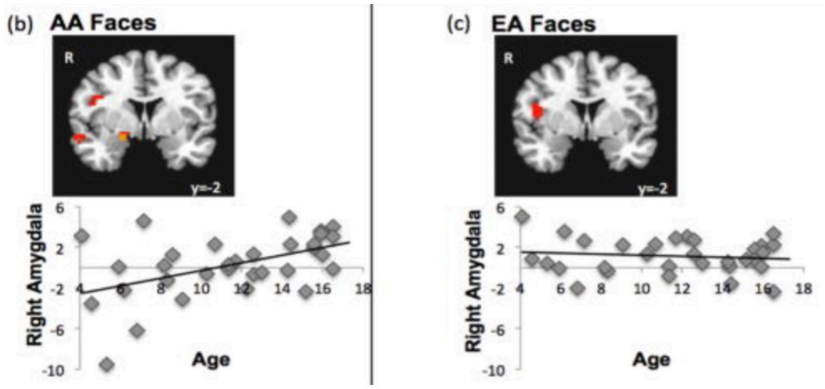

Figure 5. fMRI scans show right amygdala activity in response to images of African American faces (AA) vs. European American faces (EA) as a function of age. Graph B shows an increase in neural activity towards AA faces as age increases, whereas amygdala activity towards EA faces shown in Graph C is largely constant regardless of age. (Graph A from the original is omitted here.) Image from Telzer et al. 2012.

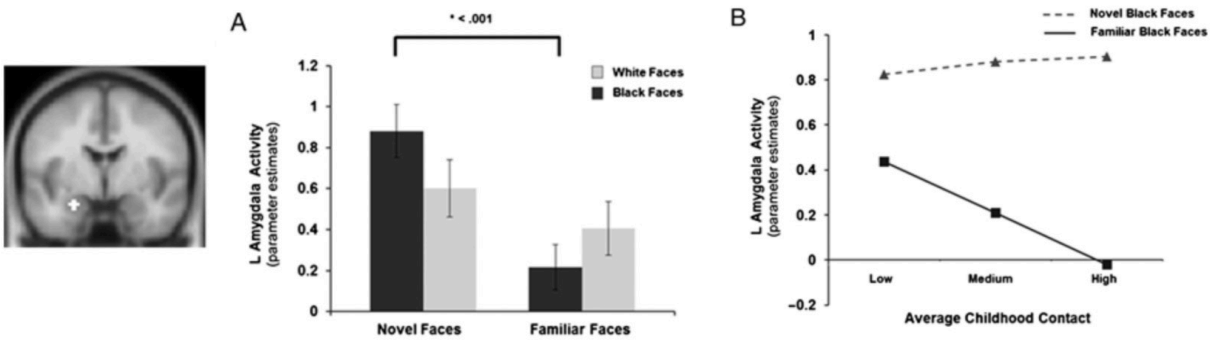

Figure 6. fMRI of the amygdala demonstrating that identification of differences begins in pre-adolescence and that associated bias begins in adolescence in the absence of familiarity. Image from Cloutier et al. 2014.

can combat the formation of implicit biases during childhood.

Implicit racial bias is likely even more pervasive than conscious racial bias, especially in the United States. While explicit, conscious bias is easier to detect and prevent, implicit bias may be much more challenging to control given its unconscious nature. Even examining the correlation between neural activity in the amygdala and implicit racial bias has its limitations–while studying the amygdala can aid in detecting implicit bias, it does not provide insight into the causal mechanisms of such bias. However, even these unconscious biases may be prevented from developing. As discussed above, diverse childhood environments are associated with less neural activity in the amygdala, which is associated with lower levels of racial hostility. These findings on the amygdala emphasize the need for a largely environmental remedy to implicit racism, particularly by addressing racial bias in a systematic manner and fostering diverse, accepting communities where racial, ethnic, and cultural differences are encouraged rather than hidden. Of course, the implementation of this solution is easier said than done and requires a population-wide effort to combat both the sources and effects of implicit racial bias. It is imperative that we as a society promote recognition of racial differences and inequity in academic, professional, and social spaces and improve teacher and student diversity in the classroom to unlearn and prevent the implicit racial bias often endemic to our society and minds. ❧

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Claire is a first year majoring in Neuroscience and Behavioral Biology and minoring in Spanish. Her intersts are in gene therapy and immunotherapy, especially pertaining to food allergies and cancer research.

