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Cover photo by Rachel Xue

EMORY UNDERGRADUATE MEDICAL REVIEW

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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 President Sterk.

LETTER FROM THE EDITOR

Dear Reader,

In the first ever issue of the Emory Undergraduate Medical Review, the founder wrote on EUMR's purpose: "to keep undergraduates engaged with interesting and important topics in the medical world by publishing peer-reviewed student-written articles." It is my hope that, now in our sixth year and counting, we have not only fulfilled that purpose but exceeded it.

We began the year 2019 with change in mind. Most notably, we expanded our online presence, commencing renovations on our website which were long overdue, and reinventing the original "blog" as EUMR Open Access. To keep up with this new demand for content, we expanded our staff to the largest editorial board yet, made up of more than fifty members across all academic years.

Moreover, the issue you have open on your laptop or are holding in your hands right now has an entirely reimagined design. We implanted the original EUMR vision within an updated and modern format, taking inspiration from professional journals. The content, assuredly, is very much the same and I encourage you to flip ahead to read about a detailed history of assisted reproductive technologies, the resurgence of measles from the anti-vaccination movement and how acupuncture from Eastern medicine can help stroke patients heal.

I would like to take the time to thank our dedicated editorial board in making another EUMR volume possible. This publication is entirely student-run, meaning that a lot of midnight oil was burned churning out articles, edits, and revisions. My guess is that my many messages and emails got old as the semester wore on, but hopefully the end product made it all worth it.

Many thanks, as well, to all of the professors and doctors who make up our advisory board and take time out of their busy schedules to mentor undergraduates. Your guidance is important to all the aspiring doctors and budding writers within EUMR.

With that said, please enjoy this issue. I promise it is much less boring than this letter.

Cordially,

Daisy Li
Editor-in-Chief
EUMR 2019-2020

Antibody drug conjugates: hope for the future of cancer treatment

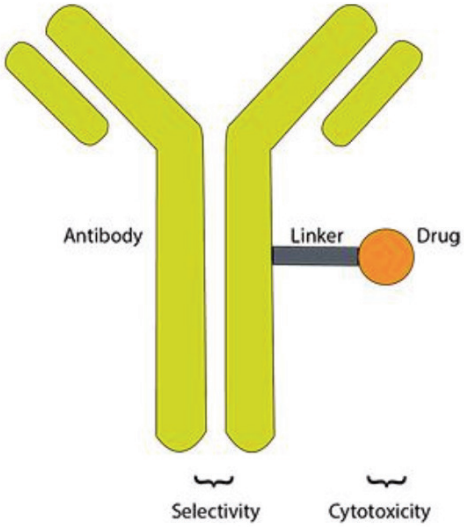

Figure 1. The basic mechanism behind antibody drug conjugates. Image from Castro 2017.

LARISA KOYEN
Staff Writer

In 2018, over 600,000 people were estimated to have died from cancer in the United States alone ("Cancer Statistics"). Despite being one of the oldest known human diseases, cancer continues to puzzle the medical and research communities. While researchers have managed to decrease the number of cancer-related deaths by 27 percent, many of the therapies used in hospitals today put additional stress on the body's healthy cells and further risk the life of the patient. (Siegel, Miller & Jemal, 2019). Current methods can provide a path towards cancer remission, but they typically lack specificity and the ability to distinguish between healthy and cancerous tissue. This leads to some of the particularly painful and devastating side effects of cancer treatment ("Get ready," 2018). Luckily, antibody-drug conjugates (ADCs) address many side effects of commonly used cancer treatments. As their name implies, the conjugation of an antibody with a cytotoxic drug creates a "guided missile," that delivers a lethal dose of drug to targeted cancer cells (Panowski, Bhakta, Raab, Polakis, & Junutula, 2014). In order to provide an introduction to antibody-drug conjugate chemistry, we will discuss the mechanisms by which ADCs work, the unique advantages they have over other cancer treatments, and details on the current ADC market.

...many of the therapies used in hospitals today put additional stress on the body's healthy cells...

The combination of precision, provided by an antibody, and the cytotoxicity of a potent drug is what gives ADCs their unique power to singularly target cancer cells. An ADC is comprised of an antibody, a linker, and a cytotoxic payload. These components work together to deliver a lethal dose of the payload to a cancer cell, manipulating the identifying antigen present on a cancerous cell. In ADC production, one requirement of the antibody is for it to bind to the antigen on the surface of the specific cell of the cancer that the ADC is treating (Junutula et al., 2008). The conjugated potent drug is referred to as the payload because it is, in a simplified sense, "carried" by an antibody. Intuitively, the target antigen on the cancer cell should be displayed on the tumor surface, allowing interaction with the antibody binding region of the antibody-drug conjugate. Through

this interaction, the cancer cell will internalize the antibody-drug conjugate and the cell's transport vesicles will carry the complex to a lysosome for degradation (Panowski et al., 2014). Upon degradation of the ADC, the linker, antibody, and payload are unconjugated, releasing the drug into the cell. The cytotoxin then paralyzes the cell through the inhibition of tubulin polymerization or DNA damage (De Goeij & Lambert, 2016).

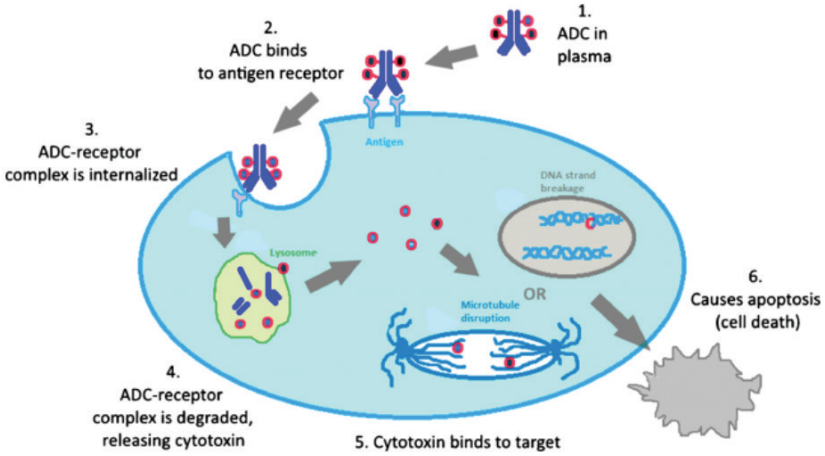

Figure 2. The detailed process of ADC binding and cell response. Image from Castro 2017.

The linker is the connecting site between the antibody and the cytotoxic drug. Electrostatic interactions and steric hindrance play major roles in the stability of the conjugation site. Since they hold the antibody and cytotoxin together, linkers are required to be stable in the blood, yet can be easily broken down by a lysosome. This ensures that the lethal drug is not active anywhere in the body other than the inside of the target cancer cell. There can be anywhere from two to eight antibody-drug conjugation sites on any given antibody, represented by the drug-antibody-ratio, or DAR (Jackson, 2016). The ratio is typically monitored to ensure that a sufficient amount of drug is bound to the antibody. The ADCs must be competent in drug transport, but still conform to safety standards ("Using Automated", 2015).

On its own, an antibody's unique binding region allows it to identify foreign cells through interactions with the epitope of specific cells. In ADC creation, isolating and using an antibody with a high affinity (Kd < 10 nM) for cancerous epitope binding is ideal. Furthermore, ADC antibodies should correspond to target receptors that are only presented on cancer cells. This prevents the ADC from binding to other healthy cell epitopes and initiating cell death for anything besides the cancerous tumor (Panowski et al., 2014).

Together, these capabilities allow ADCs to hijack cancer's defense mechanisms.

This carefully crafted therapy has additional advantages over other, more commonly used cancer therapies. Whereas many cancer cells can utilize efflux to pump out anti-cancer drugs and resist multiple drug chemotherapy, the use of hydrophobic linkers in ADC conjugation has been shown to decrease resistance in cells with high multidrug resistance protein counts (Mukherjee et al., 2019; Naito, 2000). Therefore, the use of ADCs can prevent relapse in remissioned patients. Antibody-drug conjugates also exhibit the bystander-killing effect, where in addition to destroying cancer cells that display the target antigen, some ADCs can induce the death of proximal cancer cells even if they do not exhibit the target antigen (Byun & Jung, 2019). Together, these capabilities allow ADCs to hijack cancer's defense mechanisms.

