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Cover photo by Daisy Li

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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,

If all goes well, this might be the last issue to be fully produced and published in the midst of a global pandemic. We can't quite say we'll miss the experience, but it has certainly made our college days, in a word, interesting.

On the subject of lasts, this is also the last semester that we will be serving as co-editors in chief of EUMR, so we'll keep this short and sweet. What an honor it has been to usher, between the two of us, four issues of the journal from inception to completion in the last two years.

Many thanks are in order: to our lovely executive board for all the behind the scenes work; to the writers and editors of the editorial board who, despite all odds, stuck to deadlines and showed up to yet another Zoom meeting; and to our advisory board, who, per usual, gave excellent advice and guidance.

To all our graduating seniors, congratulations! We'll miss you. And to everyone else, we are eager to see you, maybe for the first time, in the fall.

To the new executive board, we confidently pass the torch to you. We know you will achieve great things throughout your tenure, and we'll always be available for all the questions you may have.

We wish everyone a happy, normal summer. Speak soon.

Cordially,

Daisy Li & Nathan Jacob
Editors-in-Chief
EUMR 2020-2021

Steroid injections to treat osteoarthritis: Good or bad?

GANESH CHILUKURI
Staff Writer

Osteoarthritis is the most common form of arthritis, affecting more than 330 million people worldwide, many of whom are over 60 years of age (CDC, 2020). This chronic condition is associated with substantial morbidity risks, including disability, reduced quality of life, and death (Nelson, 2018). Furthermore, only a few effective treatment strategies have been developed in response to this disease, and even these treatments are subject to scrutiny based on patient feedback. Fortunately, steroid injections have arisen as a popular treatment method for osteoarthritis, but even so, certain limitations exist that hinder the effectiveness of corticosteroids in reducing inflammation and relieving pain.

Previously thought of as a "wear and tear" disease, osteoarthritis actually involves a complex process that causes the destruction of a joint's articular cartilage and leads to subsequent inflammation. Articular cartilage is the smooth cartilaginous tissue at the end of long bones and between intervertebral disks that provides a low friction surface for effective motility (Mandl, 2018). The breakdown of a joint's cartilage leads to bone rubbing and pain. Inflammation further aggravates the progression of osteoarthritis. Specifically, two types of inflammation— active synovitis and systemic inflammation— play key roles in exacerbating the pathogenesis of osteoarthritis. First, degraded cartilage may induce a foreign-body reaction within synovial cells, leading to an immune response which causes further cartilage destruction. Moreover, systemic factors such as obesity, atherosclerosis, imbalance of endocrine hormones, and aging contribute to the prevalence and development of osteoarthritis (Abramoff & Caldera, 2019).

Inflammation further aggravates the progression of osteoarthritis.

Arthritic symptoms can range from mild discomfort and difficulty functioning to debilitating chronic pain that requires orthopedic surgery. The condition is most prevalent in individuals who are older than 45 years of age. The United States has the greatest proportion of individuals with arthritis with over 54 million diagnosed patients total

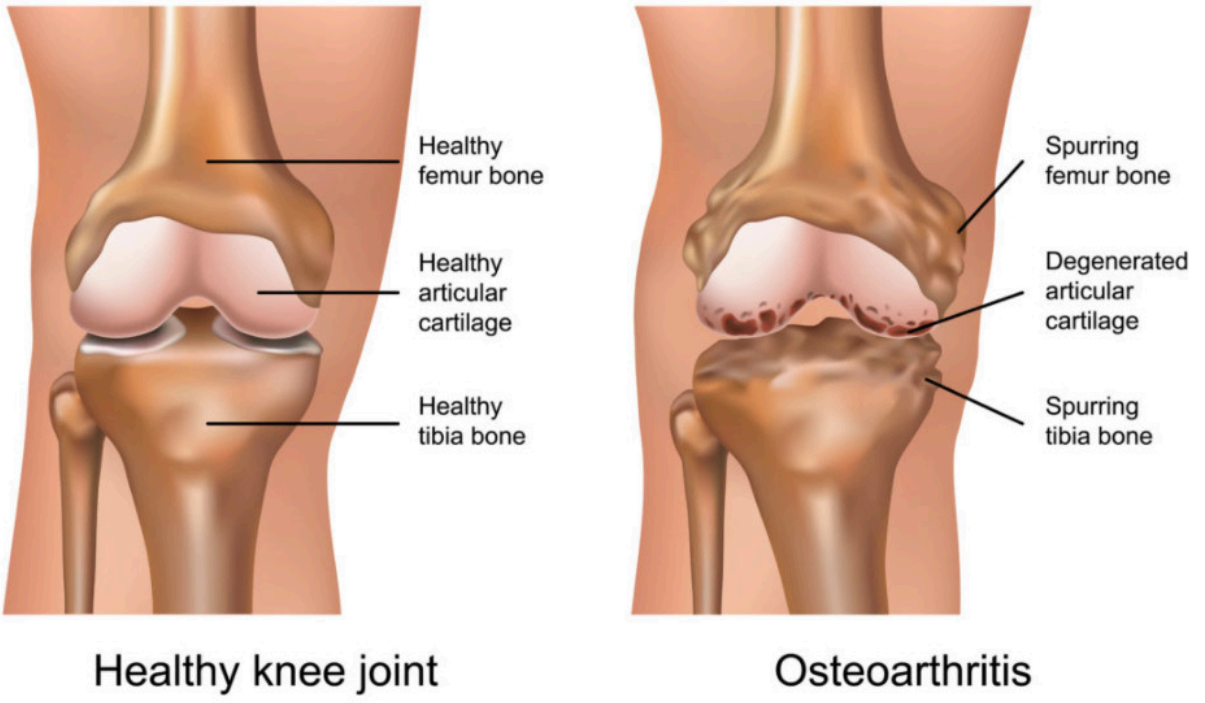

Figure 1. This figure shows the pathogenic visual of an osteoarthritic knee joint compared to a healthy knee. Image from Flannery 2018.

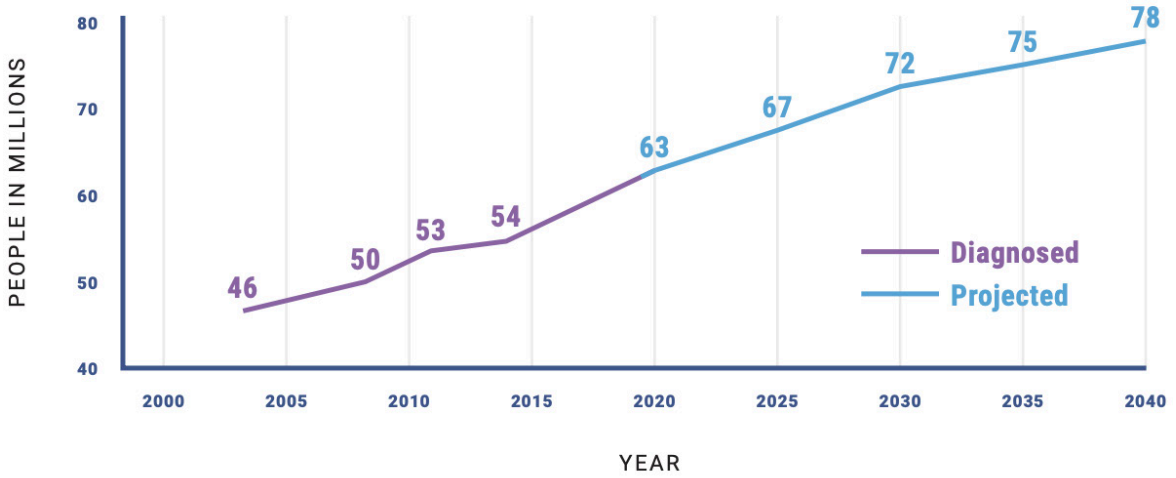

Figure 2. This figure shows a graph representing the number of individuals historically diagnosed and projected to be diagnosed with arthritis. Image from Osteoarthritis Action Alliance 2019.

(CDC, 2020). More than half of the US's patient population with arthritis is diagnosed with osteoarthritis as well, making it the most common form of arthritis (OAAA, 2019). The prevalence of arthritis has been gradually increasing in the US over the past three decades, and research predicts that the diagnosis of arthritis, specifically osteoarthritis, will continue to escalate in the coming years. As such, finding effective treatments for osteoarthritis is a pressing issue for the medical community.

Interestingly, physicians still lack compelling evidence that corticosteroids provide long-term pain relief and inflammation reduction.

The most permanent solution for osteoarthritis is joint replacement surgery, which is an expensive and invasive treatment option. Usually, this surgery serves as a last-resort treatment for patients experiencing unbearable pain. As such, most physicians and patients prefer other treatment options that manage osteoarthritis rather than cure it. Among the most common treatment options for people with osteoarthritis are exercise and medication therapies (Nelson, 2017). Medication therapy involves the use of nonsteroidal anti-inflammatory drugs, which primarily work to resolve musculoskeletal pain but do not necessarily provide a cure for the pathophysiology. Alternatively, exercise helps strengthen the muscles and bones near the diseased joint, helping to slow the progression of the disease and alleviate pain (Selten et al., 2020).

Over the past two decades, physicians have begun to implement intra-articular corticosteroid therapy as another alternative method for treating osteoarthritis (Zhong et al., 2020). Corticosteroids are powerful drugs that relieve joint pain by reducing the inflammation in and around the joint (Schmerling, 2019). Cortisone, which is a synthetic cortisol-related hormone, is the most popular corticosteroid used to treat osteoarthritis. During a cortisone injection procedure, the physician inserts a needle into the inflamed joint using ultrasound or x-ray fluoroscopy for guidance. Once the needle is in place, the physician releases the medication into the joint. Usually, the shot includes the corticosteroid to relieve pain and inflammation over time, as well as an anesthetic to induce immediate relief (Torborg, 2019). The cortisone medication starts to fight the inflammation in the joint quickly, and patients achieve pain relief within three to five days.

While corticosteroid injections are a relatively novel treatment option, they have quickly grown in popularity. Nonetheless, the positives and negatives of corticosteroids are controversial among researchers, physicians, and patients alike. It is important to note that cortisone injections can provide pain relief, which is why physicians recommend steroid therapy for osteoarthritis patients; however, the length and degree of pain

relief vary drastically between patients (Shmerling, 2019). Interestingly, physicians still lack compelling evidence that corticosteroids provide long-term pain relief and inflammation reduction. While some patients receive significant relief for three to four months (which indicates that corticosteroid therapy may be ideal for them), other patients only receive pain relief for a few weeks. Every time the pain returns, the patient is urged to receive another injection which entails higher medical costs and repeated risk of side effects including increased stress and allergic reactions (Bennell & Hunter, 2012). Furthermore, as time goes on, the body's responses to the steroids are lessened, which means that larger doses of steroids are required for treating the pain. Most patients require several corticosteroid injections per year for prolonged pain relief since the efficacy is limited and short-lived in the majority of cases.

Furthermore, corticosteroids function to reduce pain by lessening inflammation around the joint that is specifically caused by synovial cells; thus, this inhibits the immune system's complications in the joint (Nelson, 2017). As such, corticosteroids provide a positive treatment outcome for the vast majority of patients with osteoarthritis but not all. A recent study found that, "about 7% to 8% of people getting steroid injections seem to worsen, with their arthritis accelerating beyond the expected rate" (Kompel et al., 2019). In fact, another two-year patient study found that, "the anti-inflammatory effects of steroids, at least in the short-term, are not operating as a disease-modifying agent" because they enhanced cartilage destruction in a few patients (Mandl, 2018). Most physician consent forms include this serious risk, but the effects are often downplayed or ignored due to the patient's desire for rapid pain relief.

Given the rising popularity of intra-articular corticosteroid injections, physicians and patients must be fully informed of the benefits and risks.

Other side effects of intra-articular corticosteroid injections also exist, but the most drastic side effect (besides a rare fatal reaction) is known as a cortisone flare. A cortisone flare describes intense pain that centers around

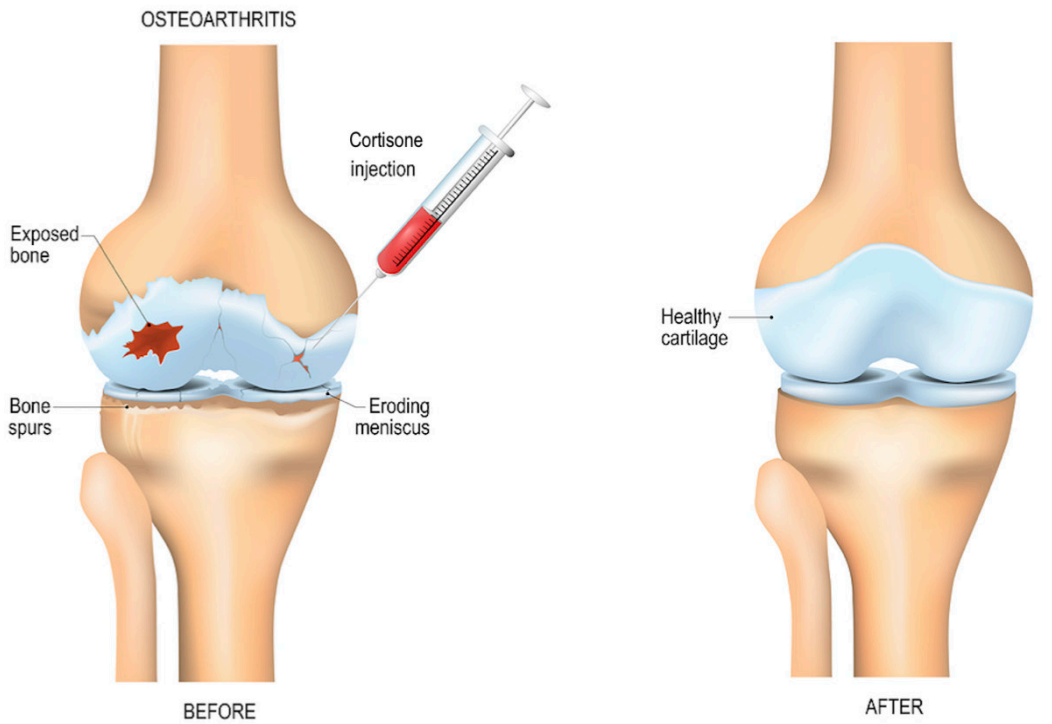

Figure 3. This figure illustrates the injection of a corticosteroid into an arthritis knee joint to facilitate the alleviation of inflammation and pain. Image from Schilling 2019.

the joint within 48 hours of a steroid injection. The pain can range from mild annoyance to seriously debilitating pain that requires hospitalization and powerful pain medications. The pain occurs due to the injected steroid forming crystals around the joint (i.e. crystalline synovitis), which elicits a foreign-invader reaction from the immune system and causes even more inflammation (Mayo Clinic, 2020). Fortunately, cortisone flare reactions are almost always short-lived. The patient may use medications to cope, but the pain subsides by itself within a few days, especially after the corticosteroid starts to have its intended effects of reducing inflammation and alleviating pain.

Given the rising popularity of intra-articular corticosteroid injections, physicians and patients must be fully informed of the benefits and risks. Health care providers and prospective patients should acknowledge three questions before deciding to participate in corticosteroid therapy. One, is the patient fully aware of the risks? Two, does the patient know that steroid therapy may or may not effectively treat osteoarthritis? And three, are the physicians and patients physically and mentally equipped to handle the corticosteroids and the potential side effects during each cycle of injection? Answering these questions will provide a basic foundation for patient safety and physician responsibility, which will greatly enhance "the standard of care" of osteoarthritis. ❧

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The mystery within our blood

NIKI PATEL
Staff Writer

One of our most basic forms of immunity can be found flowing through our arteries, veins, and capillaries, locked onto the surface of our blood cells: our blood type antigens. The International Society of Blood Transfusion currently recognizes 33 blood group systems, including the more popularly known ABO (ie. Type A, B, AB, or O) and Rhesus (Rh) systems (ie. + or - signifiers) (Mitra, 2014). The variations seen in blood types (eg. A+, A-, B+, etc.) likely offer selective evolutionary advantages in a given population, one of which is the protection conferred by ABO blood group antigens against diseases caused by bacteria, parasites, and viruses. Specifically, the association between an individual's ABO blood group and his/her susceptibility for more severe *E. coli*, malaria, and SARS-Cov-2 infections is an interesting relationship to explore, and one that probes into one of the most fundamental building blocks of life.

The ABO blood system antigens are composed of glycoproteins (polypeptide chains associated with carbohydrate molecules) attached to the external surface of red blood cells, and these antigens play a key role in the identification of foreign molecules and the mediation of the body's response to particular infectious diseases (Dean, 2005). Only individuals with the blood types A, B, or AB have these specific sugar attachments on the surface of their red blood cells. Type O blood carriers do not produce a type "O" antigen; however, they produce anti-A and anti-B antibodies that attack red blood cells with A, B, or A and B antigens present on their surface. Matching the ABO blood group and Rhesus factor between donors and recipients serves as the basis for both successful organ donation as well as blood transfusions; a mismatch between the two can lead to death due to incompatible antigens and antibodies ("Facts About Blood and Blood Types," 2021). For this reason, a patient with type O blood cannot receive a transfusion from a person with type A blood because their anti-A antibodies will attack the transfused type A red blood cells. On the other hand, a patient with type A, B, or AB blood can receive a transfusion or organ donation from a person with type O blood because there is no type O antigen and thus no anti-O antibody to attack the donated organ or blood. This form of adaptive immunity, a specific and coordinated immune response, serves as the basis for the relationship between blood type and infectious diseases. Certain bacterial, viral, and parasitic strains present

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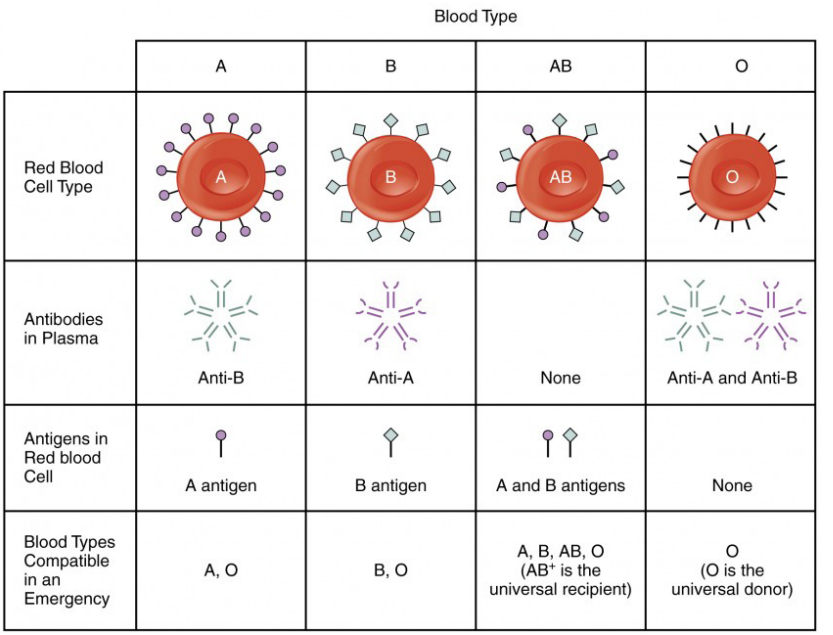

Figure 1. Red blood cells present specific antigens on their surface that are coded by one's gene for blood type. Image from Lumen Learning n.d.