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First surgery before first breath

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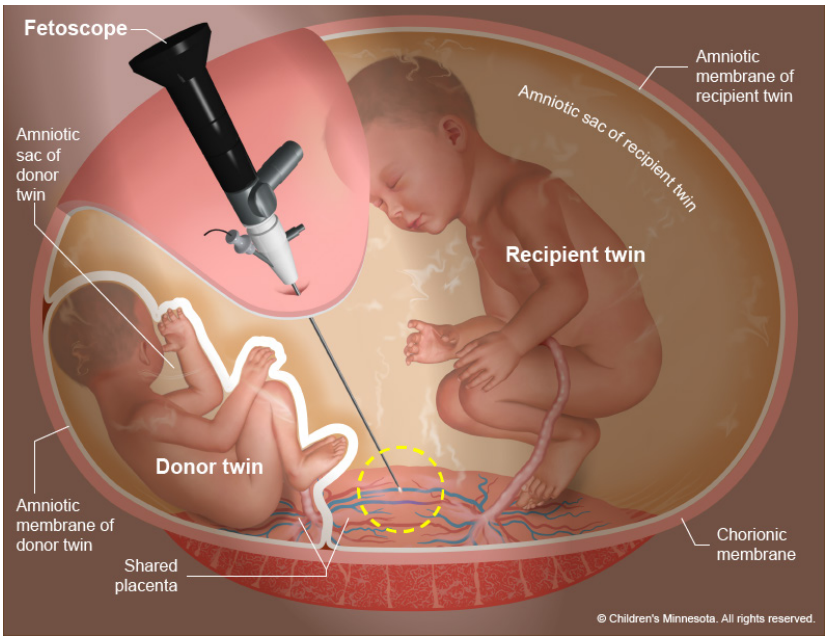

Figure 1. This diagram depicts how TTTS can occur. This case is between twins, which is the most common form of TTTS. The twins share a placenta which provides them with their nutrients and blood flow. The larger twin has greater access to the blood flow of the placenta. This is evident in the larger area of the placenta its amniotic sac occupies. The smaller twin has restricted access to the blood flow of the placenta and is thus deprived of nutrients. Image from Children's Minnesota Hospital 2021.

Surgery dates to 5000 years ago – when ancient peoples practiced "trephining," a procedure of cutting small holes into the skull to "release evil spirits" (Clunie, 2020). Though separated by thousands of years, archaic surgeries and most complex modern ones share a common purpose: treating patients after birth. However, there has been a recent focus on fetal surgery, extending the realm of surgery into the womb, aiming to work with natural fetal processes to correct abnormalities before the baby is born.

Fetal surgery is useful to correct several fetal deformities, such as Twin-to-Twin Transfusion Syndrome (TTTS). Twin-to-Twin Transfusion Syndrome is a rare pregnancy condition in which a set of twins (or multiple fetuses) share a singular placenta, resulting in one fetus receiving more blood than the other(s) and thereby increasing the risks of malnourishment and organ failure in the donor twin (Twin-to-Twin Transfusion Syndrome (Ttts), 2021). This syndrome is characterized by the presence of placental anastomoses, cross-connections between adjacent blood vessels, which results in the development of an unbalanced chronic blood transfer between the two fetuses (Baschat et al., 2011).

...TTTS can be deadly for both mother and fetus, especially considering the only treatment available is invasive.