The potential impact of ADCs in cancer therapy has not gone unseen. In the years since the first FDA approval of an antibody-drug conjugate in 2001, three more ADCs have received approval for distribution in the market. In total, the four antibody-drug conjugates available for use treat metastatic breast cancer, lymphoma, acute lymphoblastic leukemia and acute myelogenous leukemia. One of these antibody-drug conjugates, gemtuzumab ozogamicin, was retracted from the market in 2010 for a potential connection to fatal liver complications. However, this acute myelogenous leukemia ADC was reapproved in 2017 after the creation of a smaller dosing schedule (Li et al., 2019). The

resolution of this complication demonstrates the ongoing development and research of ADCs. As of 2013, 35 ADCs were being tested in clinical trials, foreshadowing that antibody-drug conjugate therapy may soon be a common cancer treatment. Since these clinical trials typically require approximately six years of study, it is possible that by 2020, new ADCs will be available to patients with various cancers.

It is important to note the relatively unimportant relationship between antigen target and corresponding ADC payload. Among the 35 ADCs in clinical trials, the vast majority unsurprisingly utilize one of five different cytotoxic payloads. (Beck & Reichert, 2014). Drug development is more difficult and takes longer, due to the delicate biochemical balance within the human body. Thus, there are currently few drugs that can satisfy the extensive list of properties required of an effective ADC payload.

As patient use of ADCs increases, it is imperative that lab experimentation continue, in order to ensure their efficiency and safety. Now that the general mechanisms and interactions between the linker, payload and antibody are better understood, professionals in the field are looking to improve ADC production by investigating two areas: homogeneity of the final ADC product and the drug payload (Su et al., 2018).

With approximately 62 sites available for conjugation on a general antibody, heterogeneity in ADC production typically occurs because conjugation reactions are not specific to a single site between the antibody and drug payload. As a result, current research is focused on engineering site-specific reactions that will produce homogenous ADCs that are exact replicas of one another (Jackson, 2016). Heterogeneous ADCs in cancer treatment can cause unwanted side effects in the patient, and research into homogeneous ADC production can better inform medical professionals of what exactly is being put into patients' bodies.

As of 2013, 35 ADCs were being tested in clinical trials...

One way to accomplish this is to ensure that the payload is sufficiently conjugated to the antibody. Steric hindrance of chemical groups surrounding an antibody's site of conjugation allows the antibody to both carry and protect the payload. The antibody protects its payload by shielding it from substantial interaction with the surrounding media, which could motivate premature deconjugation. Therefore, it has been shown that the ideal conditions to prevent unwanted deconjugation consist of a sterically-hindered site on the antibody and a short linker (Su et al., 2018).

While not all questions about antibody-drug conjugates have been answered, it is clear that they have the potential to be a promising cancer treatment. Their unique properties give ADCs advantages over current cancer treatments and provide hope for a less debilitating cancer treatment. Many structural aspects of an ADC can be altered and controlled, allowing for a large range of possibilities in ADC cancer treatment. It is exciting to think that in the future, patients undergoing cancer treatment might suffer less physical pain and encounter fewer unwanted side effects that are typically associated with the common cancer treatments of today.

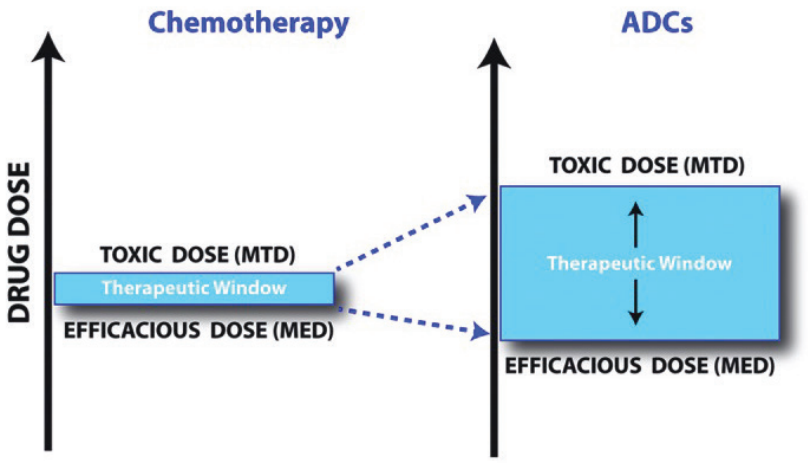

Figure 3. Comparison between traditional chemotherapy and new ADC treatment. Image from Panowski 2014.

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AUTHOR BIO

Larisa Koyen is a third year in the college, majoring in Biology. An interesting fact about her is that she was born in Ukraine.

Edited by Lauren Flamenbaum, Jahnvi Jain and Dr. Michael Crutcher

Placed by Albert Liu

Platelet-rich plasma as a non-surgical treatment option for orthopedic injuries

NICHOLAS RYU
Staff Writer

A common misconception regarding cases in orthopedic sports medicine is that surgery is usually necessary and the most effective treatment available. Although surgery may be a viable option, it is not the answer to every injury. For example, certain patient-related factors may make surgery "risky," such as old age, high blood pressure or a high body mass index. Orthopedic clinics commonly treat injuries with injections rather than surgeries, and an innovative new non-surgical treatment known as Platelet Rich Plasma (PRP) injections is transforming the field. PRP reduces swelling, inflammation, pain and helps regain range of motion. As Le describes, "PRP is, comparable to corticosteroid injections." (Le, et.al, 2018).

Although PRP is a promising advancement in non-surgical treatment, there are some concerns behind its effectiveness. It is important for patients and physicians to take into consideration the type of injury and context of the situation as they determine the best treatment plan.

PRP is used in clinics because it is a safe treatment and has many unique regenerative contents. These injections are made up of the patient's own cells and DNA and must be prepared by drawing up the patient's blood and spinning it down in a centrifuge. This process separates the components of the blood, and the plasma is selectively extracted as the PRP which is then injected into the treatment site. PRP contains both growth factors and a multitude of platelets which induce the secretion of growth factors, including TGF- β, a key growth factor in the generation of collagen, VEGF, which stimulates the development of new blood vessels, and CTGF, which stimulates cartilage regeneration (Dhillon, et.al, 2012).

The growth factors in PRP play various roles in promoting the generation of cell growth...

The presence of these growth factors and platelets is what gives PRP its distinctive healing properties. In injuries, the body will send growth factors to the affected area in order to stabilize conditions and initiate the healing process. These growth factors play various roles in promoting the generation of cell growth and new tissues. TGF-β, for example, is specifically responsible for promoting mesenchymal and epithelial cells to divide, increasing the growth

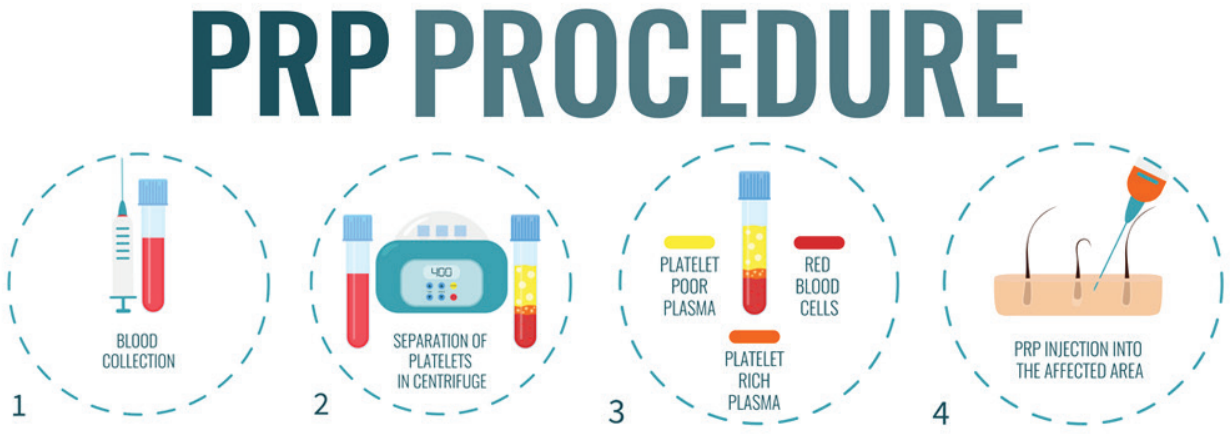

Figure 1. PRP is produced from the isolation of a patient's platelets through a blood draw and centrifuge. Image from Tennessee Orthopedic Alliance.

of collagen and extracellular matrix (Dhillon, et.al, 2012). Introducing PRP into the system will increase the concentration of active platelets in the injection site through cell signaling, which in turn stimulates the production of more growth factors (Jain et.al, 2016). The same concept applies to other growth factors. Regarding the cell signaling mechanism, there is evidence suggesting that PRP is effective in activating platelets and initiating cell signaling sequences; however, platelet-released factors do not increase proportionally to platelet concentrations (Pavlovic et.al, 2016; Kuffler, 2018). Flooding the system with a surplus of platelets eventually becomes ineffective as platelet-released factor synthesis stops at a certain extent.