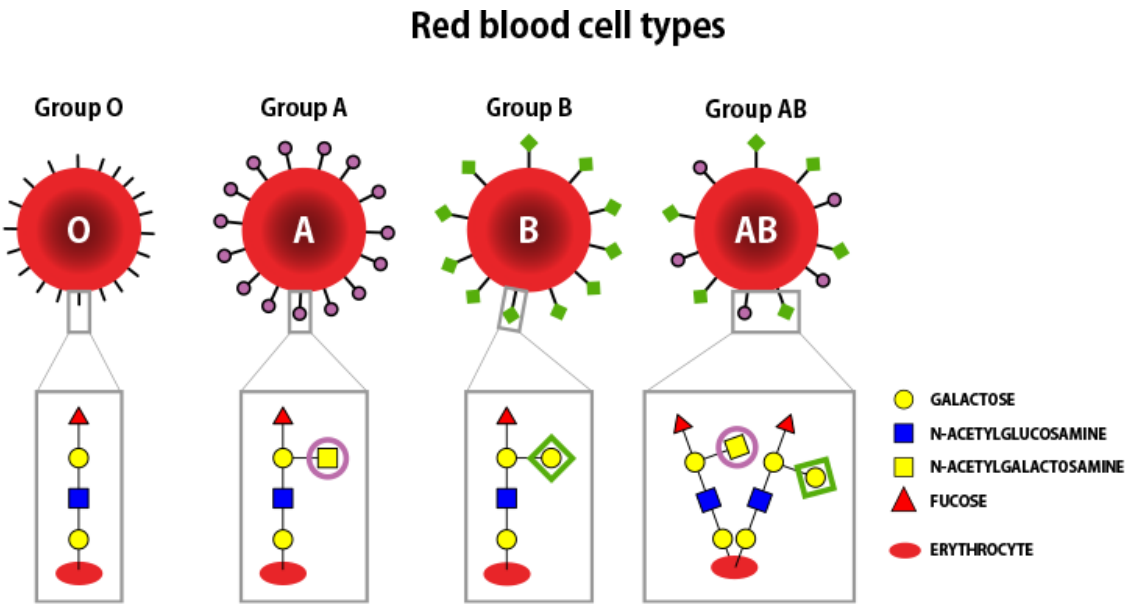

Figure 2. Each blood type is associated with a unique glycoprotein consisting of a polypeptide chain and group of carbohydrate molecules. Image from Glytech n.d.

proteins on their pathogenic components that resemble the ABO blood type antigens, prompting a negative immune response in infected individuals similar to when a foreign blood type is introduced to a patient (Ewald & Sumner, 2016). Research that synthesizes data from genome-wide association studies may prove to be particularly useful in identifying the blood group variants that are correlated with susceptibility or having more severe symptoms to infectious diseases. This could promote greater comprehension of the association between one's genetic makeup and their susceptibility to infectious diseases (Liumbruno & Franchini, 2013).

Certain bacterial, viral, and parasitic strains present proteins on their pathogenic components that resemble the ABO blood type antigens...

Emerging hematological research has found that in areas with high instances of *Escherichia coli* (*E. coli*) infections, individuals with type A blood appear to develop more grave symptoms than any other ABO blood type (Kumar et al., 2019). *E. coli* is a bacteria found in the intestinal tract of many animals. While most strains are harmless, there are forms of *E. coli* found in contaminated water or food that can cause severe diarrhea in those unlucky enough to ingest it (CDC, 2014). Researchers recently found that the *E. coli* bacterium secretes a protein that adheres only to the surface of intestinal epithelial cells in people with type A blood. As a result, researchers proposed that a drug targeting this protein would be instrumental in mitigating symptoms, such as severe diarrhea, in type A individuals who contract an *E. coli* infection (Kumar et al., 2019). An earlier study by Ewald and Sumner (2016) also suggests that the sugar molecules on the extracellular matrices of gram-negative bacteria, like *E. coli*, resemble A and B group antigens. Therefore, cells that produce anti-A or anti-B antibodies may be more effective at neutralizing this bacteria. It appears that individuals with both type A and B blood types are at greater risk for developing more severe symptoms from an *E. coli* infection because they cannot produce the proper antibodies to effectively suppress the pathogen.

Furthermore, *Plasmodium falciparum* malaria, the parasitic strain that accounts for over half the number of cases and over 80% of the deaths associated with malaria worldwide is remarkably less severe in individuals with type O blood compared to those with types A or B (Ewald & Sumner, 2016). *P. falciparum* malaria is a vector-borne illness found primarily in sub-Saharan Africa that is transmitted from mosquitoes to humans (CDC, 2020). A hallmark of *P. falciparum* malaria

appears to be malarial anemia, a condition in which membrane proteins on the surface of infected red blood cells bind to A and B antigens on the surface of uninfected blood cells, forming conglomerations of cells known as "rosettes" (Ewald & Sumner, 2016). These rosettes are dangerous because they prevent proper circulation of the blood, especially when they begin to adhere to endothelial cells lining blood vessels. Fry et al. (2007) suggest that type O blood confers "protection" against this strain as type O individuals lack ABO antigens on the surface of their red blood cells.

Research into blood type and associated susceptibility to infectious diseases has recently amassed significant attention due to findings that individuals with blood type O appear to have a decreased risk of contracting SARS-Cov-2, the novel coronavirus, as well as a lower chance of developing severe symptoms if they do test positive (Barnkob et al., 2020). While this research is quite preliminary and limited in scope because of the novel nature of the virus, multiple studies have examined how blood type and susceptibility to SARS-Cov-1 and SARS-Cov-2 may be related. The literature indicates that SARS-Cov-1 viral particles can be modified by specific ABO glycosyltransferases. These enzymes link carbohydrate groups, which are uniquely coded by the gene that determines each blood type, to antigens on the surface of blood cells through a process called glycosylation. Researchers have found that the A variant of glycosyltransferases are effective at glycosylating SARS-Cov-1 particles, enabling anti-A antibodies to incapacitate this virus (Barnkob et al., 2020). It is hypothesized that the B variant of the ABO glycosyltransferases can also glycosylate the surface of SARS-Cov-1 particles and anti-B antibodies would be similarly effective at neutralizing this virus (Barnkob et al., 2020). More research is needed to better understand the efficacy in transferring these findings about SARS-Cov-1 to SARS-Cov-2, but researchers highlight how globally, individuals with type O blood appear to have reduced instances of SARS-Cov-2 infection (Barnkob et al., 2020). Only individuals with type O blood can produce both anti-A and anti-B antibodies, and as stated above, the A and B variants of ABO glycosyltransferases have been shown to be potent enzymes capable of glycosylating SARS-Cov-1 viral matter (Barnkob et al., 2020). The two viruses are essentially strains of a common viral ancestor and are thus genetically simi-

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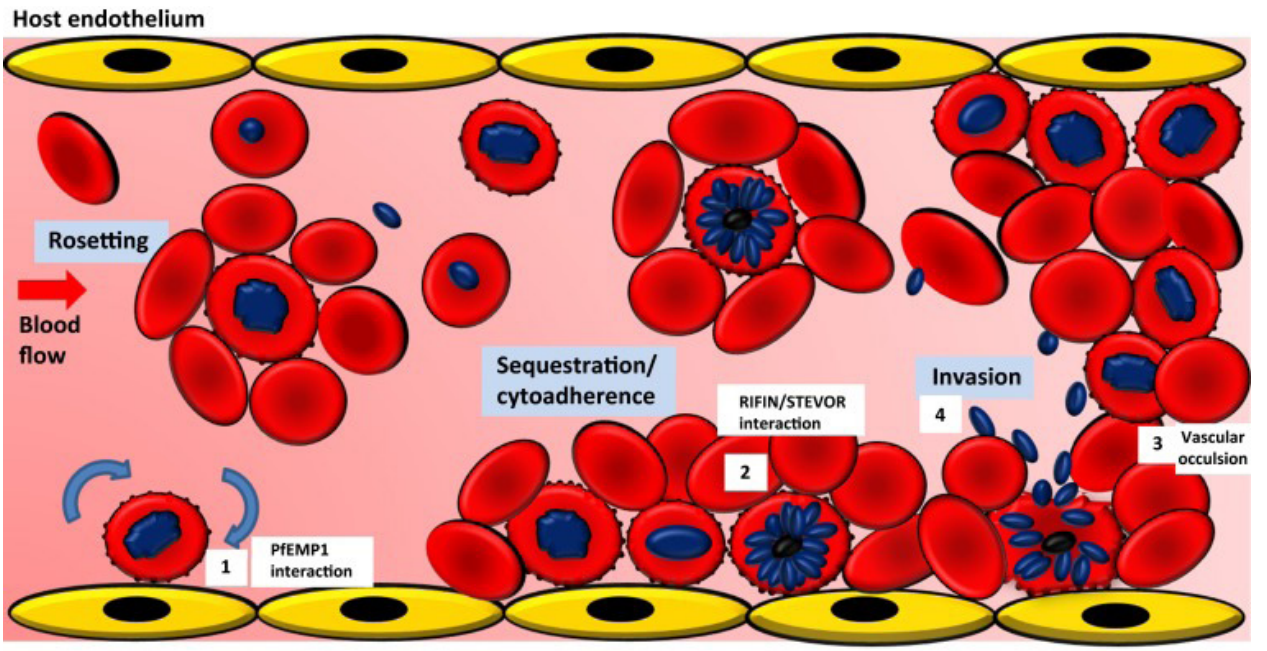

Figure 3. Erythrocyte rosette formation and subsequent blood clot formation in a blood vessel. Image from Yam et al. 2017.

lar, which may explain why type O individuals are at a decreased risk for contracting SARS-Cov-2 (Barnkob et al., 2020).

Researching the association between ABO blood group antigens and vulnerability to bacterial, viral, and parasitic diseases can serve as a powerful tool in understanding how we can live with infectious disease. Infections caused by *E. coli*, malaria, and coronaviruses are only three diseases whose lethality and severity have been correlated to specific ABO blood type. Much of this research is correlational, however, which is a significant limitation to its scope and applicability. Future studies that focus on finding concrete, causal relationships between blood type antigens and susceptibility to infectious disease could serve to provide greater credibility to these correlational findings. ❧

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A struggle with every breath

RICHARD LEE
Staff Writer

Asthma is a respiratory condition in the bronchi of the lungs, inducing spasms, shortness of breath, and general difficulty in breathing. More than 339 million people worldwide suffered from asthma in 2016, and it remains the most common disease among children (World Health Organization, 2020). However, there is no established treatment that can fully eliminate the disease in an individual, let alone a single drug cure. Varying factors contribute to the development of asthma. Apart from genetic predisposition, the inflammation in the lungs can also be exacerbated by the poor quality of air. Increasing air pollution in modern, industrialized societies could cause asthma to be one of the most devastating conditions in the decades to come. Thus, more robust treatment methods must be developed to combat chronic asthma, a permanent condition that still lacks a definite solution.

Earth is experiencing increasing amounts of pollution, compromising the quality of air inhaled by its 7.6 billion inhabitants. What results is a greater prevalence of lung inflammation and chronic conditions like asthma. Particulate matter (PM) is the sum of all solid and liquid particles suspended in the air, of which many are hazardous. Although the World Health Organization has noted a decrease in the proportion of the global population that is exposed to what it considers an excessive PM level, falling from 94% in 2010 to 90.0% in 2016, this decrease was mainly due to improvements in North America and Europe (WHO, 2020). The majority of regions have actually experienced increases in PM levels (Shaddick et al., 2020). Even though the direct relationship between PM and chronic respira-

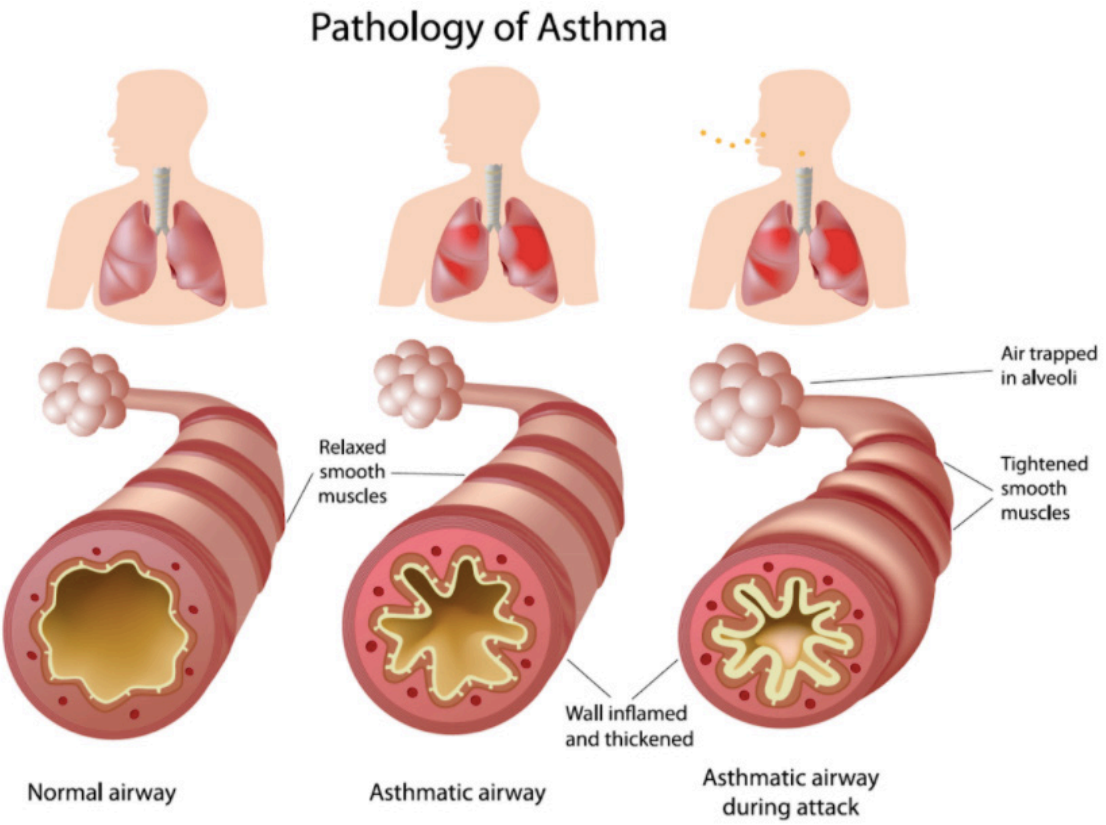

Figure 1. Asthma is grounded on a tightening airway compounded by inadequate diffusion. Image rom William Gandy 2017.

tory illnesses has yet to be determined, a number of documented inflammation cases due to PM speak of its importance. Specifically, research shows that PM triggers innate immunity inflammation, oxidative stress, apoptosis, autophagy, as well as an imbalance of T helper cells, all of which are associated with pathological changes in allergic respiratory diseases (Wu et al., 2018). Apart from associations between pollution and altered biological processes, causative relationships have also been determined. Increasing amounts of evidence suggest that long-term exposures to air pollution can contribute to new-onset asthma in children (Guarnieri & Balmes, 2014). A phase three study done by the International Study of Asthma and Allergies in Childhood, involving more than 500,000 children, identified a dose-response association between symptoms of asthma and self-reported exposure to truck traffic (Brunst et al., 2015). A multitude of factors can contribute to the development of asthma. However, the already-identified causes that show no signs of deceleration necessitate greater research into their treatment.

more robust treatment methods must be developed to combat chronic asthma, a permanent condition that still lacks a permanent solution.

Within asthmatic patients, although different degrees of severity warrant different levels of prognosis for future development or remission, all experience permanent effects. In asthma, the dominant physiological event leading to clinical symptoms is the narrowing of the airway and reduced airflow, caused by bronchial smooth muscle contraction as a response to allergens or irritants (US Department of Health and Human Services, 2020). The definition of asthma describes some sort of airflow reduction, yet the extent of that impairment is based upon predetermined and epigenetic factors. On one end, genome-wide association studies have identified genes that modulate aspects of lung development and susceptibility to more severe disease; on the other, exposures to several allergens, including dust mites or animals as an infant, have given a positive predicted value of 57% for asthma by the age of 11 (Belsky & Sears, 2014). The amount of exposure to those aforementioned substances can impose a restrictive airway on any individual, let alone ones who have genetic predispositions to the disease. Thus, rather than being a binary condition, asthma seems to rest more on a spectrum. Most commonly, many individuals seem to "grow" out of their asthma during adolescence as their clinical symptoms lessen, no longer requiring the use of medication. However, it has been determined that even atopic asthmatic children in remission have evidence of pulmonary function abnormalities and bronchial hyperresponsiveness, indicative of continued airway inflammation or previous airway damage (Warke et al., 2002). Patients with a lesser severity of the bronchoconstriction still retain the long-term damage caused by their inflammation, a continuing issue warranting the prevention of the condition combined with its treatment.

The definition of asthma describes some sort of airflow reduction, yet the extent of that impairment is based upon predetermined and epigenetic factors.