On the other hand, the recipient twin receives too much blood and is susceptible to overworking its delicate cardiovascular system. TTTS occurs in about 1 out of 2000 pregnancies, typically between weeks 15-25 (Baschat et al., 2011). TTTS is deadly if left undiagnosed or untreated, with high perinatal and morbidity rates due to obstetric complications. In addition to profound cardiovascular consequences such hypervolemia (too much blood) or hypovolemia (too little blood), which can respectively exhaust or deprive the developing heart to cardiac failure, TTTS can also cause several physiological deficits: an underdeveloped fetal renal system, cerebral palsy, and other associated neurological conditions due to compression in the womb on the donor twin from uneven growth (Twin to Twin Transfusion Syndrome - Risks, 2021). In short, TTTS can be deadly for both mother and fetus, especially considering the only treatment available is invasive. The donor twin TTTS is diagnosed through serial ultrasounds done in a 2-week period and is confirmed by the detection of hydramnios or excess amniotic fluid through a system called Quintero-staging that uses levels of amniotic fluid

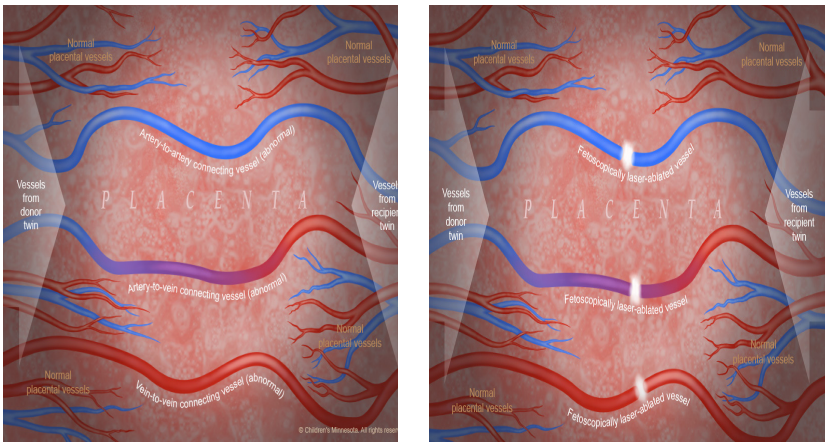

Figure 2. Left diagram shows how blood vessels are misconnected in cases of TTTS. These mislinks create the uneven flow of blood between the fetuses. The right diagram shows the same blood vessels after being subjected to Fetoscopic Laser Ablation. This gets rid of the misconnected vessels and allows for more even blood flow. Image from Children's Minnesota Hospital 2021.

and hemodynamic changes to determine the ratio of placental blood flow.

To treat TTTS, obstetric surgeons perform fetal surgery by using a fetoscopic laser to correct the blood flow in the placenta by operating on the fetuses in utero, coagulating the abnormal placental vasculature with a laser and then resewing tissues to keep the twins in utero (Torrents-Barrera, 2019). The first trials of Fetal Surgery took place on sheep and primates in the 1940s, with the desire to determine a surgical procedure which would allow safe access to the amniotic cavity (Depreset et al., 2010). As surgeons became more confident in this practice through controversial and repeated trials on animals, they began performing surgeries in human fetuses, beginning in 1981. The goal of this surgery was to place a shunt in the urethra of fetuses with Lower Urinary Tract Obstructions (Depreset et al., 2010). Despite the initial enthusiasm, this surgery failed to prove successful and practicing fetal surgeons established ethical guidelines for what conditions could be treated. TTTS was included on that list, despite the location of the placenta being abnormal and lacking effective animal models for this condition. Dr. Julian De Lia suggested a method to coagulate placental anastomoses in a central location where both fetuses can get an adequate supply of blood using hysteroscope. This method proved to be extremely successful; 87% of children treated under this method had normal neurodevelopment, there was a 25% increase in survival, and delivery time increased to 33 weeks vs. the average of 29 weeks for an untreated TTTS delivery. Newer fetal surgical methods such as Serial Amnioreduction and Fetoscopic Laser Ablation improve upon this technique. Fetoscopic Laser Ablation allows lasering anastomoses from the donor to the recipient twin with more precision as to directing blood flow while Serial Amnioreduction involves siphoning off excess amniotic fluid in a relatively non-invasive way. These surgeries offer significantly higher survival rates of 18-83% and 55-69%, respectively.