In orthopedics, PRP is mostly used to treat chronic injuries in cases of arthritis, tendinopathy, and surgical augmentations. One of the most common orthopedic ailments is osteoarthritis (OA), the degeneration of protective cartilage in joints. The symptoms of this disease include discomfort in the joints, decreased range of motion, swelling, and pain. PRP is injected into these affected areas to reduce pain symptoms and restore joint functionality. Treatment is most successful and effective in the knees and hips (Shen, 2017).

PRP can also be used to treat many forms of tendinopathy such as lateral epicondylitis, plantar fasciitis patellar tendinopathy, Achilles tendinopathy, and rotator cuff tendinopathy, all of which involve inflammation of tendon tissues. Of these four cases, lateral epicondylitis, commonly known as tennis elbow, exhibits the best response to PRP treatment. Injections are administered to the elbow to relieve symptoms of swelling and pain (Le et.al, 2018). Although effective in lateral epicondylitis, there is no proof that the use of PRP in the other three cases is as effective.

Across studies, PRP usage overall has had variable success.

Surgical augmentations are another domain in which PRP is used. Following a surgical procedure, PRP is injected into the treatment site for support in post-operative repair and healing. Surgeons use PRP to maximize the probability of patients having a successful post-operative recovery and reducing rates of re-injury. Common surgical procedures supplemented by PRP include rotator cuff repairs, Achilles tendon repairs, and ACL reconstructions (Le et.al, 2018). PRP is effective in reducing re-tear rates in small to medium sized rotator cuff repairs, but there is inconsistent evidence regarding Achilles tendon and ACL surgical augmentations (Saltzman, 2016; Le et.al 2018). Across studies, PRP usage overall has seen variable success.

PRP effectiveness depends not only on the type and severity of injury, but also on the patient. Due to factors relating to the patient's physiology, there is a significant chance the injections may not prove useful. PRP composition and methods of preparation are major factors contributing to the variability of treatment success. Healthy patients have PRP ranges varying from 150,000 to 450,000 platelets per μL (Kuffler, 2018). Patients with lower platelet counts will not be as receptive to treatment. PRP preparation methods are also not standardized, resulting in different techniques yielding highly variable platelet concentrations (Middleton, 2012; Kuffler, 2018). For example, a PRP preparation kit from Ar-

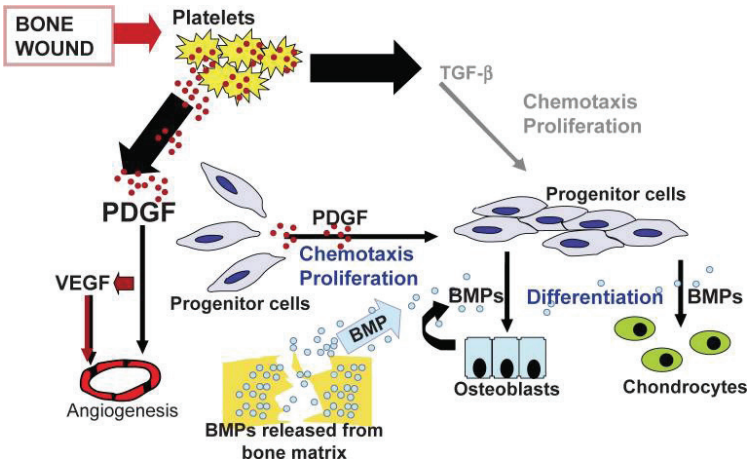

Figure 2. PRP cell signaling mechanism involves activated platelets producing growth factors in the healing process. Image from Ghodadra & Singh 2008.

threx has a much lower platelet concentration yield than one from Biomet Biologics (Kuffler 2018). These different techniques also result in different levels of platelet-released factor biological activity. Lifestyle choices such as the consumption of other drugs, glucose levels, stress, and even diet can further impact results (Kuffler, 2018). The combination of patient physiology, habitats and PRP preparation variability has made it difficult to define the optimal platelet concentration per injection.

In addition to inconsistent PRP treatment results, a series of PRP injections is very expensive. The cost of one injection can range anywhere from $500 to $2000 depending on the provider (Jones, et.al, 2018) and it is typical for patients to receive up to 3 injections. Due to a lack of evidence supporting the benefits of PRP, insurance agencies do not cover this form of treatment (Dhillon, et.al, 2012), and patients receiving PRP injections will have to pay a generous amount of money to their providers entirely out of pocket. As a result, PRP treatment is currently limited by financial barriers, which may discourage a population of people who need the treatment but cannot afford it.

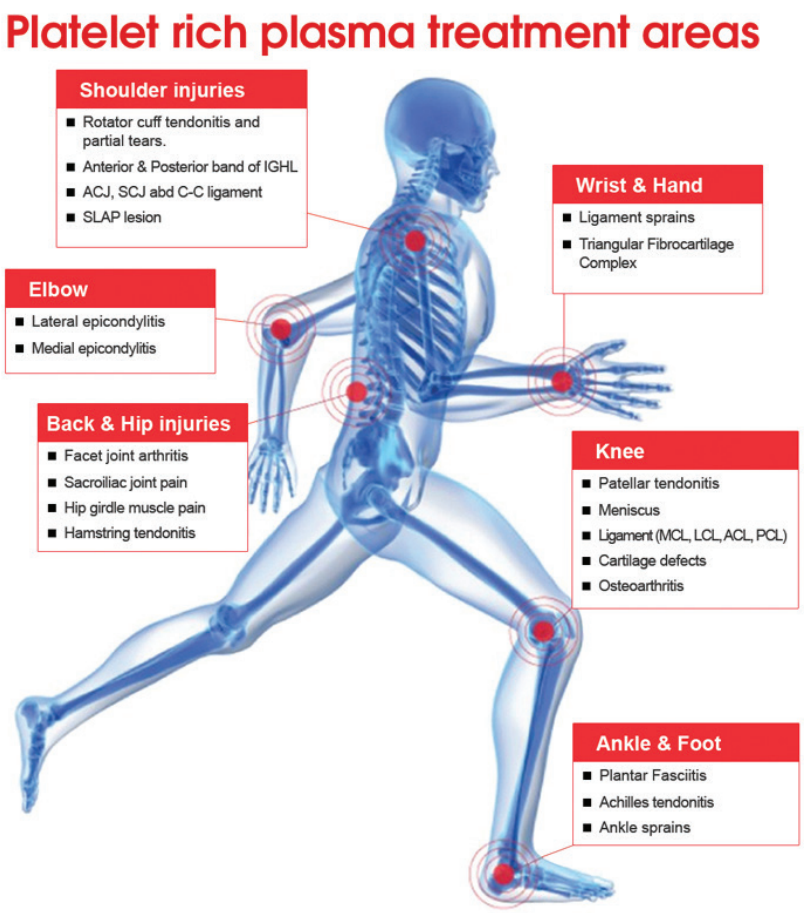

Figure 3. PRP is often injected into these areas for treatment of chronic injuries and surgical augmentations with mixed results. Image from Spoc Orthopedics 2018.

PRP composition and methods of preparation are major factors contributing to the variability...

The development of Platelet Rich Plasma as a form of nonsurgical treatment and surgical augmentation may prove to be a valuable addition to orthopedic practices. Future directions for PRP research should include elucidating the cases and injury types that respond most effectively to these injections. Identifying patient factors that influence the efficacy of the intervention will also be important in determining how PRP should be prepared. If proven effective in a wide range of applications, there will most certainly be new forms and combinations of treatments to supplement the original PRP regimen. In the meantime, it is the role of the providers to help patients who are interested in trying PRP injections understand the current state of treatment effectiveness and the expenses that come with the therapy. ❧

AUTHOR BIO

Nicholas Ryu is a second year majoring in Anthropology and Human Biology with a minor in Predictive Health. He is very interested in sports medicine and orthopedics.