Despite the impending effects of asthma, inaction from countries and global powers have continued to exacerbate the condition. The growing issue of pollution has not been adequately addressed by recent country superpowers, including the United States. Just one day after the 2020 US Presidential Election, former President Trump withdrew from the Paris Agreement, a legal contract set on keeping the global temperature at lower levels as well as reducing carbon emission rates (Graham Research Institute, 2020). As one of the leading emitters of carbon, the United States has a dominant role to play in the battle against environmental pollution. Although the US has since rejoined the contract, this recent falter signifies a lack of commitment from countries most responsible for the environmental causes of asthma. Additionally, systems like the US Healthcare have made access to treatment almost unobtainable, with a single inhaler costing upwards of one hundred dollars (Papi et al., 2007). When the underserved populations are also the most at risk for chronic illnesses, a per-

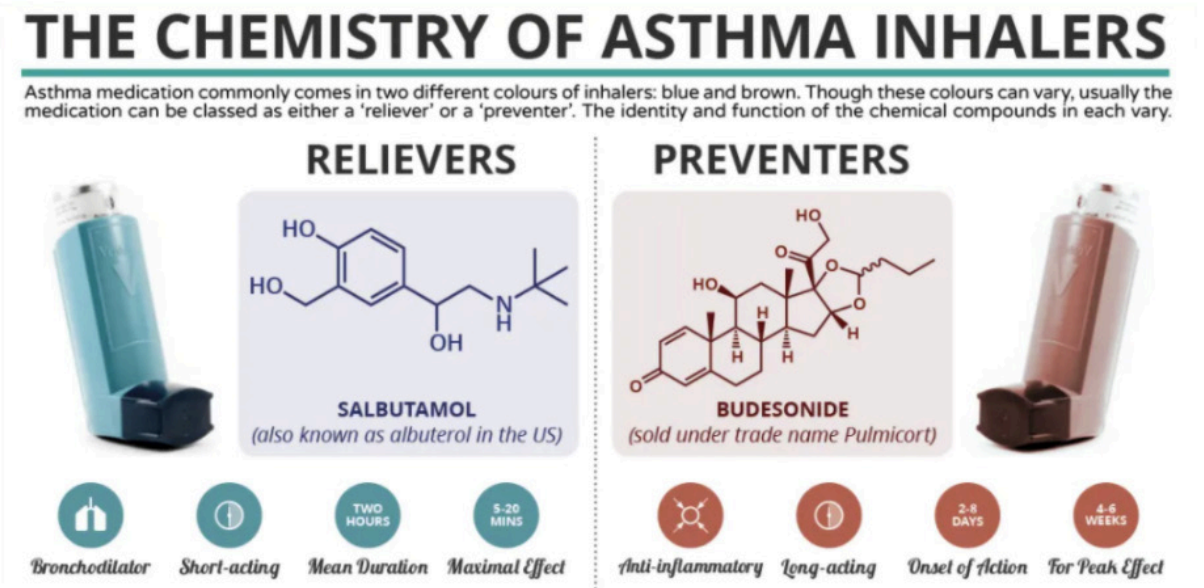

Figure 2. Both inhaler relievers and preventers allow for stable control of asthma. Image from Stuart B. 2014.

petual cycle of sickness without remedy ensues.

While there is no natural cure for the disease, a variety of novel drugs still show promising results amidst the increasing pollution. Protein caspase-11 belongs to the caspase family, responsible for hydrolyzing proteins to activate cell death upon encountering inflammation (Huang et al., 2019). Recently, a group of researchers at Trinity College Dublin have found that caspase-11 activity can be inhibited by prostaglandin 2, ultimately reducing the presence of molecules called interferons responsible for activating the inflammation response in human cells (Zaslona et al., 2020). While this *in vitro* study only begins to analyze the potential impacts small molecules and proteins can have on chronic respiratory illnesses, it is nonetheless important to realize the pipeline these studies can establish for more clinical applications in the future. In addition, researchers at the University of Kiel in Germany found that Dupilumab, an anti-interleukin 4 receptor and alpha monoclonal antibody, drastically increased the forced expiratory volume of a group of 210 asthmatic patients, meaning they were able to exhale more air following treatment (Rabe et al., 2018). It is most evident that more pathways are being explored to paint a holistic picture of the physiology behind asthma, supporting the necessary approaches to countering this nuanced disease.

Despite the impending effects of asthma, inaction from countries and global powers have continued to exacerbate the condition.

Asthma's interconnected nature with pollution, public policy, and research makes it increasingly pertinent in a society bent on natural resource consumption and unaffordable healthcare. Its clinical presentation can be transient, yet permanent, and treatable, yet incurable. Although corticosteroids in the form of inhalers have catered to a vast population of asthmatics, they are neither guaranteed nor sustainable, especially for those who cannot afford them. Only bringing attention and resources to tackling the environmental problems can ultimately serve as a sustainable and effective approach to the growing issue of asthma, along with more research into potential treatments. As research develops and new relations are discovered between asthma and other metabolic processes, one can predict more efficient and established treatments for this oftentimes chronic condition. ❧

AUTHOR BIO

Richard Lee is a second year in the college double majoring in Biology and English. He used to be left-handed, until his dad wrote with his right hand everyday for a year.

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Body fat: Tricking the body to lose it

SRIDHAR KARNE
Staff Writer

As one of the body's most important macronutrients, fat is necessary for our survival. Biologically, fat cells are responsible for storing energy in the form of triglycerides while also providing insulation against the cold. In our contemporary society, however, there is often a stigma attached with having excess body fat, and as a result, many individuals find ways of reducing their body fat in an effort to change their appearance (Bacon & Severson, 2019). *Figure 1* illustrates how excess fat is stored underneath the skin, which ultimately gives the appearance of body fat on a person. To reduce overall body fat, fat cells must be liberated from adipocytes through fat metabolism which can be induced if the body is not consuming food (El-Zayat et al., 2019). When the body is starved of energy, fat cells, as one of the body's main energy sources, are liberated to fulfill this energy deficit. Apart from the aesthetic motive, others may desire to reduce body fat because obesity can lead to comorbid diseases such as cardiovascular disease, hypertension, sleep apnea, and diabetes (El-Zayet et al., 2019). There are many ways of increasing fat metabolism, but they are not all equally effective. This warrants an investigation into whether one approach is more efficient than the others while still maintaining a person's health.

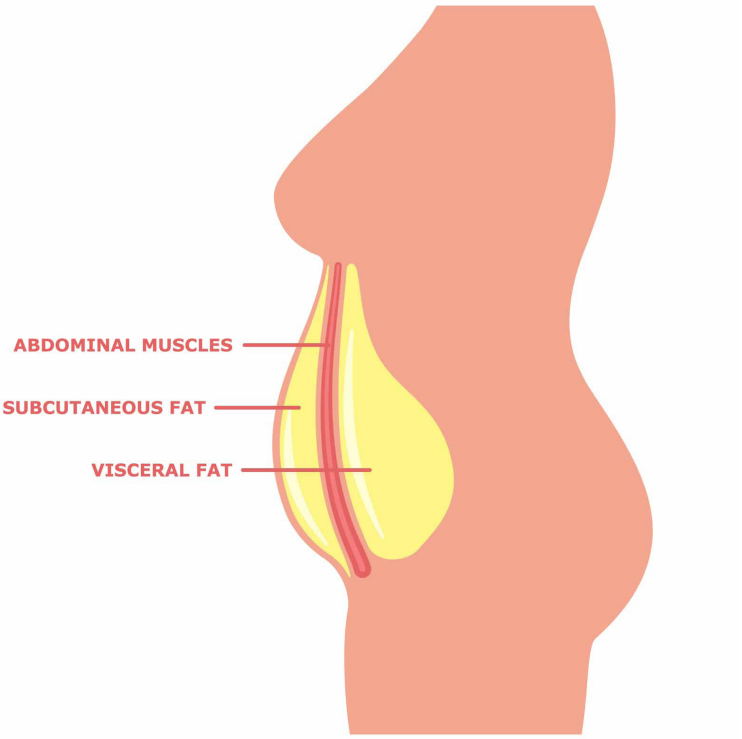

Figure 1. Diagram of fat storage in the abdominal region gives the appearance of body fat underneath the skin. Image from CoolSculpting 2020.

A common new year's resolution is to get in the gym or run on a treadmill. However, individuals may not realize that conventional aerobic exercises may not be the best way to reduce body fat. While any physical activity is better than none, one should be mindful about how to exercise based on the desired outcome. One review article emphasized the advantage of High Intensity Interval Training (HIIT) over aerobic exercises when it comes to reducing body fat. In fact, the paper suggested that there is no effect of aerobic exercise on the body (Boutcher, 2010). The argument stems from the fact that HIIT leads to a catecholamine response, specifically inducing the release of the hormone epinephrine in the body which drives lipolysis, or the breakdown of fats, from intramuscular fat stores (Boutcher, 2010). The release of epinephrine is beneficial in this case because epinephrine is involved in the fight/flight response. Evolutionarily, the body has been programmed to respond rapidly in a threatening situation. When a person finds themself in a situation that poses a threat, the flight/fight response can be activated to fuel energy to the body's

...conventional aerobic exercises may not be the best way to reduce body fat

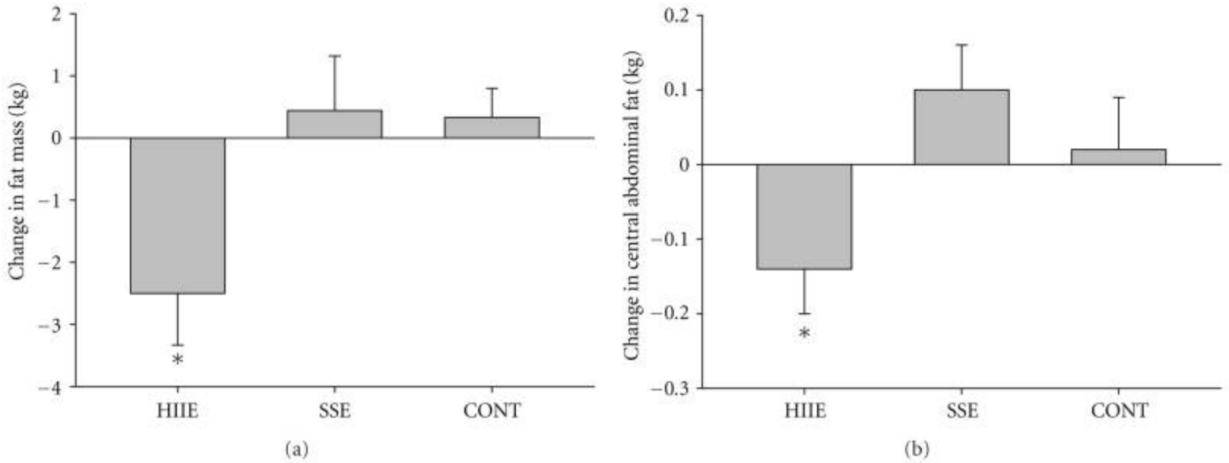

Figure 2. Decrease in Subcutaneous and Abdominal Body Fat through HIIE method. Image from Boutcher et. al, 2010.

muscles in order to be prepared to flee quickly and escape. As a result, by adding one extra sprint to the end of a routine 20-minute aerobic exercise, the body can be tricked and mimic the flight/fight response which may lead to increased endogenous levels of energy through the metabolism of fats (Boutcher, 2010). Furthermore, there is evidence that muscle aerobic capacity is increased following HIIT due to AMPK activation (Boutcher, 2010). AMPK is an enzyme that is involved in fatty acid metabolism. Therefore, body fat composition can be directly altered through HIIT exercise because it can activate an enzyme involved in the breakdown of fats. The advantage of HIIT over aerobic exercise is also empirically supported. A study conducted by Trembley et al. (1994) followed subjects through a fifteen-week program, and the results showed that the High Intensity Interval Exercise (HIIE) group lost significantly more subcutaneous and abdominal fat when compared to the steady-state exercise and control groups (Figure 2) (Boutcher, 2010).

HIIT seems to be a plausible approach to cutting body fat, but another approach to consider is through adding muscle mass to the body. When the body is an energy-deficit, muscles rely on energy from both glucose and fatty acid stores to generate energy. Glucose provides energy to the body through a metabolism mechanism called glycolysis while fatty acids provide energy to the body through a process called beta-oxidation. Ultimately, the body can use these molecules and strip them apart to break them down into the basic unit of energy called ATP. Increasing muscle mass composition works for reducing body fat composition because muscles consume plenty of energy and increasing the composition of muscle will increase total energy requirement by the body (McPherron et al., 2013). One common way of actually increasing muscle mass is through weight lifting, which forces tension and resistance on the muscles, leading to muscular hypertrophy. Muscular hypertrophy is the process of increasing the size of pre-existing myofibrils and overall muscle mass (Egerman & Glass, 2013). A study done by Lemmer et al. (2001) looked at the effects of strength training on a person's resting metabolic rate. Participants completed a full body, 24-week strength training program, and the researchers found that the average increase in resting metabolic rate when compared with the baseline metabolic rates in participants was +7%.

...[evidence] supports the effectiveness of a High-Protein diet paired with resistance exercise workouts

A third strategy for body fat reduction is based on the adoption of various regimented diets. *Figure 3* presents the results of a clinical trial that investigated the effect of different diets on fat mass loss and lean mass loss (Willoughby et al., 2018).

The data suggests that high-protein diets may achieve the most significant fat loss while minimizing lean muscle mass

loss (Willoughby et al., 2018). In a high protein diet, 10-35% of the total calories must come from proteins throughout the course of a day (Willoughby et al., 2018). The clinical trial evaluated a group of obese women who followed three different protein diets (low, moderate, high), and were simultaneously enrolled in a circuit-type resistance exercise program (Willoughby et al., 2018). The results showed that following a reduction in daily calories that the body is accustomed to, increasing the proportion of protein consumed paired with resistance exercise led to more significant declines in fat mass when compared to a control group that only participated in the exercise program. This supports the effectiveness of a High-Protein diet paired with resistance exercise workouts in order to lose body fat.

Yet another dietary-based approach to losing fat is through consuming supplements such as creatine, amino acids, and chromium picolinate ($Cr(pic)_3$). Creatine and amino acid supplements are used to help build muscle while ($Cr(pic)_3$) is marketed to help burn fat. Creatine supplementation works through providing a supply of quick energy supply in the form of creatine phosphate for the person working out their muscles (Beck et al., 2007). The supplement helps the body build muscle, because when a person is working out, the availability of creatine phosphate allows the body to have more energy and perform high-intensity workouts. Amino acids supplements, on the other hand, are often added to drinks, and are thought to expedite muscle recovery by supplying more amino acids to repair the muscle fibers that have just been exercised (Beck et al., 2007).

...potential deleterious effects such as neurological toxicity [due to $Cr(pic)_3$]

Ultimately, these supplements could help with fat loss because they could allow the body to build more muscle and increase a person's base metabolic rate.

To test whether supplementing creatine, amino acids, and protein combined with a ten-week exercise program would lead to changes in body composition, Beck (2007) performed a randomized, double-blind experiment on men. However, the results found no significant difference between the control and experimental groups. This suggests that taking these advertised supplements may not actually be useful if a person is trying to lose body fat.

Similarly, another study looked at the effects of $Cr(pic)_3$ as a dietary supplement (Vincent, 2003). The element chromium plays a role in maintaining carbohydrate and lipid metabolism which is why it has been a direction of study as a fat loss supplement (Vincent, 2003). The

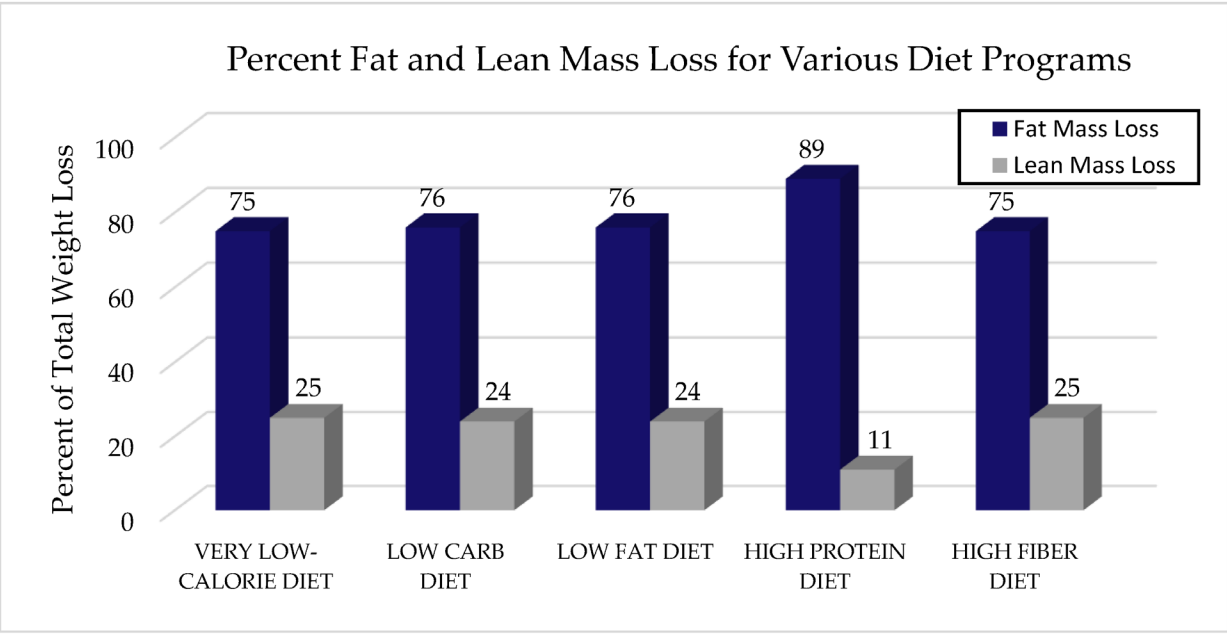

Figure 3. High protein diet shows largest percentage of fat mass loss. Image from Willoughby et al., 2018.

initial reports of $Cr(pic)_3$ being used as a weight loss supplement started with a paper published in 1989; however, the USDA patent associated with the paper is not specific to chromium, so it is misleading that many advertisements suggest otherwise (Vincent, 2003). The supposed effects of $Cr(pic)_3$ may be due to confounding variables that led to the reported fat loss. Though the relationship between $Cr(pic)_3$ and body fat is currently uncertain, $Cr(pic)_3$ still remains a popular supplement, even if the data suggests that it has no significant effects on body fat composition (Vincent, 2003). Further research is required to evaluate the concerns of this supplement because of potential deleterious effects such as neurological toxicity (Vincent, 2003). The safety concerns brought forth by the paper express the potential relationship between the picolinate released in the body from the supplement and the negative effects of motor function and symptoms of depression such as low mood feelings (Vincent, 2003).