These surgeries offer significantly higher survival rates of 18-83% and 55-69% respectively.

The large impacts of fetal surgery are paralleled by the ethical issues that originate from its use. Fetal Surgery has the ability to save fetuses that would otherwise be terminated for medical reasons and could substantiate the view that fetuses can be considered people. The concept of fetal personhood embraces this stance: "an unborn child...as [a] human being, specifically including an unborn child in utero at any stage of development, regardless of viability" (Chatman, 2019). On the other hand, there still exist numerous statistics and qualifications from scientific research that may suggest otherwise, including the classification of personhood. Even within the concept of fetal personhood there are differing opinions as to when a fetus moves from being classified as a mass of cells to a living breathing person, with the recommended gestational period being at 26 weeks (Lincare, 2017).

With fetal surgery becoming increasingly accessible and advanced, surgical intervention before birth may become the new normal. Teratology, a branch of embryology which focuses on malformed fetuses, aims to "formulate new laws that would permit this recent science to compete with nature, perhaps to surpass it as well" (Casper, 1996). The emergence of elective fetal surgery will raise pertinent ethical questions: If the surgery doesn't focus on simply saving

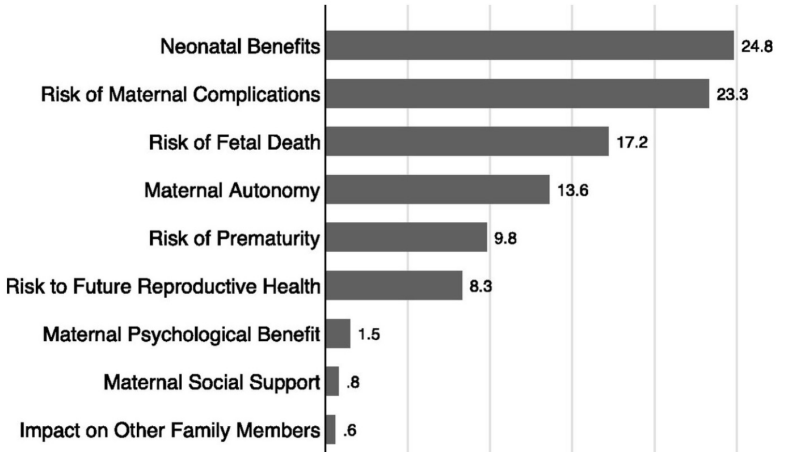

Figure 3. Top Social and Ethical Concerns regarding Fetal Surgery according to Physicians. Image from Antiel et al. 2017.

the life of an unborn child due to complications, where does one draw the line? Are procedures to correct severe congenital defects acceptable? What about mild congenital defects or elective cosmetic procedures? When answering these questions, it is important to reflect on how being differently abled is viewed in the 21st century and whether allowing elective procedures is promoting ableism. Putting at risk a mother's life (and inherently the life of the fetus as well) for avoidable medical procedures begs the question whether the perceived benefits are worth the risk.

...is optional surgery an infringement of autonomy or medical paternalism?

Another pertinent issue raised is the relation between women's autonomous medical decision-making and fetal surgery. There is much debate regarding whether women should be the sole party responsible for deciding treatment plans or should clinicians hypothetically be allowed to engage in paternalism to regulate what level of risk is acceptable, to both the fetus and the mother (Casper, 1996).

Being a relatively new field, fetal surgery has evolved rapidly throughout the years, as a staggering 3% of all babies worldwide are born with birth defects. Currently, fetoscopic laser treatments are the preferred treatment but due to the invasive nature of the procedure and the numerous complications, the search is on for safer and more efficient treatments. Non-invasive treatments are on the horizon with High-Intensity Focused Sound, often used to kill prostate cancer cells, being repurposed to use the highly focused ultrasound to block blood supply in treating TTTS. Developing an MRI-based placental mapping, or other technological advances, may be crucial to mapping vascular anastomoses, resulting in the more accurate severing of vessels (Bamberg & Hecher, 2019).