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Placed by Rachel Xue

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Awareness of colorectal cancer burden and affected populations

LAURA PAULE
Staff Writer

Cancer is the second leading cause of death in the United States, exceeded only by heart disease (CDC, 2016). Excluding skin cancers, colorectal cancer (CRC) is the third most common cancer diagnosed in the U.S and the second deadliest for both males and females (Keum & Giovannucci, 2019). There were over 145,000 new colorectal cancer cases in 2019 alone. Colorectal cancer typically begins with a polyp — an uncontrolled growth in the inner lining of the colon or rectum. Left alone, these polyps can spread over time, grow into blood vessels or lymph nodes, become cancerous and metastasize to other body parts (ACS, 2019). Although this type of cancer is most prevalent in men over the age of 50, there has been a sharp increase in incidence rates among a younger population of both men and women. By looking at colorectal cancer's common risk factors, causes, detection methods, prevention plans, and unique interventions, researchers can understand how to better reduce the risk of this deadly cancer.

Excluding skin cancers, colorectal cancer (CRC) is the third most common cancer in the U.S...

Some of the risk factors for colorectal cancer are heritable or difficult to minimize. Age, for example, is a major risk factor for developing CRC. While most diagnosed patients do not report a family history of CRC, one in three affected people have an affected relative, indicating that family history is an important risk factor for developing the disease. A history of polyps or inflammatory bowel disease increases the likelihood of being affected by CRC. Race has also been linked to the development of this cancer, with African Americans having the highest incidence and mortality rates. In addition, people with type 2 diabetes are more prone to developing these cancerous polyps (ACS, 2019).

There are other key risk factors that can be minimized with lifestyle changes. Obesity, for instance, has been linked to an increased risk of colorectal cancer (Scazzocchio et al., 2019) (Moon, Kim, Oh, Kong, & Kim, 2019). Adipose tissue, or fat, releases cytokines (proteins, peptides) called adipokines, and studies have shown that there is an association between adipokines and colorectal cancer. Apelin is one of the secreted peptides involved in signaling pathways associated with tumor metastasis, portraying how this adipokine increases the risk of CRC (Podg, Diakowska, & Pietraszek-gremplewicz, n.d.). Furthermore, El Sherity et al. showed that the most frequent CRC recurrence after surgery occurred in obese patients, and obesity was further linked to higher mortality rates for colorectal cancer (El Sherity, A Shalaby, Hassan, El-Masry, & El-Banna, 2019).

Lifestyle and nutrition can be modified to reduce risk and are often utilized to develop prevention strategies (Fliss-Isakov et al., 2019). The World Cancer

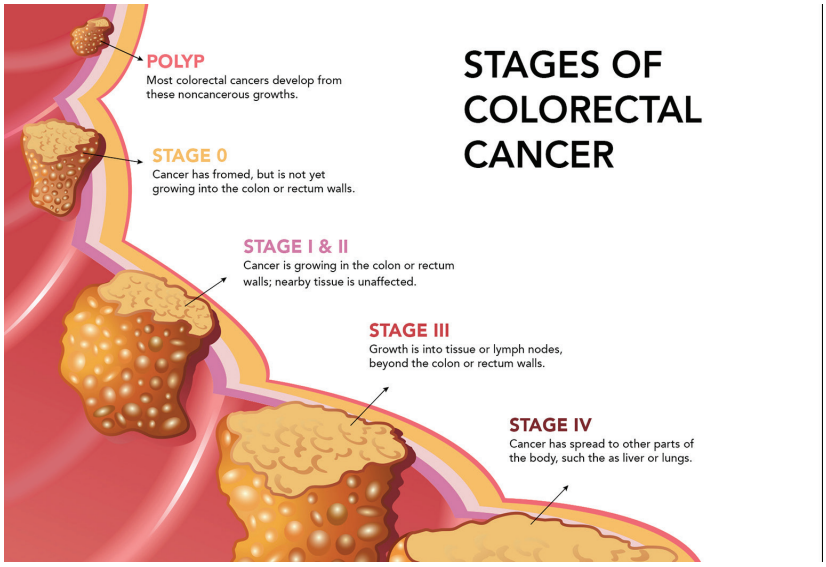

Figure 1. This image portrays the different stages of colorectal cancer, starting as a very small polyp and eventually becoming cancerous and metastasizing. Image from Parkway Cancer Center 2019.

Research Fund (WCRF) and American Institute of Cancer Research (AICR) showed that obesity, low physical activity, poor diets (high red and processed meat), and alcohol are all risk factors for CRC. The ethanol present in alcoholic beverages for example, is metabolized into acetaldehyde, a carcinogen dangerous to humans (Keum & Giovannucci, 2019). Prolonged sitting impairs skeletal muscle function, promoting colorectal carcinogenesis. Physical activity helps by increasing gut motility, decreasing inflammation and benefiting metabolic hormones. There is also mounting evidence that suggests smoking is linked to irreversible damage in DNA, which can affect the colorectal mucosa and trigger a cascade of changes at the cellular level that can promote cancer growth.

To mitigate CRC's clinical and economic burden on society and the healthcare system, a wide variety of prevention strategies have been implemented. There are primary prevention measurements, such as the establishment of public policies to lower the risks of CRC, and people independently taking initiative to set healthier lifestyle goals and habits. For example, the "CDC's Colorectal Cancer Control Program provides funding to state health departments, universities, and tribes to increase colorectal cancer screening rates among people between 50 and 75 years of age" (Centers for Disease Control and Prevention, n.d.). Secondary prevention strategies include CRC screenings for timely polyp detection and surgery for polyp removal. Colonoscopies are especially effective in detecting CRC, and can also remove precancerous polyps in the same session (Li, 2018). Tertiary strategies involve treating the cancer once it is invasive and developing new treatments that have not been implemented to alleviate the effects of the disease. (PAHO, 2016).

The US Preventive Services Task Force recommends beginning CRC screening in individuals over the age of 50 (USPSTF, 2008). However, with colorectal cancer incidence rates increasing among those born after 1950, the American Cancer Society now recommends starting screening at age 45 (Sauer, Siegel, Jemal, & Fedewa, 2019). Recent studies have shown an increasing CRC risk among the younger populations as well, with worse outcomes in minority populations. A recent analysis of the National Cancer Database showed that African Americans young adults have a survival rate five years lower than Hispanics, and non-Hispanic Whites, despite receiving equal standard of care (Alese et al., 2019).

There are epidemiologic studies revealing that firefighters are at a higher risk of developing site-specific cancers when compared to the general population in the United States (Caban-Martinez et al., 2018). This is in part due to combustion byproducts released during fire suppression. The constant exposure to smoke, coupled with limited access and hesitancy towards seeking healthcare aid, increases the likelihood of cancer development, CRC being one. As a high-risk group, the firefighters should be given greater attention, and more research should be done to implement strategies that reduce the rates of CRC in this population.

Colorectal cancer is not only one of the most common, but also one of the deadliest cancers among males and females. Future steps could include creating specific preventive measurements that target high-risk groups, such as providing free screening for African Americans and firefighters, as well as requiring screenings at an earlier age to prevent an outbreak of CRC among the rising generations. More efforts need to be invested in studying and optimizing screening of these high-risk groups. ❧

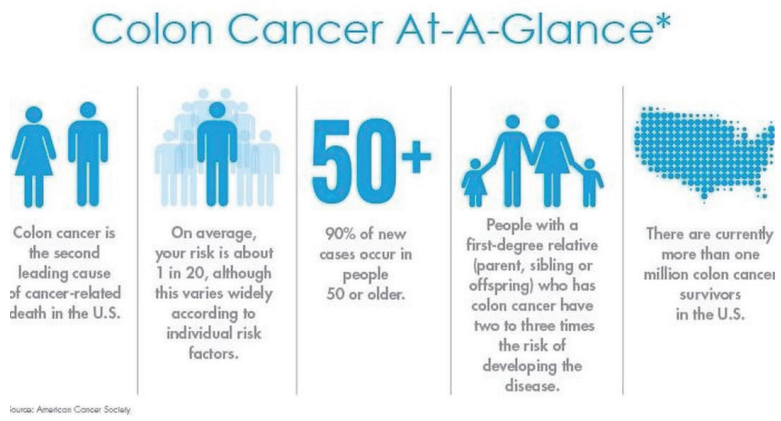

Figure 2. The American Cancer Society reports statistics on colorectal cancer and its impact across the United States. Image from American Cancer Society 2014.