Considering the three approaches, while there are benefits to each, combining multiple methods seems to be the most productive way to lose body fat. All the studies discussed did not use a single method alone to achieve a reduction in body fat but, instead, paired a certain form of exercise with a diet plan. Furthermore, the literature suggests that muscle-building supplements and fat burners may not be all that useful for reducing body fat composition. Instead the risks shoulds be understood and carefully weighed before recommending them for consumption. Nevertheless, through discipline and determination, it is possible to lose body fat by exercising and eating a healthy diet. ❧

AUTHOR BIO

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Disparities in health outcomes of suburban gentrification

SABRINA JIN
Staff Writer

Gentrification has been sweeping across American cities in waves since the 1970s. This process involves an influx of wealthy residents in relatively low-income suburban neighborhoods, whose movement breaks open concentrated poverty pockets, often improves environmental quality, and increases access to healthcare. Politicians have long praised the ability of gentrification to benefit public health in neighborhoods with previously low socioeconomic conditions; however, emerging evidence adds a level of nuance that indicates otherwise. While the financial growth contributes to overall improved health outcomes, the process simultaneously widens economic and health disparities between new residents and long-term residents in two particular subgroups: people of color and the elderly (Bhavsar et al., 2020). Gentrification further contributes to a change in the cultural landscape, which is theorized to increase stress among vulnerable populations in gentrifying suburbs (Crewe, 2017). Given the complex advantages and disadvantages to health, it is important to analyze consequences of gentrification through an intersectional lens in order to best support vulnerable subgroups.

Gentrification positively impacts public health through economic, demographic, and cultural changes within the neighborhood (Figure 1). First, there is a strong, positive association between neighborhood wealth and public health outcomes. Improvements in environmental quality, such as the reduction of pollution and increased access to green spaces, contribute to benefits in respiratory health and greater levels of physical activity. Neighborhood wealth also reduces crime rates and increases ease of access to healthy foods and health-related resources. Furthermore, urbanization promotes the establishment of quality education and health-promoting recreational organizations (Bhavsar et al., 2020). Secondly, changing demographics may increase ethnoracial and socioeconomic diversity within previously homogeneous neighborhoods, creating wider social support networks. The subsequent increase in perceived levels of collective efficacy serves as an important measure of neighborhood social cohesion and sentiments of friendliness and cooperation (Steinmetz-Wood et al., 2017). Given the highly social nature of public health, there is a strong correlation between perceptions of collective efficacy and overall health outcomes (Browning & Cagney, 2002). Therefore, gentrification supports neighborhood health not only through an influx of wealth but also through the promotion of positive attitudes towards community collectivism.

While the financial growth contributes to overall improved health outcomes, the process simultaneously widens economic and health disparities...

At the same time, the process

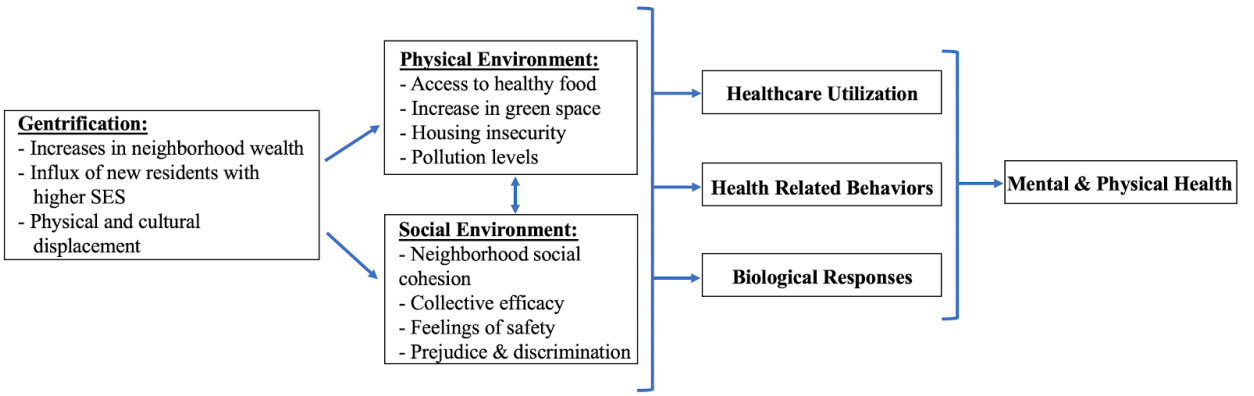

Figure 1. Theoretical framework for the impacts of gentrification on mental and physical health outcomes through interactions with the physical and social environment. Image from Bhavsar et al. 2020.

of gentrification often contributes to the displacement of long-term residents who may no longer afford to live in a city with rising property values. This phenomenon disproportionately affects historically African-American and Hispanic communities, which are often replaced by the movement of wealthier white residents (Richardson et al., 2019). While traditional sociological studies may report a reduction in poverty within a given city, this fails to capture the bigger picture of displacement associated with gentrification. Long-term residents who can afford to stay may also suffer from an increasing wealth gap that contributes to differential access to a polarizing quality of resources, including education, food, environmental health, and healthcare (Wilder et al., 2017). Growing disparities between the new, wealthier residents and the long-term residents may also hinder the ability for long-term residents to participate in health-seeking behaviors (Lorence & Park, 2007). Furthermore, the internalization of workplace and economic stress has been shown to manifest itself in poorer mental health outcomes, increased levels of cholesterol and cardiovascular disease, and more preterm births (Dole et al., 2003; Kivimäki et al., 2002). Higher levels of depression and anxiety in lower income residents of gentrifying neighborhoods are especially prevalent among children (Garcia, 2019).

Within long-term residents who stay in gentrifying neighborhoods, negative health impacts are most pronounced among people of color (Figure 2). These communities face a disproportionate risk of displacement due to increased public housing demolition as a result of gentrification (Goetz, 2011). This constant fear of displacement contributes to chronic illness, as mediated by stress (Izenberg et al., 2018). Changes in predominant ethnoracial identities from colored neighborhoods to white neighborhoods may further alienate long-term residents and increase levels of anxiety and depression (Smith et al., 2020). As people of color are increasingly replaced by affluent white gentrifiers, conditions may arise that heighten the risk of racial violence (Richardson et al., 2019). Community-level forms of racism, such as prejudice and discrimination, serve as salient mechanisms of reducing health outcomes among this vulnerable subgroup (Gibbons & Barton, 2016).

As people of color are increasingly replaced by affluent white gentrifiers, conditions may arise that heighten the risk of racial violence

Elderly long-term residents form another subgroup of individuals who are disproportionately impacted by the negative health outcomes produced by gentrification. Many are financially dependent on retirement packages with fixed-rate payments, resulting in an inability to keep up with inflation and increasing property values (Smith et al., 2018). Furthermore, the process of gentrification often alienates elderly residents due to the influx of younger, wealthier residents who bring vastly different cultural traditions (Crewe, 2017). The changing cultural landscape and loss of familiarity contribute to poorer health among elderly individuals not only due to a decrease in community support, but through internalization of stress as well (Browning & Cagney, 2002).

Despite the mixed impacts that gentrification has on public health overall, the process is expected to continue unfolding across American suburbs in the foreseeable future. The effects of economic changes, generational movement, and the evolution of cultural traditions is an ever-present reality. Fortunately, a number of gentrifying neighborhoods are also composed of diverse immigrant populations in response to an increase in career opportunities. First-generation immigrants and their descendants report a strong sense of belonging and neighborhood pride, pointing to increased levels of collective efficacy with other immigrants from different parts of the world (Walton, 2016). Their similar socioeconomic status, as well as shared modes of suffering that are unique to immigrant populations, provide an incomparable level of camaraderie (Dillahunt & Malone, 2015). This type of immigrant-centered community holds promise as a model for future gentrification in American suburbs.

Due to the wide array of differing health outcomes for differing populations, the study of gentrification must be further assessed from a multidisciplinary perspective to implement policies that may support vulnerable

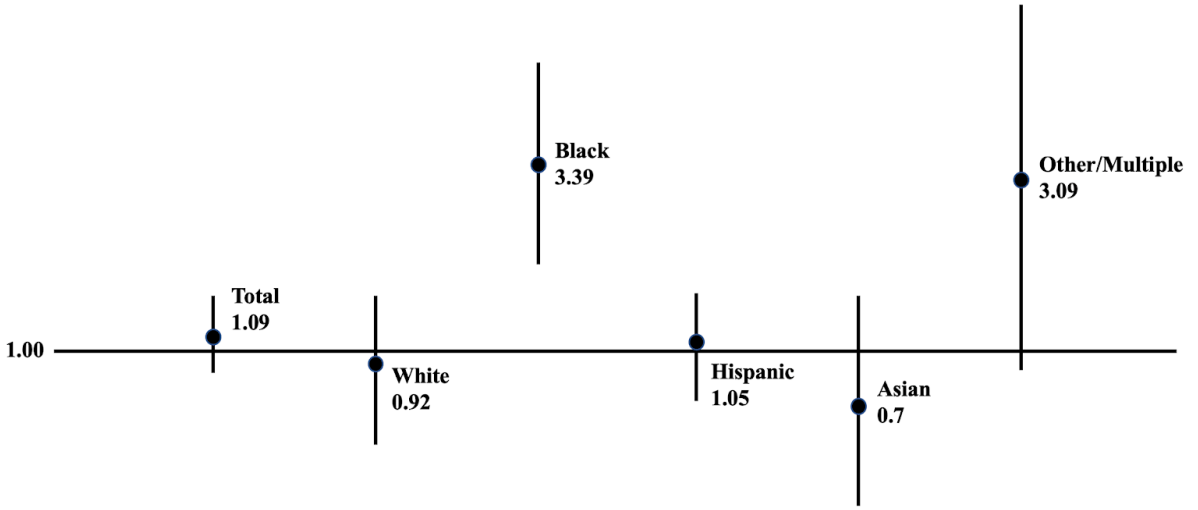

Figure 2. Adjusted odds ratios of self-rated health for different ethnoracial groups living in gentrifying tracts of California's four largest metropolitan areas. Values greater than 1.00 indicate positive association between gentrification and adverse health outcomes. Image from Izenberg et al. 2018.

subgroups (Agbai, 2018; Smith et al., 2020). Furthermore, future research involving gentrification should seek to refine the definition of gentrification. Sociologists increasingly acknowledge gentrification as a multifaceted process that cannot be understood through the binary categories of "yes" or "no," but should be examined through asking "how" and "to what extent." Viewing the process as a singular phenomenon without attempts at exploring individual attributes of gentrification will hinder the development of robust theoretical research, especially regarding the intersection between gentrification and health. Once individual attributes of this process are further assessed, researchers and policymakers may best implement structural changes to optimize neighborhood health without disproportionately imposing negative health outcomes upon people of color and long-term elderly residents. Activism may also be seen on the local level, as long-term residents and state governments resist public housing demolition by designating certain streets as historical landmarks, thus protecting vulnerable populations from displacement. As always, intersectional analysis is fundamental to understanding the impacts of changing cultural landscapes on neighborhood health such that communities may achieve the goal of American diversity and reap the benefits of collective efficacy. ❧

Sociologists increasingly acknowledge gentrification as a multifaceted process that cannot be understood through the binary categories of "yes" or "no,"...

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Sabrina Jin is a third year in the college double majoring in Biology and Cultural Anthropology. An interesting fact about her is that she raised about nine insect species last semester and was fortunate enough to witness the hatching process of around 120 wheel bugs.

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White coat, business formal: The doctor's reach beyond the examination table

SARINA ADELINE
Staff Writer

Editor's Note: This story includes graphic imagery and language.

In November 2018, nine months after the tragic school shooting in Parkland, Florida, the flurry of news articles and debates about gun control had already begun to subside.

Networks moved on to air new stories, newspapers found different scoops, and the rhythm of the American news cycle steamrolled forward. But for medical and mental health professionals dealing with the aftershocks of gun violence *as well as* the ongoing incidents of violence, the story never went away; it lingered. Many doctors continued their grassroots push for gun control legislation (Stanbrook, 2019), citing personal experience in the examination room, at the operating table, or worse, in the dark morgue in the underbelly of the hospital. On November 8, the The National Rifle Association of America (NRA) responded with a scathing tweet:

"Someone should tell self-important anti-gun doctors to stay in their lane. Half of the articles in Annals of Internal Medicine are pushing for gun control. Most upsetting, however, the medical community seems to have consulted NO ONE but themselves."

A few hours after the NRA posted this tweet, a man shot and killed 12 people at a country music bar in Thousand Oaks, California. The tweet elicited a near instantaneous response from doctors. Many of them championed the Twitter hashtag, *#ThisISOurLane*. Forensic pathologist Judy Melinek wrote, "Do you have any idea how many bullets I pull out of corpses weekly? This isn't just my lane. It's my f****** highway." Other doctors responded similarly, unearthing the brutal impact of gun violence in a way that the public had rarely seen before.

To enact change, doctors needed to trade in their white coats for business formal...

Doctors, serving on the front lines of a gun violence epidemic, knew that the fight didn't end with shocking pictures circulating on Twitter. To enact change, doctors needed to trade in their white coats for business formal; the doctor's role beyond the examination table suddenly became a vital part of the gun control debate. Rep. Robin Kelly (D-Ill.), who authored multiple bills aimed at reducing gun violence, remarked that the involvement of doctors in policy work helped to make the process more bipartisan

Figure 1. NRA Tweet. Image from NRA 2018.

(Roubein and Ollstein). In 2019, more than 160 medical, public health, and research groups signed a letter from the American Academy of Pediatrics. They directed the letter to congressional appropriators, asking that they allocate funding toward gun violence research, which was previously not mandated (Roubein and Ollstein, 2019). The 20 year freeze on gun violence research stemmed in part from the Dickey Amendment, which slipped into the 1996 United States federal government omnibus spending bill. The bill stipulated that "none of the funds made available for injury prevention and control at the Centers for Disease Control and Prevention (CDC) may be used to advocate or promote gun control," effectively blocking research efforts to track the impact of gun violence (104th Congress, 1996). Treating bullet wounds or conducting autopsies, in an ideal system, is the last line of defense. In a reality where doctors consistently witness the failure of system level policy, some understand that their role also translates into one of advocacy (AMA J Ethics, 2018).

Treating bullet wounds or conducting autopsies, in an ideal system, is the last line of defense.

Doctors' involvement in issues of American social and legal policy did not begin—nor does it end—with gun control. The doctor's role in shaping the United States' legal system has early roots, dating back to the 18th and 19th centuries (perhaps even earlier outside of the U.S.) In 1838, psychiatrist Isaac Ray published *A Treatise on the Medical Jurisprudence of Insanity*, which served as a major authoritative text in the legal system for decades (Gutheil, 2005). The book was the first printed English text to examine the relationship between psychiatry and the law (Overholser, 1962). It prompted ethical questioning of the interactions of illness and crime. It also initiated some difficult conversation about balancing accountability, humanity, and mercy in a legal system designed primarily to punish. Isaac Ray was by no means a perfect doctor. The harm that he caused through his psycho-medical investigations often came at the expense of under-resourced and exploited people, including low-income individuals and women (Weiss, 2013). Recognizing Dr. Ray's

Figure 2. Doctors respond to a vitriolic tweet from the NRA claiming that "self-important" doctors should "stay in their lane" over issues of gun violence. Image from Stephanie Bonne 2018.

work, however, is not intended to glorify or romanticize him as a historical figure; rather, it demonstrates the critical importance of a physician's role in informing some of the most essential structures of American society. Understanding this relationship may empower future doctors to enact systematic change outside of the medical field. Most policy changes arrive at a snail's pace: incremental compromises that inch into progress. However, doctors such as Isaac Ray show that radical ideas from the medical field have the capacity to do more than just inch.

While doctors have initiated many "firsts," like Isaac Ray starting the field of Forensic Psychiatry, they also play a part in improving pre-existing structures. Trained to reconcile highly technical and specialized field expertise with patient interfacing, doctors are uniquely situated to critically examine the efficacy of systems and its impact on stakeholders. Neuroscientists and scientist-physicians often intervene in the legal system by questioning the validity of age-old practices, such as polygraphs and eyewitness testimony. Once widely used to determine the truth of a statement by crudely measuring three physiological biomarkers (heart rate/blood pressure, respiration, and skin conductivity), the infamous "lie detector" test is now widely discredited. Without intervention from doctors, it is likely that people would continue to be indicted based on a test that is as likely to detect anxiety as a lie. Doctors have provided similar guidance in addressing the limitations of eyewitness testimony, which is a ubiquitous practice of evidence collection and investigation. Findings of physicians and doctors suggest that eyewitness reliability is poor; even when telling the truth, testifiers are likely to both misrepresent *and* misremember a sequence of events (Gardner, 2006). Human memory is simply not built for the rigid, black and white paradigm of veracity demanded by the courtroom. In recent years, physicians and physician-scientists have been at the forefront of studying and using neurotechnology, including fMRIs, to investigate the reliability of memory. This has major implications for how the legal system approaches eyewitness testimony, now and into the future (Lacy and Stark, 2013). Doctors have the potential

Figure 3. Doctors' endorsements cause a ripple effect across industries which, when poorly placed, can cause generations of harm. Image from R. J. Reynolds Tobacco Company "More Doctors Smoke Camels" Campaign 1946.

As the medical field advances, so does its understanding of the complex ways in which social, physical, and psychological health factors interact.

to serve as part of a checks and balances system that pursues equity and accuracy in legal processes and policy. Today, doctors inform a variety of programs and policies that are not always visible to the public. To name a few examples, doctors influence public school lunches by setting nutrition guidelines, help regulate the accessibility of tobacco products, and shape the public's perceptions of the meaning of individual wellness.

Unfortunately, with so much authority and expertise, doctors have the capacity to do as much harm as good when left unchecked. Before the extensive research on the long-term impact of tobacco products, doctors played a major role in selling tobacco to the public (Gardner, M. N., 2006). Tobacco giants, like Camel, co-opted the weight and credibility of medical support, inciting a public health crisis that still has consequences today. As physicians started to understand the danger of smoking, the damage was already done. It took decades for doctors to undo the field's misguided endorsement of smoking.