While these important advances are paving the path to minimally invasive TTTS treatments with better survival rates, the field still heavily relies on invasive procedures. Fetal surgery, while still in the works, is one of the most promising solutions to save lives. The social and political stressors are sure to impact the field, both in terms of research and in practice, in ways that cannot be foretold. Yet the discord that exists shouldn't dissuade physicians from advancing the field. Without these advancements many cases will be left untreated, many will be diagnosed too late, and many will succumb to their first surgery before they draw their first breath. ❧

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EUMR's main advisor is Dr. Michael Crutcher, one of the many distinguished faculty members in Emory's Neuroscience and Behavioral Biology Department. Having received his PhD in Physiology from Johns Hopkins University, he joined the Department of Neurology and of the Neuroscience Ph.D. program at Emory in 1991. His research is primarily focused on the neural mechanisms of visually guided reaching movements in monkeys.

Dr. Crutcher has taught many NBB courses over the years such as: freshman seminar courses (NBB 190) on Brain Enhancement, Curiosities of Neurology and Neuroscience, and Neuroethics as well as Perspectives in Neuroscience and Behavioral Biology (NBB 401 SWR), Biology of Movement Control (NBB 370), Neuroscience Research Methods (NBB 221), Functional Neuroanatomy (NBB 470), and Topics in Neuroscience and Behavioral Biology (NBB 270).

Emory Undergraduate Medical Review articles are peer-reviewed by medical professionals from more than a dozen leading academic institutions. The Emory Undergradute Medical Review would like to extend its thanks to the following advisors.

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Dr. Eisen is a professor of pedagogy at the Center for Ethics at Emory University. He 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 and continues to be involved in many projects at Emory.

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Anjanay is a third year majoring in Chemistry and co-majoring in Quantitative Sciences. He originally joined EUMR as a first-year liaison and organized the first Data Science Symposium with the School of Nursing. As Editor in Chief for copy, he spearheads the editorial process and communicating with the Advisory Board. He has survived the pandemic by learning how to cook and catching up on his favorite movies and shows.

RICHARD LEE

Editor in Chief - Layout

Richard is a third year majoring in Biology and minoring in English. He joined EUMR as a contributing writer and became involved with the Events team in his last two years. As Editor in Chief for layout, he leads the creation of the semesterly journal along with the layout editors. Outside of the organization, Richard conducts research at Winship Cancer Institute, swims for Emory Club Swimming, and enjoys playing both classical and acoustic guitar.

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Ganesh is a third year majoring in Neuroscience and Behavioral Biology with a minor in South Asian Studies. He began EUMR as a contributing writer and now has served as treasurer for two years, working on budgeting for all operations and the club's dealings with SGS. Outside of EUMR, he is also involved in Emory Synapse and works as a student ambassador for prospective/incoming students. In his free time, Ganesh loves listening to music of all genres and later composing them into pop sonnets.

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Josie is a second year majoring in Human Health. She first joined EUMR as a contributing writer for Open Access and now as secretary, is involved in facilitating communication across EUMR, planning events, and leading social media initiatives to further the organization's presence across campus. Outside of EUMR, she's also involved in Emory Planned Parenthood and Emory Red Light. In her free time, she enjoys spending quality time with friends and family, visiting the beach, and getting creative with art, baking, and yoga.

NATHAN JACOB

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Nathan is a fourth year majoring in Biology with a minor in Philosophy. He began as first-year liaison, went on to serve as the club secretary, and as editor in chief - copy last year. Outside of EUMR, he is also involved in organizations such as club tennis and is a pre-health peer mentor. Nathan was an extra in Spider-Man Homecoming and you can actually see a blurry image of him during the first ten minutes of the movie!

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Daisy is a fourth year majoring in Anthropology & Human Biology and co-majoring in Integrated Visual Arts. She originally joined EUMR as a first-year liaison and organized the first Suture Lab with the Emory School of Medicine, eventually going on to serve as editor-in-chief for two years. Daisy's main goal is to continue expanding EUMR's presence and reach across campus. That aside, there is nothing she loves more than a day with no agenda spent on all sorts of creative endeavors.

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