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Assisted reproductive technology: the solution to infertility

ANDY CHEN
Staff Writer

A century ago, the reproductive technology of today would have seemed like science fiction. What many could only dream of became reality when Louise Brown, the world's first "test tube baby," was born in England in 1978. This momentous occasion was not only a victory and testament to the empirical nature of science but also a glimmer of hope for couples struggling with infertility. Not long after, assisted reproductive technologies (ARTs), a term referring to all fertility treatments in which both the egg and embryo are handled outside the body, rapidly expanded as both scientists and health care professionals sought to investigate and treat male and female factor infertility in their laboratories and clinics. With an estimated 72.5 million couples worldwide facing infertility in 2015, the demand for ART is high and has since only increased (Kumar & Singh, 2015). As a rather nascent technology, the potential and impact of ART should be analyzed in conjunction with the ethical concerns that arise from the adoption of this technology.


Daily Mail
THURSDAY, JULY 27, 1978
8p
WORLD EXCLUSIVE
And here she is...
THE LOVELY LOUISE

Figure 1. Contributing to the normalization of test-tube babies, media portrayals on the birth of Louise Brown were highly positive and humanizing. Image from Daily Mail 1978.

Infertility, defined by the World Health Organization (WHO) as the inability to conceive after one or more years of frequent unprotected sex, results from numerous factors including both male and female factor infertility (Gurunath, Pandian, Anderson, & Bhattacharya, 2011). As a broad term, infertility encompasses all complications in the process of conceiving a child. ARTs are designed to treat both male and female infertility.

...citing female factor infertility as a reason for divorce and male factor infertility as a negative reflection of a man's masculinity.

Male factor infertility is diagnosed by a sperm analysis that examines several features of the male gamete. The parameters, as defined by the World Health Organization (WHO), require an examination of the concentration, motility, and morphology of the sperm (Kumar et al., 2015). Results from the analysis are then compared to reference points before making a diagnosis. Suboptimal parameters ensue from any combination of low concentration, poor motility, or abnormal morphology of the sperm. Environmental and behavioral factors such as alcohol and drug abuse,

lack of exercise, and exposure to chemicals or environmental toxins can all contribute, and are simply treated by adopting a healthier lifestyle. Other factors such as disruption of testicular or ejaculatory function, hormonal disorders, and age may be more difficult to address (Harris, Fronczak, Roth & Meacham, 2011).

Female factor infertility arises from conditions affecting the ovaries, fallopian tubes, and/or uterus, which are all essential for pregnancy. Ovarian function can be disrupted by polycystic ovary syndrome (PCOS), hypoestrogenic states, or menopause (Meniru, Hecht, & Hopkins, 2002). Fallopian tubes can be obstructed by pelvic infections, abdominal surgery, and sexually transmitted infections such as chlamydiasis. Any physical abnormalities affecting the uterus can also engender infertility (Meniru et al., 2002). Similar to men, women who smoke, consume drugs and alcohol in excess, experience significant levels of stress or weight loss, and/or are older are at an increased risk for infertility.

Various kinds of ARTs have been designed to help increase the odds of pregnancy for couples struggling with infertility. The most commonly used ART is in vitro fertilization (IVF) which was used by Patrick Steptoe and Robert Edwards, the pioneers of fertility treatment, to treat female infertility caused by obstructed, damaged, or absent fallopian tubes (Brinsden & Brinsden, 2009). In this procedure, eggs are extracted directly from the ovaries and fertilized outside the body in a laboratory before being implanted in the uterine lining.

An IVF treatment cycle is comprised of four main components: (1) ovarian stimulation, (2) egg retrieval, (3) fertilization and embryo culture, and (4) embryo transfer. These processes require precise timing, multiple quality checks, and the use of medications to increase the chances of a successful cycle. During ovarian stimulation, medications — sometimes referred to as "fertility drugs" — are used to stimulate the growth of multiple eggs in the ovaries rather than the single egg that normally develops each month (Montag & Morbeck, 2017). If the treatment cycle is unsuccessful due to having an inadequate number of developing ovarian follicles or premature ovulation, the cycle is cancelled at this stage. However, if fruitful, egg retrieval is then be performed by transvaginal oocyte retrieval (TVOR) to enable fertilization outside the body (Assisted Reproductive Technology, 2015).

Following egg retrieval, examination of egg maturity occurs before they are placed in IVF culture medium for sperm fertilization. During this step, intracytoplasmic sperm injection (ICSI) may be performed to address issues of male factor infertility where the probability of the sperm being able to successfully fertilize an egg is low (Assisted Reproductive Technology, 2015). In ICSI, a single healthy spermatozoa is directly injected into each individual mature egg to increase the odds of fertilization. Between days three and five of embryo development, when the zygote grows from eight cells to a blastocyst, embryo transfer is carried out by drawing the embryo into a transfer catheter and guiding it through the cervix for implantation in the uterine cavity (Assisted Reproductive Technology, 2015). While multiple fertilized embryos can be implanted to increase the odds of pregnancy, only a few embryos are transferred at once to reduce the chances of having twins or triplets, which could pose risks to both the mother and babies (Nardelli, Stafinski, Motan, Klein, & Menon, 2014).

Other forms of reproductive technology include but are not

Figure 2. Stages of IVF from ovarian stimulation to embryo transfer. Important to note: the image shows fertilization in embryo culture with and without the use of intracytoplasmic sperm injection (ICSI). Image from Medical News 2019.

limited to: variations of IVF such as intrauterine insemination (IUI) and gamete intrafallopian transfer (GIFT); the use of donors to provide healthy sperm or eggs; and lastly, surrogacy (CDC, 2011). These new possibilities provided by ARTs are able to meet the demands of not only heterosexual couples with infertility but also homosexual couples and single parents who need clinical assistance to conceive. The demand for ARTs has only grown since the birth of Louise Brown, and it continues to revolutionize the field of reproductive medicine and change the definition of family.

Nevertheless, ART, with all its glory, is not impervious to controversy. In its conception, few were willing to experiment with the idea of in vitro fertilization of human gametes and creating life outside of what was viewed as "normal." Dr. Patrick Steptoe's lecture on the use of laparoscopy to obtain oocytes for use in in vitro fertilization at the Royal Society of Medicine in London in 1968 drew criticism and the method was deemed unacceptable (Litynski, 1998). Despite this heated discussion, Edward Roberts approached Steptoe and offered his aid in developing the techniques that would later lead to the birth of Louise Brown (Litynski, 1998).

In one case, 61 people have claimed Dr. Donald Cline, a fertility specialist, as their biological father.

While much of the controversy surrounding IVF was quelled by positive media portrayals of the world's first test tube baby as being healthy and human, issues regarding IVF remain. For one, privacy and anonymity remain a top concern among couples who choose fertility treatments involving donor sperm and eggs. Ayo Wahlberg's ethnography of sperm banking in China provides critical insights on both the need for ART and its stigma, specifically surrounding the use of artificial insemination by donor (AID) (Wahlberg, 2018). Informants often discussed the negative implications of infertility for couples, citing female factor infertility as a reason for divorce and male factor infertility as a negative reflection of a man's masculinity (Wahlberg, 2018). Despite the need for ART, the stigma surrounding the use of artificial insemination by donor (AID) is comparable to the shame of being childless, which originated with the one-child policy in the late 1970s (Wahlberg, 2018). The main concern, as reflected in the policies of sperm banks, is the matter of privacy. Couples consent to hide information about the use of AID from their children and neither they nor their children are allowed access to information regarding the donor (Wahlberg, 2018).

With the rising popularity of consumer genetic testing done by companies such as 23andMe and AncestryDNA, other ethical concerns have been exposed. As recently as August 21, 2019, the New York Times released an article titled, "Their Mothers Chose Donor Sperm. The Doctors Used Their Own." exposing the fertility frauds that have been committed by doctors (Mroz, 2019). The article brings to light cases in which genetic testing revealed that children conceived by AID were the offspring of the fertility specialists that treated their mothers and not related to the donor whose sperm was selected. In one case, 61 people have claimed Dr. Donald Cline, a fertility specialist, as their

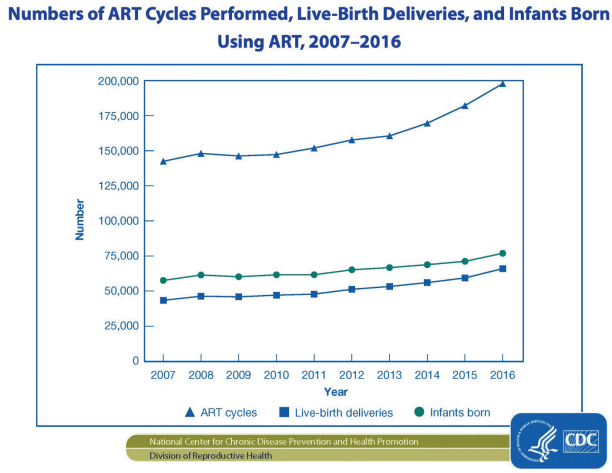

Figure 3. From 2007–2016, the number of ART cycles performed had only been increasing. The number of live-birth deliveries and infants born follow a similar pattern with number of infants born being slightly greater due to multiple pregnancies occurring within a cycle. Image from CDC 2019.

biological father (Mroz, 2019). These incidents have prompted laws criminalizing the behavior as a form of sexual assault in three states (Mroz, 2019).