The authority of doctors is an incredibly powerful tool. How that authority is wielded can influence the major determinants of general population health as well as individual wellness, and this reality is re-illuminated by the COVID-19 pandemic. In the era of technology and social media, the voices of doctors are more elevated and visible than ever before. As the medical field advances, so does its understanding of the complex ways in which social, physical, and psychological health factors interact. One thing is clear: the role of a doctor does not stop in the examination room. Doctors hold immense potential for instigating social and political change, and their findings in the clinical setting can empower them to be an impetus for positive impact.

Future doctors and young physicians face a monumental decision—or rather, a series of decisions—on how to use their authority and knowledge. For better or for worse, the world is listening. The rest is history. ❧

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The impact of climate change on COVID-19

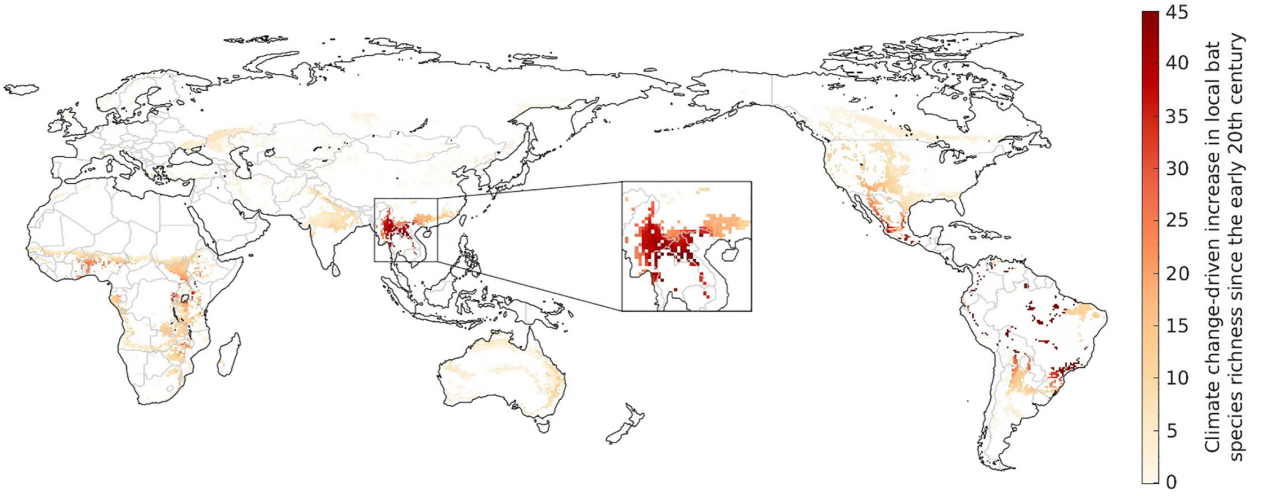

Figure 1. Regions highly susceptible to climate change-driven environmental alterations showcase an increase in the local bat species richness. Image from Beyer 2020.

MUSKAN DUBEY
Staff Writer

Understanding the interrelationship between climate change and its impact on the emergence and transmission of COVID-19 is of paramount importance, especially in regards to combating other zoonotic diseases and curtailing the spread of COVID-19. It can help us better understand the natural history of the pandemic, how we respond, and what the possible course of this infectious outbreak may be. Several contemporary studies also indicate that climate change might have driven the emergence of COVID-19 by establishing a more habitual environment for a diverse species of bats (Beyer, 2021). Bats have commonly been associated with the origins of numerous zoonotic diseases, which are infectious diseases that are transmitted between species from animals to humans, and have caused the MERS CoV epidemic of 2012 and more recently SARS-CoV-2 (Beyer, 2021). Climate change has also played a central role in the spread of COVID-19, with climate factors (Beyer, 2021). Therefore, to gain a holistic understanding of the emergence and spread of COVID-19, we must put it in the context of the augmenting effects of climate change on the world. It is crucial to combat future zoonotic viruses, and to do so, the dynamics between these diseases' emergence and dissemination must be understood within the context of climate change.

Bats are considered to be animal pathogen hosts and contain the highest proportion of zoonotic viruses in the entire mammalian order...

The contraction of these diseases can be traced to human interactions with the environment and encroachment into wildlife habitat (Wannous, 2020). Specifically, humans have caused severe habitat destruction, which has had major ramifications on existing wildlife, while climate change has caused even more geographical overhaul. For example, the landscapes of regions such as the Chinese Yunnan province, Myanmar, and Laos have transformed into global hotspots for various species of bats. Climate change factors such as higher carbon dioxide levels and altered precipitation rates have drastically shifted the biomes of these regions from tropical savannahs to deciduous woodlands. Bats are considered to be animal pathogen hosts and contain the highest proportion of zoonotic viruses in the entire mammalian order, with a third of their genome harboring coronaviruses. This climate change driven environmental shift has caused an increase in the bat species richness, leading to an inadvertent increase in coronavirus in

the region (Beyer, 2021). "The estimated climate change-driven increase of around 40 bat species across the region corresponds to a rise in the local number of bat-borne CoVs in the order of 100 viruses, given that each bat species carries on average 2.67 CoVs" (Beyer, 2021). Ultimately, by introducing bats to an environment that is new to them, there is a higher possibility of novel host-pathogen interactions which may aid in the evolution and transmission of harmful diseases (Lorentzen, 2020).

Climate change indicators such as humidity and temperature also align with the seasonal spread of COVID-19. This is supported by the COVID-19 outbreak in Wuhan, China, which showed a direct correlation between infection rates and extreme weather conditions (Lin, 2020). Scientists noticed that warmer, less humid conditions suppressed the spread of the virus while colder, high-humidity environments increased the virulity of the virus (Kroumpouzos, 2020). It is noted that drier, colder environments can dehydrate the mucosal membrane, thereby reducing the effectiveness of the protective cili which supports the development of viruses. This is highlighted by David et. al, who "explored the linear and non-linear relationship between the annual average temperature compensation and the confirmed COVID-19 cases in the capital city of Brazil. It was found that the daily cumulative number of confirmed cases decreased by 4.8951% when the temperature increased by 1 °C" (Lin, 2020). Higher humidity also increases the spread of virulent viruses by increasing the aerosol quality and therefore the concentration of aerosol particles that can serve as a medium for infection (Kroumpouzos, 2020). A 1 °C rise in the relative humidity caused an increase in the average daily rate of COVID-19 cases from 11% to 22% (Shakil, 2020). Ultimately, human coronaviruses show a strong winter seasonality between the months of December and April and tend to remain dormant during the summer months (Sajadi, 2020). Also, COVID-19 started in the low temperate areas of China, with major outbreaks following in South Korea and Japan. It should be noted that new epicenters for the virus are characterized by similar temperatures and lie on the 30° to 0°N" (Kroumpouzos, 2020). Other meteorological indicators such as wind speed and air quality also seem to affect the spread of these infectious diseases. Studies in cities such as New York City found a positive association between wind speed and concentration of crowd with COVID-19 transmission rates (Shakil, 2020). Therefore, countries should consider climate shifts and enact more powerful measures to minimize the risk of a re-outbreak of COVID-19.

It is noted that drier, colder environments can dehydrate the mucosal membrane... reducing the...protective cili which supports the development of viruses.

Climate change and COVID-19 are deeply intertwined; they are both responsible for "creating social impairment, with social isolation, place and sex inequality, and food and shelter insecurity occuring disproportionately in vunerable popu-

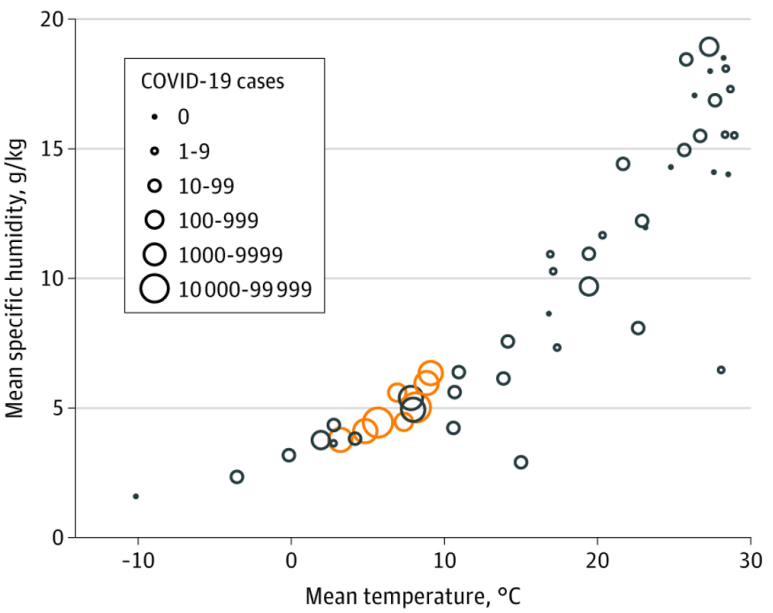

Figure 2. Colder, less humid regions showcase higher levels of COVID-19 cases as compared to more temperate and humid regions. Image from Sajadi 2020.

lations" (Joshi, 2021). Scientists are in consensus that alterations in large-scale climate trends may lead to irreversible processes with unforeseeable consequences on the pandemic (Wannous, 2020). Reducing the risk of zoonotic outbreaks in the future can be accomplished by enacting measures to protect our natural habitats, impose restrictions on wildlife hunting and trade, as well as, legislate animal welfare standards on farms, markets, and transport vehicles. Globally speaking, countries must restrict worldwide transport to curtail inter-continental spread of these viruses and implement strict border patrol regulations on the entry of animal goods from disease-ridden countries. Food hygiene and personal hygiene are of utmost importance in preventing infection, as well as having access to clean, drinkable water. Overall, all these measures can lessen direct contact between humans and animals, thereby reducing the risk of contracting zoonotic illnesses (Wannous, 2020).

Reducing the risk of zoonotic outbreaks in the future can be accomplished by enacting measures to protect our natural habitats...

Climate change has fostered a favorable environment for the emergence of future pandemics with higher virulence. It is an enabler, an accelerant, and an engine for the possibility of novel disease interactions. Consequently, societies must invest in maintaining global health to safeguard the health of its population. We must invest in measures that mitigate climate change conditions, thereby curtailing the probability of contracting zoonotic diseases. In the light of climate change, we must ensure sustainable livestock practices and overall animal welfare to mitigate chances of novel host-pathogen interactions. Furthermore, by installing an emergency system or information management system that continuously tracks changes in climate with disease incidences, it could better aid our understanding of the emergence of these diseases and determine accurate measures of preventing their dissemination (Wannous, 2020). ❧

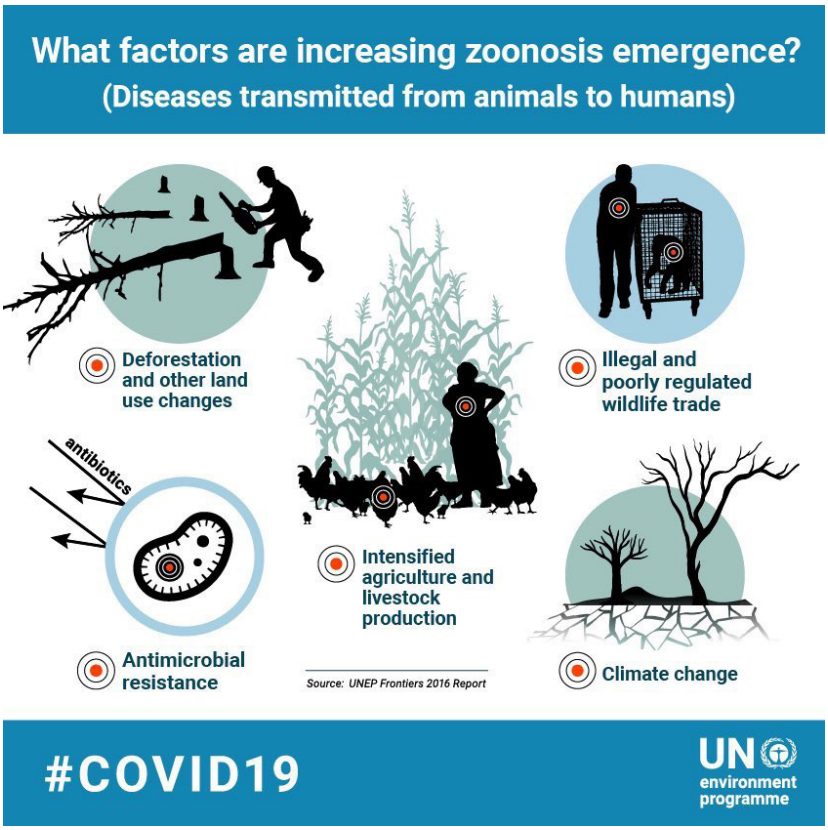

Figure 3. There are several ways of reducing the emergence of zoonotic diseases. Specifically, developing measures to reduce climate change and livestock production is of utmost importance. Image from UN.

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Blurred vision: The false perception of drugs in America and its racist consequences

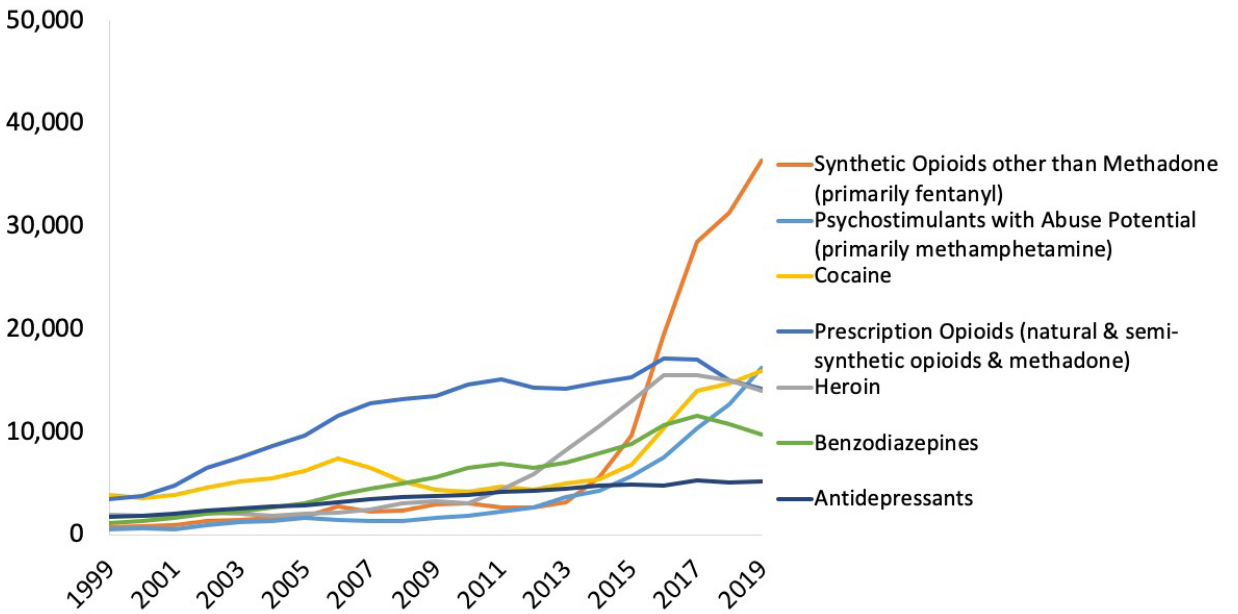
Figure 1. Image depiction of drugs and brain. Image from Harvard Health Publishing 2020.

AIDAN SPRADLIN
Staff Writer

In 1961, an overworked John F. Kennedy went to his physician complaining of back pain. One might assume that President Kennedy was prescribed an over-the-counter Tylenol, or even a stronger painkiller like Voltaren. However, President Kennedy was given injections of methamphetamines almost daily in the oval office for years to come. Contrary to the popular and political discourse surrounding drugs in America, psychoactive drug use has a rich history in many cultures around the world. In the United States, recreational psychoactive drug use has long been a staple in the American family's celebrations and social gatherings. Acceptance and the attitude surrounding these different practices, however, largely depends upon the socioeconomic and racial privilege of those taking part in them. From the christening of a newly purchased yacht with champagne to passing a joint around at a concert, psychoactive drugs are consumed in different arenas of American public life. While the elite pop open bottles and take puffs of relaxation, there simultaneously exists sharp criticism and stigma surrounding drug use within the United States' low-income neighborhoods and communities of color. A pastime for some is branded as criminal activity for others. While the argument over the health benefits of both legal and illegal drugs remains highly contested, there is strong evidence that the demonization of drugs disproportionately harms people of color. This blurred vision of drugs and its consequences must be acknowledged and eradicated.

In order to adequately address the injustice in the conversation surrounding drugs, we must first unveil the intrinsic smokescreen of misinformation. It is critical to recognize the weaknesses in the evidence

Figure 2. National Drug-Involved Overdose Deaths*, Number Among All Ages, 1999-2019



*Includes deaths with underlying causes of unintentional drug poisoning (X40–X44), suicide drug poisoning (X60–X64), homicide drug poisoning (X85), or drug poisoning of undetermined intent (Y10–Y14), as coded in the International Classification of Diseases, 10th Revision. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2019 on CDC WONDER Online Database, released 12/2020.

Figure 2. National Drug-Involved Overdose deaths over time separated by form of drug use. Synthetic Opioids are among the largest contributors to fatal drug overdoses seen in the United States. Image from NIDA 2021.

regarding addiction. Surprisingly, there exists no observed neurobiological substrate to differentiate people with or without addiction (Hart et. al., 2012). Lack of a definite neurobiological substrate responsible for addiction unveils the lack of a firm, non-objective definition for addiction. And while many institutions define addiction as a brain disease, the evidence does not necessarily show addiction as 'damage' to the brain, but simply a difference in function (Hart, 2020). How this information is interpreted is entirely dependent on the scientist presenting the work. Furthermore, the *Diagnostic and statistical manual of mental disorders* requires that addiction causes "distress" to the addicted individual or those around them. It also asserts "the word ['addiction'] is omitted from the official DSM-5 substance use disorder diagnostic terminology because of its uncertain definition and its potentially negative connotation" (Edition, 2013). Addiction, as described previously, possesses a less concrete definition than many might believe. The very fact that the 'manual of mental disorders' omits the word due to 'uncertain definition' shows a lack of scientific consensus. It is estimated that only 10 to 30% of users of most stigmatized drugs, such as heroin and methamphetamine, meet these requirements for addiction (Hart, 2021). In short, blaming drugs for what people commonly characterize as an 'addiction' is analogous to blaming food for an eating disorder. And while *dependence* is very real and dangerous, the stigma surrounding drug addictions and addicts does not correlate with the evidential and scientific understanding of the word.