Evidently, the history of ART is quite complex. ART has certainly revolutionized the field of reproductive medicine by bringing happiness to childless couples, but this joy coexists with the cultural stigma surrounding its use and its history of abuse mandates. Considering factors such as the growing trend of having children later in life and the use of genetic testing for disease screening, the advantages of ARTs are only becoming more attractive. Addressing the stigma and abuse of ART while providing for patients ultimately necessitates that tighter regulations monitoring the use of donor material be introduced and implemented. Eventually, ART utilization may reach the point where the technology itself is both safer and more widely accepted by different cultures. ❧

AUTHOR BIO

Andy Chen is a third year in the college double majoring in NBB and Anthropology & Human Biology. Aside from his academic interests, he firmly believes in the power of storytelling and the insights we can garner from simply listening.

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Mathematics: the secret to the complexities of nature

SHREYA RANA
Staff Writer

To many, mathematics appears to be a subject that is incredibly esoteric with little importance in the "real" world. On the contrary, mathematics is an ever-present force that dictates the harmony of the world. The functions of numbers are not merely abstract and theoretical jargon, but rather they serve as representations of patterns in nature that can be applied to understand the inner workings of complex systems, such as the human brain. The term "system" refers to a "collection of interrelated objects" of which the functions between these objects are not fully understood (Motta, 2012). In order to analyze some of these systems, especially in regards to networks of biological systems such as the human body, researchers often use mathematical models to decode the mechanisms behind different processes. The specific area of mathematics that will be examined in this review is the field of biocalculus. Systems of biocalculus are often created to achieve certain criteria, such as including the different "components of biological systems" along with diagramming their "transition and communication" that in the end, must provide "information essential for stimulation" (Nagasaki, 1999). The following applications notably use differential equations to model certain measurable qualities of a system using a set of variables. (Lutzen) This review will examine how mathematical models are being used to study the intricacies of cancer metastasis, synaptic memory formation and neural development.

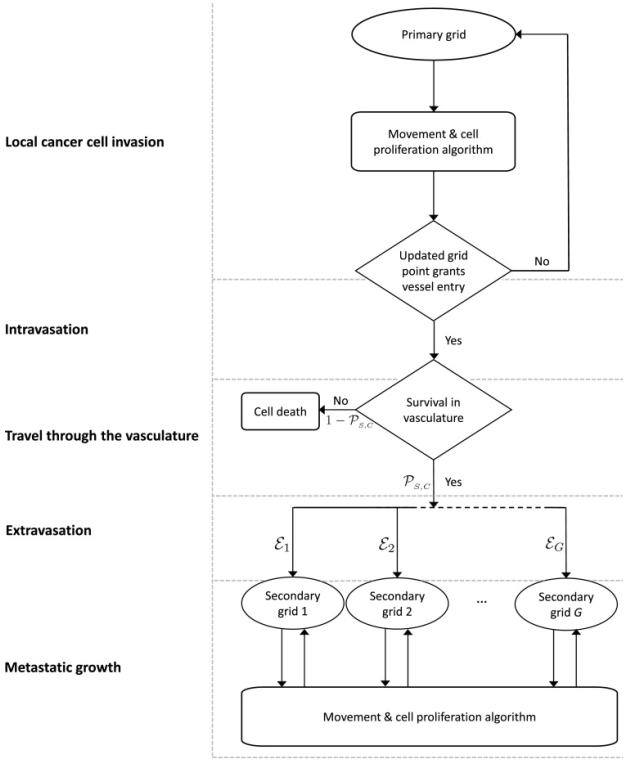

Figure 1. Pathway of Cancer Metastasis. Image from Franssen 2019.

One of the most groundbreaking applications of mathematical models is through the analysis of cancer metastasis. Being familiar with the different phases of cancer growth is imperative to understanding this model. The process by which cells from a primary tumor spread to sites elsewhere in the body and colonize is known as the "invasion-metastasis cascade"(Weinberg 2013). The first phase of this cascade is known as "local cancer cell invasion" where invading cancerous cells need to penetrate the extracellular matrix(Franssen 2019). The next phase is referred to as "intravasation," the process by which cancer cells seep into the blood system, also known as the vasculature. The cells then travel through the vasculature while encountering a number of hurdles such as natural killer cells. Successful cancer cells are those that are able to reach the secondary metastatic site, and only a small proportion of these cells actually go on to form malignant tumors. Previous cancer invasion models have been either "local" or "non-local" in nature and have relied on the use of partial differential equations, with the former focusing on cancer cells in relation to their surroundings and the

latter modeling cellular interactions in regards to adhesion and movement. A novel model is then proposed that incorporates all the phases of the invasion-metastasis cascade, starting from the primary tumor sites and describing the pathway all the way to metastatic sites, as diagrammed in Figure A. In the diagram, Ps,c represents the probability of survival for circulating tumor cells (CTCs) with cells travelling and dividing according to a "Movement and Cell Proliferation algorithm." Different spatial domains are created and represented through their positions, extracellular matrix densities, and other relevant functions. The movement probabilities of cancer cells within these domains in each of the different phases of the cascade are then determined through partial differential equations. After running simulations of the algorithms, the results were promising and realistic (Franssen 2019) To improve this model in the future, they hope to incorporate the effects of cell mutations and other biochemical processes into the model.

Along with cancer metastasis modelling, another novel application of mathematical modelling is the study of memory storage in the brain. A recently proposed memory model takes into account the linear relationship between the number of synapses and memory capacity, as well as the bidirectional movement between "fast variables," where memory info is initially stored, and "slow variables" that contribute to memory consolidation.(Benna 2016) A major flaw in previous memory models was the failure to incorporate the fact that some synapses have more plasticity, while others are more rigid, and this influences how well a synapse can preserve old and new memories. The new model, however, is able to incorporate both plasticity and rigidity as constituents of the synapse by making the variables more flexible. This newfound complexity allows researchers to better understand memory performance based on "memory lifetime and the strength of the initial memory trace." This synaptic memory model diagram is depicted in Figure B, which is constructed by making an analogous comparison to a chain of growing beakers which represent the accumulation of memory from different adjoining circuits. In the diagram, the "u" functions represent "different biochemical processes," the "g" functions are the "strength of the bidirectional interactions" and "c" represents the sizes of the beakers, which in turn represent the fast and slow variables themselves. The transport between the beakers is based on certain timescales and this demonstrates the positive correlation between memory strength and lifetime. Complex differential equations are then used to model the fluid flow between the beakers which is analogous to the information transfer between different synapses and circuits (Benna 2016). There are many memory-based circuits in the brain. However, there are a vast number of circuits that contribute to other complex functions.

The functions of numbers are not merely abstract and theoretical jargon...