While the elite pop open bottles... there simultaneously exists sharp criticism and stigma surrounding drug use within...low-income neighborhoods and communities of color.

Despite the popularized mis-

conceptions of addiction, many illegal drugs can actually be beneficial to a person's health. JFK was quoted saying "I don't care if it's horse piss, it works" when discussing the amphetamine injections he received from his physician (Kempe, 2012). Research at Johns Hopkins shows that psilocybin mushrooms (i.e. magic mushrooms) are capable of reducing depressive symptoms in 71% of patients with severe depression, and also helps people stop smoking tobacco (Johnson, et. al., 2017, Jesse, 2014). Methamphetamine is shown to treat ADHD, and marijuana is shown to treat depression, anxiety, epilepsy, and multiple sclerosis (Cunha, 2018, Keyhani, 2018). Researchers tend to exaggerate the harmful effects of illicit drugs. Many neuroimaging drug researchers conclude that any brain difference between drug users and non-drug users are deficits representing "brain damage" (Hart et al., 2020). However, these differences are commonly within the range of human brain variability and cannot be definitively considered a deficit (Hart et al., 2012). The blurred lines for what classifies as brain damage in neuroimaging highlight the objectivity in research surrounding drugs.

While the benefits of these drugs are often overlooked, researchers tend to exaggerate the harmful effects of illicit drugs.

While this evidence might seem to support an overactive use of illicit drugs, it is certainly not right to say that all aspects of psychoactive drugs are good. In 2019, over 70,000 Americans died from drug related overdoses (NIDA, 2021). Additionally, there exists strong scientific research on the hazards of substance use disorder. All psychoactive drugs produce a pleasurable surge of dopamine in the *basal ganglia* region of the brain. The receptors of dopamine adapt to these elevated levels after extended use of psychoactive drugs which makes it harder for the user to reach the same effect again; this is known as tolerance (Surgeon General, 2016). Substance use disorder also disrupts the prefrontal cortex which is responsible for judgement

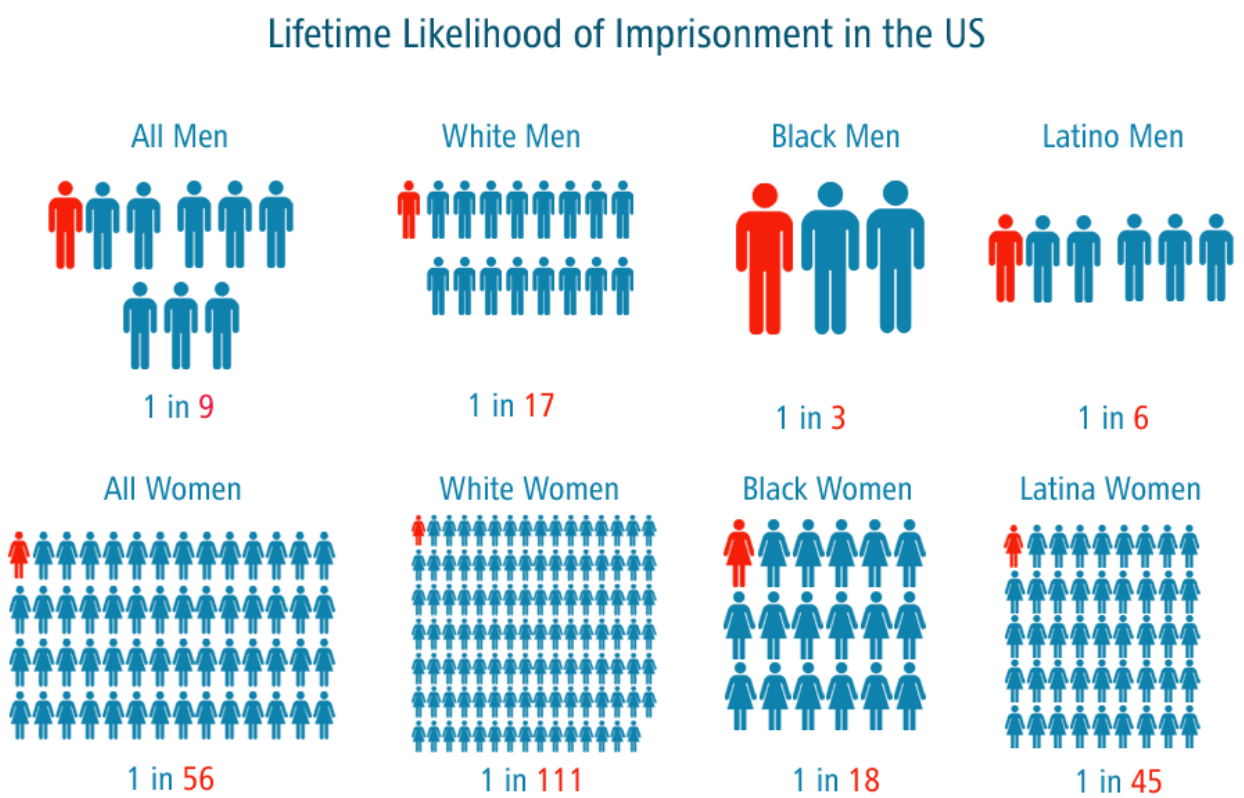


Figure 3. Visual Representation of relative likelihood of imprisonment in a single lifetime dependent on demographic; based on data from the Bureau of Justice Statistics. Image from Bonczar 2003.

and decision making (Surgeon General, 2016). Additionally, the public unanimously agrees that people should not be high, drunk, or intoxicated in any form when performing activities such as 'driving a car or taking care of a small child' (Greenfield, 1997). Certainly, the use of psychoactive drugs to intentionally or unintentionally put others in harm's way is wrong and should not be socially acceptable. However, with more regulated drug use, these dangerous incidents would likely decrease.

Research by Carl Hart, a neuroscientist at Columbia University, indicates that the majority of drug users are functional adults who experience no negative effects from consuming psychoactive drugs. He additionally asserts that no heroin user has ever died while receiving heroin in a clinic (Hart, 2021). The opioid epidemic is most concerning when discussing fatal overdoses and the deaths that occur using unregulated substances which could be laced with unknown drugs (ASPA, 2021 & Hart, 2021). According to Hart, the most dangerous aspects of drugs are the "unregulated quality and potency" as well as the "ignorance" about drug use (Hart, 2021). Observing figure 2, synthetic opioids, especifically fentanyl, are responsible for drug overdoses. Fentanyl is commonly homemade and is often mixed with other drugs creating a dangerous cocktail of drugs. The effects of drugs are predictable when the user knows what is entering their body. As soon as unknown chemicals, alterations, and other drugs are added, danger follows.

Perhaps the most impactful dangers of drugs lie not in the drugs themselves but in how they are stigmatized. There is an overwhelming amount of evidence showing that the black community is penalized more than any other group for possession and selling of illicit drugs. 62.7% of the drug offenders admitted to state prison are black, and relative to the general population, black males were reported a 13.4 times higher admittance to state prisons than white males for drug charges (Stone, 2003). However, there is no evidence suggesting that the black population consumes more drugs than the white population. In fact, the data suggested the opposite; there are five times as many white drug users than black (Stone, 2003).

black males were reported a 13.4 times higher admittance to state prisons than white males for drug charges... there is no evidence suggesting that the black population consumes more drugs...

How is it that a 13.4:1 ratio of black to white drug incarcerations mutually exists with a 5:1 ratio of white drug users to black drug users? The evidence is clear. Racial prejudice is leading to a situation in the United States where black people are disproportionately harmed.

In this discussion, it is also important to address the socio-economic aspect of the situation. Marginalization occurs most frequently towards groups who lack social resources (Room, 2005). Additionally, alcohol and drug use are extremely stigmatized topics. In 2016, the net worth of the average white family was ten times greater than the average net worth of a black family (McIntosh et. al., 2020). A wealth gap is clearly present among the black and white population, resulting from centuries of systemic racism. In order to give every citizen of the United States the "unalienable Rights...Life, Liberty and the pursuit of Happiness," the way psychoactive drugs are treated in the United States must change.

Progressing the conversation on topics such as drug inequity is just one way change can start to occur regarding injustice in the United States. Over the past century, the stigma surrounding drugs in the United States has only grown. Now, psychoactive drugs are viewed through a lens so polarized that black males are incarcerated for drug-related charges 13.4 times more often than white males. With no *cure* and many *treatments* widely contested, perhaps the most impactful thing we can do is address the facts and deconstruct the stigma surrounding drugs in America. It is through this that change is made so that every citizen has life, liberty, and happiness. ❧

AUTHOR BIO

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Precision nanoparticle-based drug delivery systems: A review of design & function

ANIRUDH RAGHAVAN
Staff Writer

Nano-based therapeutics is a relatively young yet exceedingly lucrative field focusing on small particles with immense clinical potential. The technology can potentially revolutionize the pharmaceutical industry by providing a viable alternative to existing drug delivery systems. The nanomedicine industry is projected to reach a total market value of $334 billion by 2025 (Bowman et al., 2017). Nanoparticles used for targeted drug delivery are generally less than 100 nm in size, and are composed of biodegradable materials such as natural or synthetic polymers, lipids, or metals (Suri et al., 2007). Traditional large-scale materials utilized as drug carriers are limited in some regards because of their poor bioavailability, instability *in vivo*, and their incapacity for sustained and targeted delivery to a specific site of action. Nanomedicines are candidates to address these shortcomings: due to their small size and large surface area, drug nanoparticles have greater solubility and thus increased bioavailability, a capacity for localized drug delivery, and can provide controlled and targeted drug release. Their nano-scale form factor also has certain added physiological advantages, such as the ability to be absorbed across the tight junctions of endothelial cells of the skin, traverse the blood brain barrier, and enter into the pulmonary system (Kohane, 2007). Further, some nanoparticles have been developed for use in precision medicine, with applications for diseases such as cancer, for which personalized interventions have been shown to possess an especially high therapeutic efficacy (Sahakyan et al., 2017). Nanomedicines enhance the effectiveness and safety of conventional drugs whilst minimizing their side effects, thereby improving patient compliance and reducing health care costs. With an increase in funding and pharmaceutical interest dedicated towards engineering nanoparticles for specific biomedical applications, new opportunities have arisen for the clinical translation of nanoparticle-based precision therapies in fields including oncology and *in vivo* gene editing (Mitchell et al., 2021). This uptick in new research warrants a discussion of the design and function of contemporary precision nanoparti-

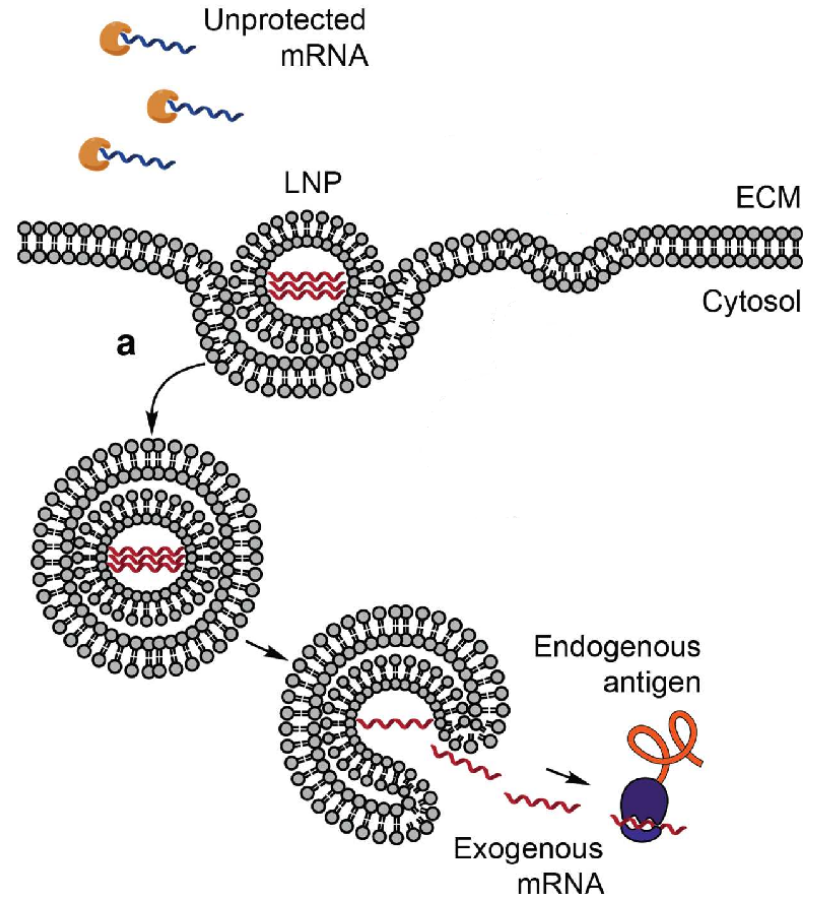

Figure 1. A schematic of mRNA vaccine delivery using lipid nanoparticles (LNPs). Lipid nanoparticles protect mRNA from degradation, as well as facilitate endocytosis. Translation requires the escape of mRNA from the endosome. Image from Reichmuth et al. 2016.

...due to their small size and large surface area, drug nanoparticles have greater solubility and thus increased bioavailability...

cle-based drug delivery systems.

Of the main nanoparticle (NP) classes, lipid-based nanoparticles are the most common FDA-approved class due to their ease of formulation, self-assembling nature, high biocompatibility and bioavailability, and capacity for carrying relatively large payloads (Sercombe et al., 2015). Even in the current vaccine against SARS-CoV-2 developed by Moderna and BioNTech, the mRNA that encodes the COVID-19 antigen is delivered via a lipid-based nanoparticle (Figure 1) (Mitchell et al., 2020). Lipid-based NPs structurally consist of at least one internal aqueous compartment surrounded by at least a single lipid bilayer. The two most notable subsets of lipid NPs currently in clinical use include liposomes and lipid nanoparticles (LNPs). Liposomes typically consist of layers of phospholipids, and the structures can be modified to form multilamellar vesicular structures, which have multiple membranous folds. These corrugations enable the liposomes to not only transport and deliver hydrophilic and hydrophobic molecular payloads, but to also capture hydrophilic and lipophilic compounds (Mitchell et al., 2021). LNPs, on the other hand, are specialized for the delivery of nucleic acids. They are characterized by an ionizable lipid composition which can form complexes with the negatively charged backbone of genetic material, aiding in intracellular delivery. Lipid-based NPs, however, often suffer from low drug loading capacity and low biodistribution due to rapid uptake by the liver, spleen, or immune system (specifically the reticuloendothelial system), so modifications are needed to promote their *in vivo* stability and circulation lifetime (Fenton et al., 2018).

The second class of NPs, and possibly the best suited for simultaneous delivery of different payloads, is termed polymeric NPs. Polymeric NPs are synthesized from natural or synthetic polymers, and different polymerization routes lead to distinct structures which can be manipulated for controlled drug-delivery loading and release efficacies. This can be achieved through the alteration of polymer composition, polymer stability, and surface charge (Patra et al., 2018). The two broad categories of polymeric NPs are nanospheres, which consist of a solid polymeric matrix, and nanocapsules, which are composed of a central cavity surrounded by a polymeric shell. Certain subclasses of nanocapsules, particularly polymersomes, have been shown to have better cargo-retention efficiency, stability within the cytosol, and

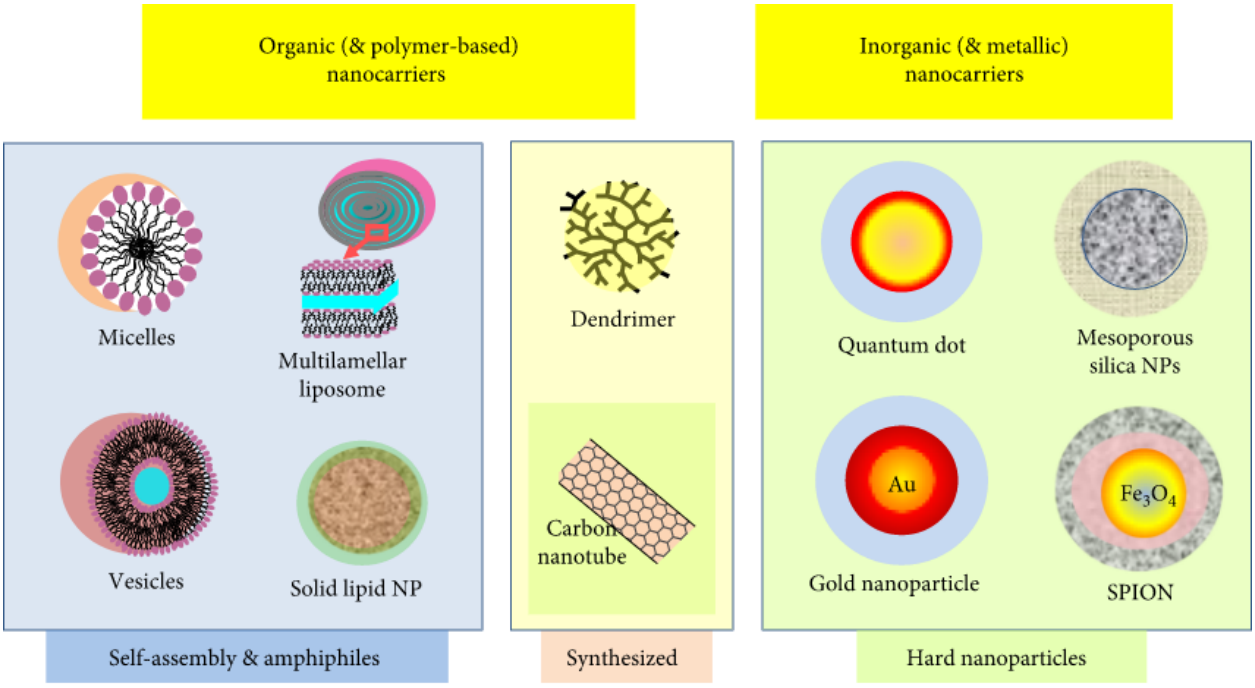

Figure 2. An illustration of the most employed organic and inorganic nanoparticles for drug delivery. Image from Lombardo et al. 2019.

circulation times, relative to liposomes. Dendrimers, a hyperbranched and complex variant of polymeric NPs, are now increasingly prevalent and undergoing clinical trials. They can deliver a wide range of biomolecules, and their movement can be tracked as well. The placement of functional groups on the exterior surface of dendrimers allow the conjugation of imaging agents to the surface, while drugs can be loaded into the interior (Mitchell et al., 2021). Despite these advantages, polymeric NPs have a greater toxicity risk due to a known propensity for particle aggregation. Currently, only a small proportion of polymeric NPs are FDA approved and used in the clinic (Anselmo & Mitragotri, 2019).

The final broad class of NPs are inorganic NPs, synthesized using metals such as gold and aluminum, which are capable of forming a wide variety of structures including nanospheres, nanorods, and nanostars (Yang et al., 2019). Inorganic NPs have unique, electrical, magnetic and optical properties owed to their metallic nature. For instance, gold-based NPs possess free electrons at their surface that continually oscillate at a size and shape-dependent frequency, giving rise to photothermal properties (Wang et al., 2020). Such properties are the basis for photothermal therapy, wherein electromagnetic radiation-induced activation of a photothermal agent causes thermal damage in the region of interest (when done at a site of a tumor, this procedure is called thermal tumor ablation). Due to their magnetic and radioactive properties, inorganic NPs

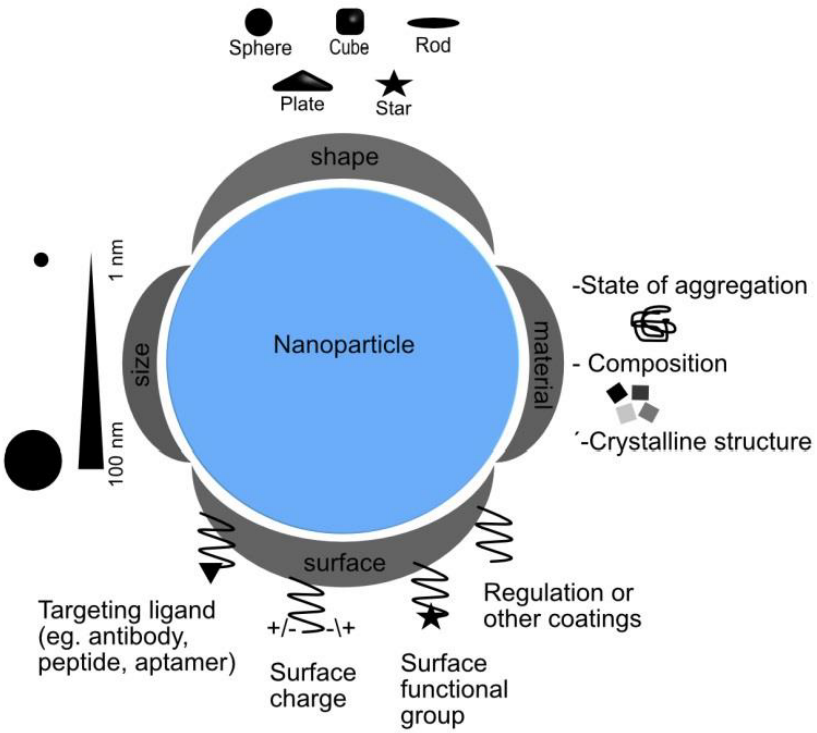

Figure 3. A schematic of the main physicochemical properties of nanoparticles which mediate interaction mechanisms in biological systems. Image from Auria-Soro et al. 2019.

are better suited than organic NPs for diagnostic and imaging applications, as well as for photothermal therapies (Mitchell et al., 2021). However, as they are often heavy metal-based, their clinical application is limited by their low solubility and high toxicity. A general overview of the aforementioned broad classes of NPs is presented in Figure 2.

Nanoparticle applications in precision medicine are an area of growing interest, and can be designed and customized to address heterogeneity in biological barriers and disease states across patient populations (Figure 3). A major application is cancer treatment, and a primary consideration of NP design in this regard relates to adapting NPs to the tumor microenvironment. Said microenvironment impacts chemotherapeutic efficiency, and thus influences patient prognosis. NPs wrapped with membranes harvested from a patient's own cancer cells, however, have been shown to adhere selectively to patient-derived cancer cell lines (He et al., 2020). NPs utilizing patient-derived membranes show a twofold to threefold increase in drug activity in comparison to free administration of the drug (Wang et al., 2020). Another mechanism of action, present in an NP design called iCluster®, features a clustered NP system that divides into smaller and smaller components as it traverses biological barriers in the tumour microenvironment (Li et al., 2016). A starting size of around 100 nm allows the initial particle to circulate extensively within the bloodstream and exploit the enhanced permeability and retention (EPR) effect seen

in tumors. This effect refers to the leaky vasculature and poor lymphatic drainage found within tumors that create a perfect environment for the accumulation of nanoparticles (Wang, 2015). At the tumor site, the acidic pH environment triggers breakdown of the original 100 nm system into dendrimers of about 5 nm in size, improving the particles' tissue penetrating abilities and expediting the delivery of chemotherapeutic agents. This effect is extremely significant: in vivo studies demonstrated that intravenous administration of a free drug inhibits tumor growth by 10%, whereas drug administration via the iCluster system inhibits growth by up to 95% (Li et al., 2016).

Nanoparticle applications in precision medicine...can be designed and customized to address heterogeneity in biological barriers...

In the realm of gene editing and genomic engineering, NPs have been utilized in gene therapies for cystic fibrosis. Cystic fibrosis is an autosomal recessive disease which impacts mucus-producing cells and epithelial cells in the body, leading to mucus that is very thick in consistency. Specifically, mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) protein impacts its ability to fold properly. The protein can normally be found on many surfaces in the body, aiding in the maintenance of salt and water balance, but the mutations effectively prevent CFTR from reaching these surfaces. As a result, chloride (a component of table salt) becomes trapped in cells, which results in lack of hydration of the cell/tissue surface. Treatment entails delivering nanoparticles into the epithelial cells, but the thick mucus presents a formidable barrier to delivery. New nanoparticle treatment strategies, however, utilize nanoparticles smaller than the pores of the mucosal matrix and coated with inert hydrophilic motifs (for example, polyethylene glycol) to penetrate through the thick mucus lining. This approach has shown promise in rodent models (Witten et al., 2018). Normal CFTR mRNA delivered in this manner results in the restoration of 10-35% of CFTR protein function, significantly reducing disease severity (Robinson et al., 2018). However, *in utero* drug delivery treatment for genetic diseases such as cystic fibrosis seem to be a more effective cure, as gene editing is most potent during the fetal stage. NP-based therapies can be directly injected into the amniotic fluid, an umbilical blood vessel, or a specific fetal tissue (Deweerdt, 2018), and gene editing driven by in utero NP delivery of peptide nucleic acids has been demonstrated (Ricciardi et al., 2018).

The heterogeneous nature of patient populations and the complexities associated with disease progression complicate NP design. Contemporary clinical successes related to the use of NPs in precision medicine have mostly been diagnostic in nature, such as determining which therapeutic route might be best for a particular patient based on specific biomarkers. For instance, as mentioned above, quantifying the EPR effect in a cancer patient can predict the efficacy of NP therapy in terms of tumor site accumulation (Lee et al., 2017). However, in developing precision medicine along with advancing NP design to increase specificity and localized activity whilst reducing consequent toxicities, the clinical effects of precision medicine therapeutics can be enhanced overall, potentially widening the populations they can benefit and improving patient outcomes. ❧

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Anirudh Raghavan is a third year in the college double majoring in Chemistry and Biology. He can read, write and converse in four different Indian languages.

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Prion diseases: Fatal neurodegenerative diseases

LAURA PAULE
Staff Writer

Prion diseases are devastating neurodegenerative diseases that have become an increasing public health concern among the scientific community. They transmit both through animal-to-human and human-to-human contact. Although prion diseases only occur 1-1.5 times per million people per year in most of the developed world (NIH, n.d.), they are lethal because no effective treatments are available.

Prion diseases can be caused via three different mechanisms: spontaneous, genetic, and acquired. Regardless of the mechanism, prions cause disease when their altered form rapidly propagates in nerve cells. Propagation occurs when a normal cellular prion protein, Prp^{C} ("C" stands for cellular), comes into contact with the misfolded protein, Prp^{Sc} ("Sc" stands for scrapie, the prion disease of goats). Upon contact, Prp^{C} turns into Prp^{Sc}, and this propagation continues exponentially (Mastrianni, 2009; Knight, 2004). This paper explores these three different mechanisms of human prion diseases, and discusses advances in the research and development of drugs for their prevention and treatment.

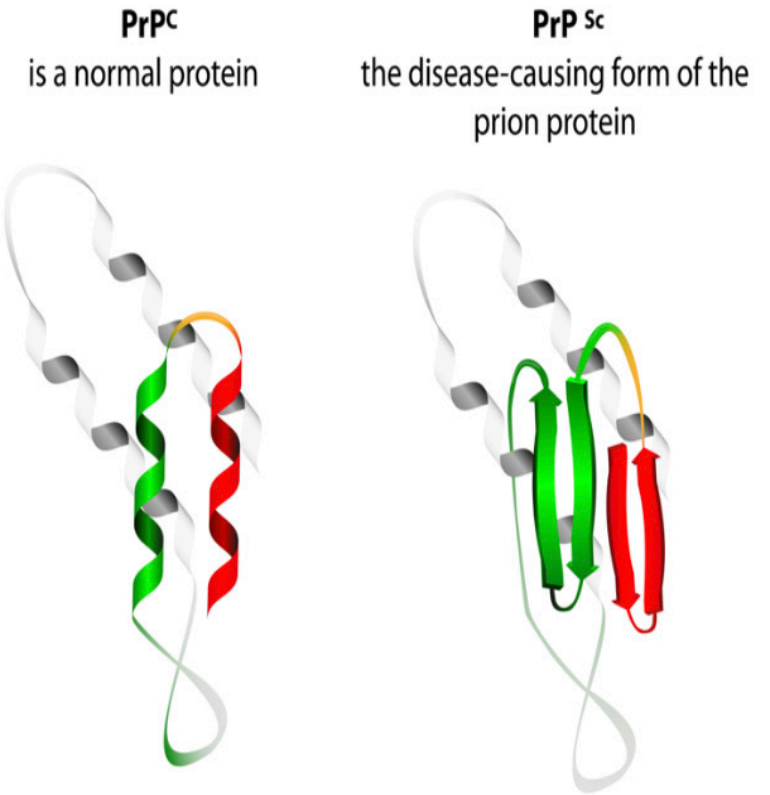

Figure 1. This image shows the normal cellular prion protein and the insoluble pathogenic scrapie prion protein. Of particular interest is the transition from the alpha-helix structure to the beta-pleated sheet structure. Image from CJD Foundation.

Spontaneous or sporadic prion disease strikes suddenly without a known cause. Sporadic Creutzfeldt-Jakob disease (CJD), the most common of all human prion diseases, is characterized by rapidly progressive dementia with major damages to cognitive skills, memory, thinking, and behavior. Although no major risk factors have been identified, sporadic CJD tends to develop later in life, at around 55 to 75 years of age (Mayo Clinic, 2021); patients who have the disease often die within a year of onset. Some of the early symptoms of CJD include fatigue, headache,

Figure 2. This image portrays the process of propagation in prion disease. These prions form aggregates that lead to neuronal damage. Image from medbullets 2018.

dizziness, blurred vision, insomnia and impaired thinking (Mastrianni, 2009). Because CJD affects many areas of the brain (CDC, n.d.), it can present as other neurologic or psychiatric conditions. In fact, CJD is known as *The Great Mimicker* for its similarities to other neurodegenerative diseases. This resemblance has led to many incorrect diagnoses. As the disease progresses, the patients suffer from worsening mental symptoms that lead to coma. Death is often the result of heart failure, infections or respiratory failure instigated by CJD (Mayo Clinic, 2021).

Prion diseases can be caused via three different mechanisms: spontaneous, genetic, and acquired.

Prion diseases may also be caused by mutations in the prion gene (PRNP) on chromosome 20. It is thought that these mutations make the prion protein, PrP^{C}, more susceptible to transformation into PrP^{Sc}, the abnormal and infectious prion protein (Prusiner, 1998). There is a significant number of mutations that have been identified to date, including base-pair insertions, the substitution of glutamic acid (E) for lysine (K) at the 200th amino acid in the protein sequence (E200K), and the codon 129V polymorphism (Will, 2003). In comparison to sporadic CJD, genetic prion diseases have a longer mean duration of illness and a lower mean age of onset. Genetic prion diseases also have a wider range of clinical phenotypes due to the variety of mutations. The age of onset ranges from childhood to the elderly, and the duration of the disease ranges from months to decades. The wide spectrum of phenotypes is not the only factor that makes it difficult to diagnose genetic prion diseases. These diseases also tend to be clinically indistinguishable from non-genetic forms, and in many cases are very similar to other neurological diseases like Alzheimer and Huntington's disease. Although these prion diseases are genetic, patients do not often have a family history of the disease (Geschwind, 2015), suggesting the mutations arise spontaneously.

Human prion diseases can also be transmitted from human to human. Acquired forms are rare, but they have had a major impact in public health. The first known acquired prion disease was Kuru. Recorded in 1957, Kuru initiated a devastating epidemic that affected the Fore people of Papua New Guinea (Mead et al., 2009), predominantly children and women. Since then, the disease has almost been eradicated due to the cessation of cannibalism, which was the primary means of transmission. Recent studies have found that a polymorphism in the prion protein at codon 127 likely provided resistance to Kuru, and in-depth understanding of this polymor-

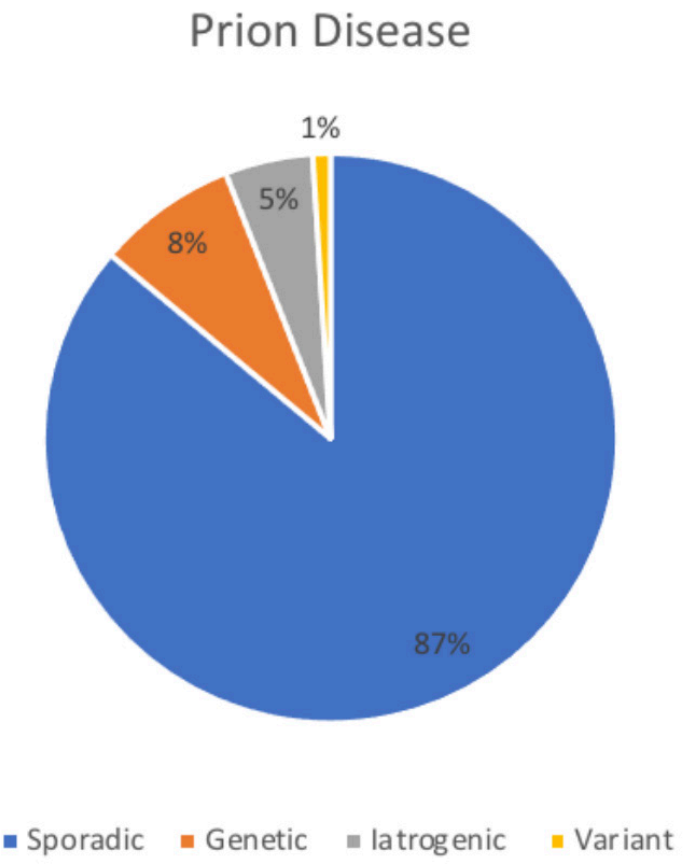

Figure 3. The proportions of sporadic, genetic, and acquired prion diseases as determined by a collaborative study of CJD in the European Union (Duijn, 1998). Image from Prion Alliance 2013.

phism could facilitate the development of treatments for prion disease (Mead et al., 2009).

Prion diseases can also be passed from human to human like infectious agents, like when tissues or organs (or instruments that have touched them) from those with prion diseases are transferred to or used on others. Multiple measures have been taken to minimize such transmission: medical institutions use man-made human growth hormone instead of hormone derived from the pituitary gland; the surgical instruments used on the nervous tissue of patients with suspected CJD are immediately destroyed; and people with a high risk of exposure to CJD are not allowed to donate blood in the United States (Mayo Clinic, 2021).

Spontaneous or sporadic prion disease strikes suddenly without a known cause.

Scientists have not yet developed effective drugs for prion disease treatment. For many years, a wide variety of tools and interventions targeting different stages of the disease have been developed, but very few have made it to clinical trials. The PrP^{C} protein has been targeted to enable removal of substrates for prion propagation, and the process of conversion from PrP^{C} to PrP^{Sc} has been targeted in the effort to prevent transmission. Although these interventions have not yielded conclusive results, experts continue to research potential therapeutic strategies, which include the degradation of PrP^{Sc} through its interaction with the ubiquitin-proteasome system (Chen & Dong, 2020).

As portrayed in this paper, prion diseases have been identified and studied since the 1950's, but no treatments are available to date. Although uncommon, prion diseases continue to pose a challenge to experts and the healthcare system. This demands vigilance regarding mechanisms of prion transmission and studies to develop treatments and methods of diagnosis. ❧

AUTHOR BIO

Laura Paule is a third year in the college double majoring in Biology and Spanish & Portuguese. The hobby she could never give up is playing chess.

Edited by Alex Sandberg, Andy Chen and Dr. Arri Eisen

Placed by Vivian Huang

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Music and medicine: Treating neurological disorders with musical therapy

Figure 1. Patient receiving music therapy intervention via playing the piano. Image from Antal 2020.

DAPHNE IH
Staff Writer

KEVIN GE
Staff Writer

Music and sound are integral to the human experience, and not just for aesthetic or survival purposes. Melodies, harmonies, and rhythms—both instrumental and lyrical—are inherently personal and relatable. In other words, music not only stimulates the senses, but also initiates a variety of other mental and physical responses. For example, the symbolic words and imagery encountered within music can trigger the release of certain neurochemicals, ultimately changing an individual's emotions and mood. Sometimes, this response can even influence movement: people may start drumming their fingers, swaying, or dancing in time with the beat (Blair, 1987 as cited in Jones, 2021; Bruscia, 1998 as cited in Jacobsen et al., 2019a; Moreno-Morales et al., 2020; Altshuler, 1954; Thaut et al., 1999; Thaut et al., 2015).