Lastly, another major application of mathematical models is to the field of neural development. To give some background on how the nervous system is formed, it is important to understand that brain development begins as a neural tube which eventually goes through several molecular and mechanical processes, such as cortical folding, and certain parts of the cortex become specialized to perform different functions. Development is also largely shaped by chemotaxis, the process by which cell migration is determined by

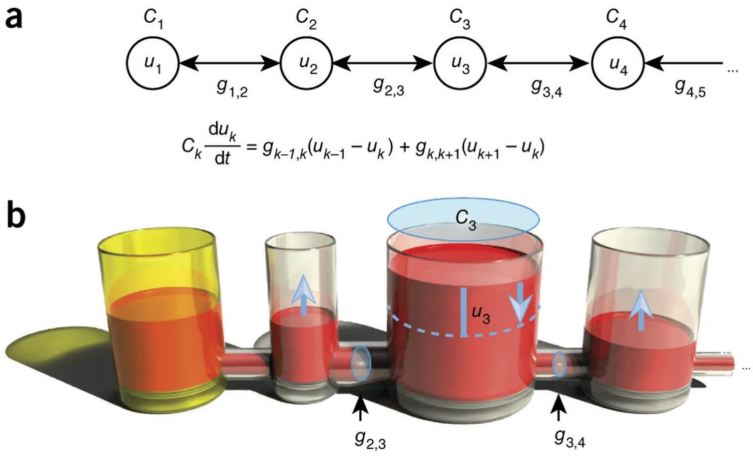

Figure 2. Synaptic Memory Formation. Image from Benna 2016.

different gradations of chemical signals. This is particularly applicable in neurons, where chemotaxis guides axons to their targets (Goodhill 190) and thus, is a key contributor to the development of the nervous system. Axon behavior is specifically vulnerable to levels of "calcium and cAMP" (Goodhill 2018) which make the axons "switch from attraction to repulsion" based on their specific concentrations. Math models that have been proposed take into account the process of chemotaxis, along with the topography of the brain to understand the development of different neural circuits. They also utilize an important concept called Hebbian learning, which is the theory that when two neurons are constantly being fired in tandem, the strength of the synapse between them is increased.(Wang, 2018) This rule has been successfully used in creating maps that outline the visual pathway. In the future, researchers hope to further extend these models to understand the mechanisms behind other sensory pathways, as well as cognitive functions such as learning.

The applications described in this review do not in any way represent the limits of mathematical models. Such models are being used from large-scale topics such as disease control and epidemiology, to much smaller-scale processes such as genetics and protein function. (Winter, 2014) The widespread applications of mathematics is a testament to it being a "science of pattern and order."(Mitchener, 1996) Analysis of the cascade of events involved in cancer metastasis, along with the neurological functions involved in synaptic memory formation and nervous system development have been simplified using mathematical models. This, however, by no means indicates that these processes are simple. While no model can be absolutely flawless, scientists can build upon existing models as new discoveries are uncovered and the predictions of these models can be used to better understand ourselves and the world around us. ❧

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Genetically determining cancer prognosis and treatment

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Genetic testing to predict cancer outcomes after concrete diagnosis is an emerging approach to treatment plan selection. Once a patient is diagnosed with cancer, the physician and patient must quickly determine the risk that the disease presents. Genetic tests precisely identify DNA changes associated with the patient's cancer. These mutations can help physicians analyze and calculate risk of metastasis and cancer-specific mortality. In addition to predicting levels of risk, generally span a continuous spectrum from low to high, genetic testing also identifies changes in the products of critical growth control genes that support cancer cell survival. While the type of test differs between cancer, they often reveal an interplay between various hormones, receptors, and other proteins. Data from populations of normal controls and cancer patients allow for the development of mathematical calculations that can be used to convert the detected changes into a numeric score. The associated risk can then be used to help the patient and physician choose between possible treatment protocols. Although genetic testing to determine cancer treatment is a fairly contemporary approach, the regimens for prostate and breast cancer are leading the way for universal incorporation.

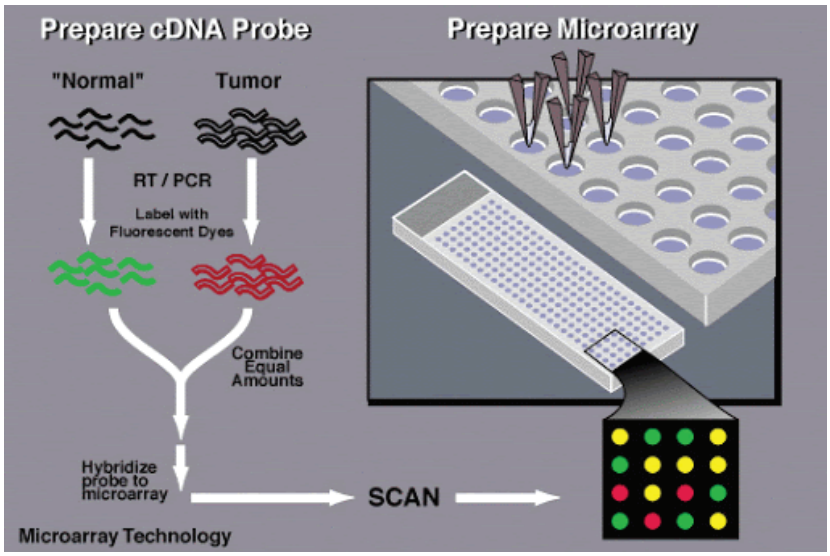

Figure 1. The process of labeling DNA with fluorescent dyes and scanning for tumor proliferating sequencing through micro-array. Image from NIH 2015.

The recent development of genetic testing has been particularly impactful in prostate cancer treatment. Approximately 220,800 men are diagnosed with prostate cancer in the U.S. each year. The severity of prostate cancer ranges from low grade to high grade tumors, and there are a multitude of treatments used to treat the disease. Determining the aggressiveness of the cancer has been problematic, leading researchers to look for better predictive tools. The Gleason score was an early attempt to determine cancer aggression, which is obtained by analyzing tissue extracted in a biopsy. However, products of recent technological advancement such as the, Decipher® test, go beyond simple tissue analysis. In this test, tumor grade/stage, prostate-specific antigen (PSA) levels, and Gleason score are factored alongside a 22 marker RNA analysis to inform a prediction of cancer aggression. (Dalela et al., 2016)

In FFPE, the tissue is embedded in wax, preserving the proteins and cells.

The 22 RNAs examined code for proteins that are associated with cell proliferation, invasion and metastasis, androgen signaling, immune activity, angiogenesis, and cell metabolism. RNA is obtained via extraction from prostate tissue. The excised specimen is placed in formaldehyde and prepared through a process known as formalin-fixed paraffin-embedding (FFPE). In FFPE, the tissue is embedded in wax, preserving the proteins and cells. Testing with antibodies allows the proteins to be quantified and the associated nucleotide sequences can also be determined (Genome.gov, 2019).

The prevalence of RNA sequences encoding proteins associated with cancer progression is determined through micro-arrays.

Similar to the mechanisms used by retro-viruses, enzymes are used to make DNA copies of the RNAs found in both the cancer and control samples. Customarily, the experimental/patient DNA is tagged with a red dye and the set of control DNA is labeled green. Both DNA samples will be mixed and added to the microarray, which holds hundreds of known DNA "probes" or sequences that can bind to the tested DNA. The binding of the probes to the sequences is a competition between the two different DNA samples in the microarray. If the limited number of DNA probes binds to more samples from the cancer sample, the dot in the microarray will appear red. Green indicates greater binding to the RNA of the control samples. Through this process, scientists are able to determine the relative expression of the 22 RNA sequences ("Genome.gov, 2019").

The 22 RNA sequences along with tumor grade/stage, prostate specific antigen (PSA), and Gleason score are combined to create a numeric score. The score generated from the Decipher® test ranges from 0-1, with higher values indicating a higher risk of metastasis and cancer-associated mortality. The genomic average risk table presents the percentage risk of High Grade Disease, 5-year Metastasis, and 10-year Prostate Cancer Specific Mortality. Based on the prognostic data, physicians and patients can then determine whether to follow active surveillance (observe the tumor without treatment) or proceed with treatment protocols that address increased risk for recurrence in the future (aka. salvage/adjuvant therapies) (Auanet.org. (2019)).

In studies that monitor the accuracy and precision of Decipher® analyses, results show that the "Decipher® test was the only significant clinical predictor of metastasis in multivariate studies" (Dalela et al., 2016). When Decipher® was compared against previous approaches to prognosis, such as using PSA doubling time and Gleason score independently, analysis showed the Decipher® method showed strong correlation for accurately predicting 5 and 10 year metastasis and biochemical failure ($p<.01$) (Dalela et al., 2016). The results have shown that Decipher® can be used to predict outcomes and quantify future risk (Van den Broeck et al., 2019).

Decipher® can be used to predict outcomes and quantify future risk.

Although Decipher® testing is a fairly new technology, the low cost and insurance-friendly aspects of the test have driven an increasing number of urologists around the world to order the tests for patients. (Fifield, 2019). The result is a broadened patient cohort and accumulated patient indexes, which the company calls the "Decipher® Grid." The database contains over 1.4 million genetic markers, termed the "whole transcriptome" (Decipher®, 2019). Researchers use the transcriptome to find associations between genetic markers and prostate cancer behavior. Depending on the types and number of genetic markers present in a prostate cancer patient, the data from the Grid can be used to predict the best choice of therapies - including radiation, chemotherapy, androgen-deprivation, and active surveillance (Decipher®, 2019).