These observed mind-body effects form the foundation of musical therapy, a type of rehabilitative intervention that aims to diminish the impairments to memory and motor activity associated with neurological illnesses and brain disorders like dementia, Parkinson's disease, autism, and epilepsy. Unlike standard clinical treatments, there is no single definition for "proper" musical therapy—rather, it is a highly individualized, qualitative experience that is tailored to a patient's background and tastes. This unavoidable ambiguity has made it difficult for scientists to conduct careful, controlled experiments that can be used to make appropriate comparisons. In fact, most conclusions regarding the efficacy of musical therapy are based on empirical observations and patient testimonies of signs and symptoms (Altshuler, 1954; Jacobsen et al., 2019b, p. 410; Moreno-Morales, 2020). Yet regardless of these limitations, musical therapy remains a promising approach.

Compared to pharmacological methods, musical therapy is

markedly less invasive and less potentially harmful to patients—which is not only a benefit in and of itself, but also avoids the possible distress of concerned family members, caregivers, and patients themselves (Devere, 2017; Moreno-Morales et al., 2020; Stegemann et al., 2019). Viable, non-pharmacological treatments like musical therapy are becoming increasingly important in a time when healthcare practitioners are often quick to prescribe intense pharmacotherapy. Despite being helpful in some cases, heavy medication is not appropriate for all patients. This issue can be exacerbated by physicians who may overlook a patient's personal needs and beliefs. Furthermore, pharmacological treatment, while effective in acute cases, can potentially be detrimental to the long-term well-being and quality of life for patients struggling with chronic disorders (Gawande, 2014; Kallivayalil, 2008).

Various musical interventions have been chronicled in the scientific literature dating as far back as the 1800s. Examples include listening to different genres of music, moving in time to metronomic beats, and improvising song and dance (American Music Therapy Association, n.d.; Bradt et al., 2010; Dawes, 1987 as cited in Jones, 2021; Moreno-Morales, 2020; Ruud, 1998 as cited in Jacobsen et al., 2019a; Skewes, 2002 as cited in Jones, 2021; Thaut et al., 1999; Zatorre, 2003). In one case study, musical instruments were used to treat childhood apraxia in a three-year-old girl named Lily (Beathard & Krout, 2008). Prior to musical therapy, Lily had difficulty articulating the sounds necessary for speech and only communicated nonverbally, through American Sign Language. Using a piano and guitar to play simple tunes like "Hello Song" and "Old MacDonald," musical therapists encouraged her to verbalize basic sounds from the song lyrics she heard. After nine months of treatment and practice, Lily learned to pronounce over 10 different syllables, combination sounds (*e.g.*, "ba", "da", "ma"), and several complete words. In addition, Lily's clinicians noted significant concomitant improvements in her social skills, ambulatory movements, and cognition.

Viable, non-pharmacological treatments like musical therapy are becoming increasingly important in a time when healthcare practitioners are often quick to prescribe intense pharmacotherapy.

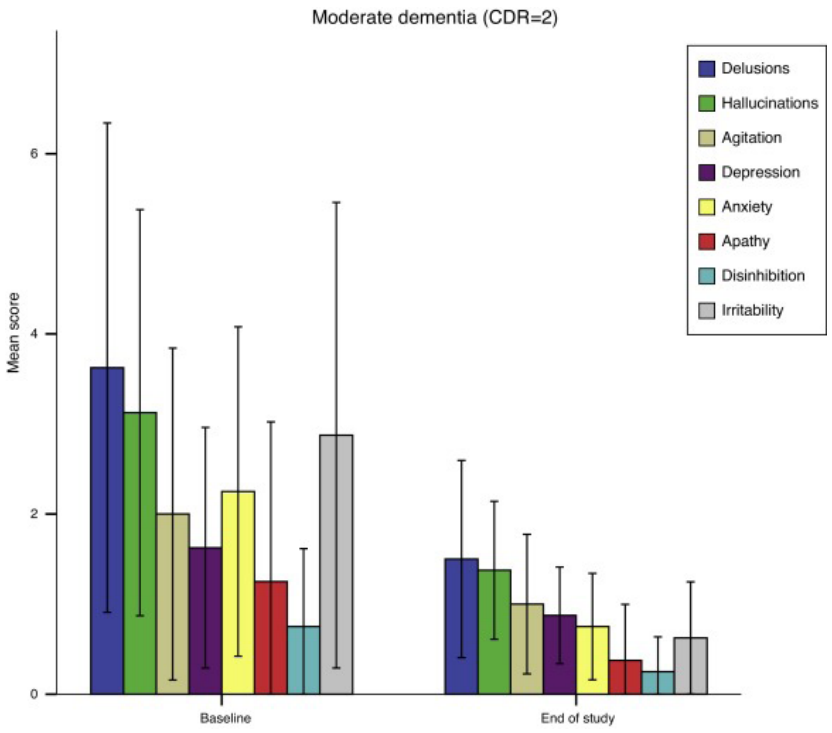

Figure 2. Decrease in Neuropsychiatric Inventory (NPI) test score, indicating less symptoms. Image from Gomez & Garcia 2017.

For years, scientists have struggled to explain the biological mechanisms behind the therapeutic nature of music. One theory proposed by the late psychiatrist and pioneering musical therapist, Ira Maximilian Altshuler, suggests that humans are inherently rhythmic beings, and he identifies heartbeats, gait, and blinking as examples of a "perpetual state of rhythmical swing" (Altshuler, as cited in Podolsky, 1954, p. 27). Because of this innate inner rhythmicity, people naturally respond to other patterned sounds and melodies, as reflected in their fluctuating emotions, attitudes, and actions (Altshuler, 1954). Speaking from

a more neurological perspective, Altshuler further reasons that music activates the thalamus, a key region of the brain responsible for sensations, emotions, and aesthetic feelings. The thalamus is connected to the brainstem and cerebral hemispheres—the center for higher-order thinking and cogitation—such that stimulation of the thalamus can activate the cortex, a region of the cerebral hemispheres, and vice versa, resulting in a feedback loop. With this "back door route," music doesn't require what we typically think of as cognitive intelligence to initiate behavioral or physical responses. Its universality is what makes it effective across a variety of conditions, particularly in cases of impaired reasoning or logic (Altshuler, 1954; Jacobsen et al., 2019a, p. 52).

The first significant research linking the auditory system to the brain and muscle was conducted by Paltsev and Elner (1967). Citing and building on the earlier theory of Altshuler, they discovered that auditory signals can activate muscles through reticulospinal pathways. Since then, other research has shown that the auditory system is functionally connected to motor centers in the brain and spinal cord through richly distributed fiber connections (Koziol & Budding, 2009). More specifically, the auditory pathway involves connections between the inferior colliculus and dorsolateral pontine nuclei in the brainstem, which influence motor activity (Tierney & Kraus, 2013). Chen et al. later found that the inferior colliculus may have circuitry that directly links sensory inputs with motor outputs (2018).

These findings regarding the inferior colliculus present an explicit relationship between motor activity and auditory inputs, emotions, and other senses. In 2013, Tierney and Kraus discovered that neural responses in the inferior colliculus synchronized to a rhythmic stimulus upon musical activation of this pathway, corroborating Fujioka et al.'s prior work, which demonstrated a link between neural oscillation patterns in the auditory system and rhythmic stimuli (2012).

Connecting this back to motor rehabilitation, additional research has shown that impaired brains can still access the motor system through rhythmic auditory stimuli. For instance, in a study of Parkinson's patients, researchers found a correlation between rhythm and step frequency in both the control group and treatment group (McIntosh et al., 1997). Moreover, they observed improvements in gait velocity (walking speed), cadence (steps per minute), and stride length in all groups in response to a

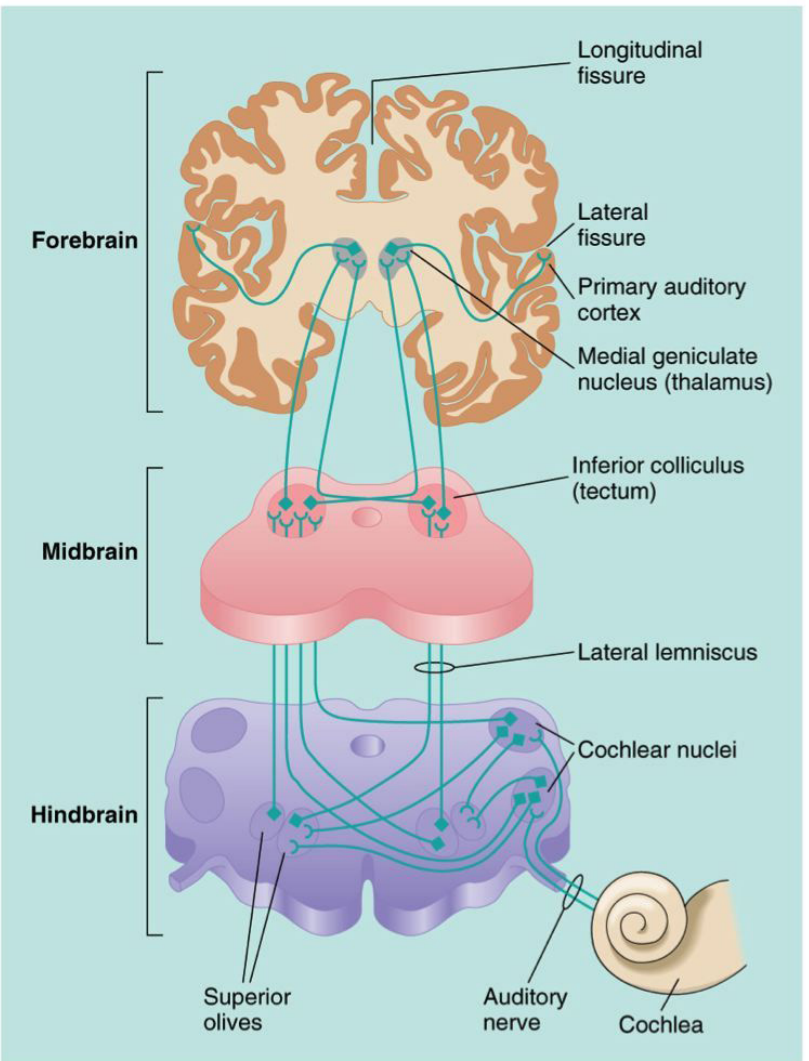

Figure 3. Diagram of the primary auditory pathway in the human brain. Image from Soderstrom.

faster rhythmic auditory stimulation. This evidence further supports Altshuler's "back door" hypothesis, which implies that rhythmic stimuli can impact motor function despite deficiencies in brain regions that control movement (*i.e.* abnormality in primary motor cortex in Parkinson's).

Given this, it is no surprise that musical therapy has been used to treat a range of brain-related diseases with notable success. Musical therapist Kirsty Ormston claims to have taught Joe—a non-verbal pediatric patient on life support with brain damage from meningitis—how to say "hello" just by playing her guitar and singing in a manner that mimicked his breathing and facial expressions. After three months of musical synchronization and stimulation, Joe demonstrated increased oxygen levels, liveliness, and confidence; this culminated in his first vowel vocalization, which doctors originally claimed to be impossible for Joe to achieve (Ormston, 2019). Recently, NPR also reported that a mother with dementia regained her memories and speaking abilities just by playing Christmas carols on the piano with her daughter. Northwestern University neuroscientist Nina Kraus explains this anecdote, stating that there is a tight connection between memory systems and auditory systems in the brain that allows music to evoke lost memories (Neighmond, 2019).

While the neural basis for music therapy is not completely understood, it still holds value as a noninvasive alternative for potentially harmful pharmacotherapy. Currently, music therapy is primarily used as a pain-reducing complement following treatments like neurosurgery. However, the intervention has already started to expand into various fields such as cognitive rehabilitation and speech and language rehabilitation. As research on the mechanisms of music therapy and its applications continues to progress, this intervention could potentially become a new staple in treating neurological disorders and other diseases. ❧

...music doesn't require what we typically think of as cognitive intelligence... Its universality is what makes it effective across a variety of conditions...

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Daphne Ih is a first year in the college majoring in Neuroscience and Behavioral Biology with a minor in Political Science. Several years ago, she wrote a 50,000-word story for National Novel Writing Month.

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Senior Lecturer and Director of Undergraduate Studies at Emory University

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).

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Dr. Marks is professor emeritus of epidemiology and public health at Yale. His research interests center around sensory disorders and perceptual experiences such as synesthesia. Though retired, he is active in writing and collaborates with other researchers in his areas of interest.

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Dr. O'Neill is a palliative medicine physician who is active in both clinical and educational pursuits. When she isn't providing medical counseling, Dr. O'Neill oversees all the educational activities of the Emory Palliative Care Center of which she is associate director.

GREGG ORLOFF

Doctorate from Emory University

Dr. Orloff is a senior lecturer at Emory University teaching biology to undergraduates and the director of the CancerQuest program which he founded back in 1998. He created the program to provide accurate information about cancer to inquiring patients and it is now been operating for more than two decades.

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LAURA OTIS

Doctorate in comparative literature from Cornell University

Dr. Otis had her beginnings in science, earning a bachelors in molecular biophysics and biochemistry from Yale and then a masters in neuroscience from the University of California at San Francisco. Now at Emory, she teaches the intersection of science and literature with special interest in nineteenth century novels.

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Dr. Blanton is an associate professor of rehabilitation medicine at Emory with a research interest in improving the delivery of family-centered care in rehabilitation. She also serves as editor-in-chief of the Journal of Humanities in Rehabilitation whose mission is to integrate the humanities into rehabilitation science.

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Dr. Soodalter is a hospice and palliative care specialist in the Emory Healthcare network. She also collaborates with physicians from places as far as Pittsburgh where she most recently completed a fellowship in 2019.

Executive Board

NATHAN JACOB

Editor in Chief - Copy

Nathan is a third year majoring in Biology with a minor in Philosophy. He began as first-year liaison, went on to serve as the club secretary, and now as editor in chief - copy, he hopes to expand EUMR's impact on bringing about awareness of the interdisciplinary nature of medicine. 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!

DAISY LI

Editor in Chief - Layout

Daisy is a third 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. Since becoming editor-in-chief, her 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.

ANJANAY NANGIA

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Anjanay is a second 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 secretary, he is involved in events planning, facilitating the editorial process, and social media initiatives to advance EUMR alumni engagement. He has survived quarantining by learning how to cook and catching up on his favorite movies and shows.

GANESH CHILUKURI

Treasurer

Ganesh is a second year majoring in Neuroscience and Behavioral Biology with a minor in South Asian Studies. He began as a contributing writer for EUMR's Open Access and now as treasurer, he works on budgeting for all of EUMR's 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.

THALIA LE

Events Chair

Thalia is a third year majoring in Biology and minoring in Chemistry. She began as a staff editor on the Editorial Board and now as the Events Chair, organizes the many on-campus events that EUMR puts on every year. Outside of the club, she does research in medicinal chemistry, volunteers through Emory Hope and CHOA, and enjoys mentoring/tutoring underclassmen. In her free time, she enjoys cooking and baking. Thalia also has alektorophobia, a condition characterized by an intense fear of chickens!

Editorial Board

copy editors

ADITYA JHAVERI
Aditya is a fourth year double majoring in Neuroscience & Behavioral Biology and Quantitative Sciences.

ALEX SANDBERG
Alex is a fourth year majoring in Chemistry. He hates cheese!

ANDY CHEN
Andy is a fourth year double majoring in Anthropology & Human Biology and Neuroscience & Behavioral Biology.

BUSHRA RAHMAN
Bushra is a third year double majoring in Anthropology and Spanish & Portugese. She has written a play before.

EDWARD XUE
Edward is a second year double majoring in Psychology and Chemistry. Drinking coffee makes him sleepy.

HELEN GRIFFITH
Helen is a second year double majoring in Neuroscience & Behavioral Biology and Spanish. She has a yellow lab puppy.

LAUREN FLAMENBAUM
Lauren is a fourth year majoring in Neuroscience & Behavioral Biology and minoring in Anthropology. She grew up in France.

LIZZY WAGMAN
Lizzy is a second year majoring in Anthropology & Human Biology with a minor in Ethics. She plays golf!

LUISA TAVERNA
Luisa is a second year majoring in Biology and minoring in Philosophy. She is fluent in Italian!

NIVETHA ARAVIND
Nivetha is a third year majoring in Human Health. She has been learning a classical Indian dance form since she was 6!

RHEA TUMMINKATTI
Rhea is a third year majoring in Anthropology & Human Biology. She enjoys singing.

SARAH KIM
Sarah is a third year studying Chemistry and Psychology. She loves taking walks and exploring music videos.

VYAS MURALIDHARAN
Vyas is a fourth year majoring in Quantitative Sciences and minoring in English. He once managed to sleep 25 hours straight!

Editorial Board

layout editors

ALBERT LIU

Albert is a third year pursuing a bachelors of arts in Economics.

ALICIA YIN

Alicia is a second year majoring in Biology. Her favorite place that she's traveled to is Jordan.

ANSHRUTA DHANASHEKAR

Anu is a third year majoring in Neuroscience & Behavioral Biology and Creative Writing. She has a black belt in karate.

CARISSA WU

Carissa Wu is a second year majoring in Biology. She has visited countries on five different continents.

HENRY MANGALAPALLI

Henry is a third year double majoring in Biology and Sociology.

JOCELYN CHOW

Jocelyn is a third year majoring in Neuroscience & Behavioral Biology with a minor in Music. She has a pet betta fish.

RACHEL XUE

Rachel is fourth year majoring in Human Health. She enjoys making friendship bracelets in her free time.

SHREYA RANA

Shreya is a third year majoring in Neuroscience & Behavioral Biology and minoring in Computer Informatics.

SRI PONNAZHAGAN

Sri is a fourth year majoring in Psychology with a minor in Astronomy.

VIVIAN HUANG

Vivian is a fourth year double majoring in Biology and French Studies. She has been playing piano for 17 years.