Genetic testing to determine prognosis has also been employed in breast cancer. While certain genetic underpinnings of the disease have been discovered, namely the BRCA1 and BRCA2 genes, until recently, there

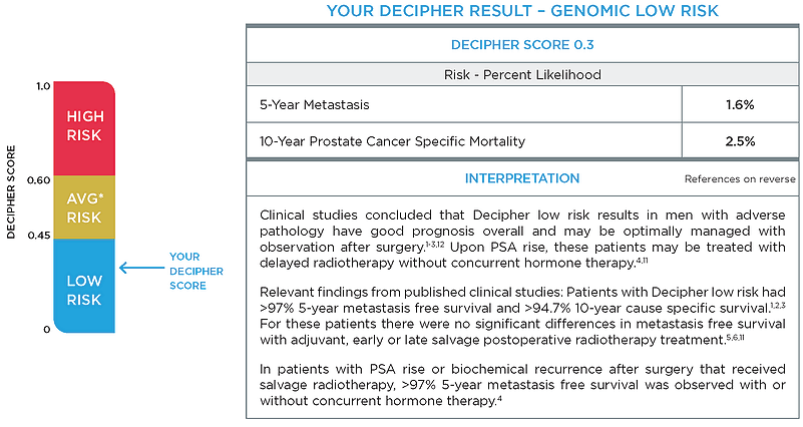

Figure 2. An illustration of the Decipher® report can help readers gauge what the test actually provides for physicians and patients. Although it is a complex test, the reports are fairly simple. Image from Prostate Cancer Markers.

were no genetic tests to predict outcomes (Shiovitz and Korde, 2015). EndoPredict®, similar to Decipher®, provides estimates for cancer recurrence and the likely impact of adjuvant chemotherapy. Endopredict® combines a 12-gene molecular score with tumor size and lymph node status to generate the prediction.

The sample is prepared via a reverse transcription polymerase chain reaction, which, like Decipher® , makes a DNA copy of the RNAs in the tissue sample. The DNA is then probed for 12 variable gene sequences including 8 signature genes, 3 normalization genes, and 1 control gene to predict the risk of future metastasis/recurrence of breast cancer. "The integration of the 12-gene molecular score with tumor size and lymph node status (EPclin) resulted in a statistically significant improvement in prognostic power above the clinicopathological factors alone" (Filipits et al., 2019). The EPclin score is used to classify tumors into low-risk and high-risk, which can be displayed on a predictive curve that is altered based on different treatments. The universal access that physicians have to Endopredict® has generated a way to quantify the risk of recurrence based on different treatment options, decreasing the variation in treatment protocols for breast cancer.

Both Decipher® and EndoPredict® provide services that reduce the uncertainty in creating a treatment plan for cancer patients. While many unknown factors in cancer outcomes still exist, the genetic tests are a significant first step in quantifying risk data for physicians and patients. ❧

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Vaccine hesitancy and the MMR vaccine

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The World Health Organization has listed vaccine hesitancy as one of the top ten global health concerns of our time. Many preventable diseases, such as measles, mumps, and rubella (MMR), have previously been eliminated through high rates of vaccination in the United States (Price 2019) and yet we are now seeing increasing numbers of outbreaks. In particular, measles vaccinations have seen a considerable downward trend, leading to outbreaks at an all-time high of 1,250 cases in the US in the year 2019 to-date (CDC, 2019).

The measles virus is transmitted via direct contact with infectious particles or by inhaling the pathogen when an infected person coughs, breathes, or sneezes. Once airborne, the virus can linger in the air for up to two hours, making it highly contagious. In addition to its resilience, measles exhibits immune amnesia, where pre-existing lymphocytes are erased, rendering the memory of the immune system useless (Laksono 2018). As a result, measles is not simply a week-long disease, but a lifelong consequence, as a person's immune system is forever tarnished. Among the many precautions that are taken to prevent the spread of measles, there exists a large amount of pushback against preventative measures such as vaccinations. While a wide range of underlying factors exist, the causes of vaccine hesitancy, in the context of measles, is primarily fueled by religious exemptions, anti-vaccination group propaganda, and parental refusal.

...measles is not simply a week-long disease, but a life-long consequence...

Many parents are unwilling to vaccinate their children due to religious and/or philosophical reasons (McKee 2016). The most controversial detail remains that many vaccines contain animal-derived gelatin and human fetal tissue. This goes against religious beliefs that preach the preservation of all forms of life and the idea that life begins at conception. Thus, religious barriers often bar parents from administering vaccines to their children.

In addition to religious doctrines, anti-vaccination groups have always been prevalent opposers of the scientific community and play a prominent role in the spread of vaccine hesitancy. Much of the anti-vaccination propaganda began with the publication of Andrew Wakefield's 1998 paper in the Lancet. In it, Wakefield claimed that there was a significant association and causally-relevant relationship

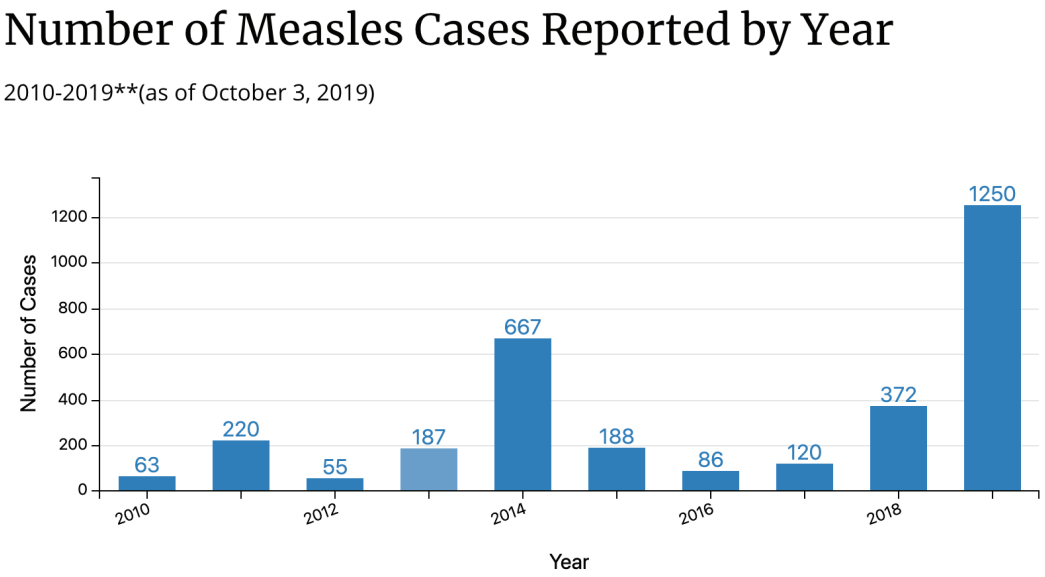

Figure 1. Measles statistics in recent years. Image from CDC 2019.

Figure 2. Anti-vaccination protesters outside of the Capitol building in Sacramento, California. Image from Bartolone 2015.

between receiving the MMR vaccination and the onset of autism. Since the publication, multiple studies have refuted the assertions made by Wakefield. Ten out of the twelve authors of the paper have since retracted their names and the Lancet officially revoked the paper from the journal. Wakefield was also found to have multiple conflicts of interest, as he had a patent on an alternative measles, mumps, and rubella (MMR) vaccine. In fact, there was evidence that Wakefield had blatantly fabricated his data by purposefully enrolling children with signs of early-onset autism into his study and giving them MMR vaccinations. These children were later diagnosed with autism following the vaccination (Sarret 2019). This led to his spurious conclusions that the MMR vaccine itself had caused the autism. Despite the frank dishonesty of the study and its authors, many anti-vaccination groups still use the paper as evidence for their cause.

Many anti-vaxxers truly believe the information they are preaching, and they sometimes target specific audiences who are especially vulnerable to their brand of misinformation. In one case, anti-vaccination groups reached out specifically to Somali Americans, whose children have a disproportionately high level of autism compared to the rest of the population in the U.S. It is a sore spot for many Somali American families and their communities have formed groups that try to understand and address this issue (Akshir 2017). Anti-vaccination groups entered the conversation by convincing them that the MMR vaccine was the cause of their children's autism. As a result, the MMR vaccination rate in the Somali American population halved, going from 91 percent in 2011 to 54 percent in 2017. Minnesota, with a large Somali American population, saw 79 new cases of measles in 2017, and 64 of those cases were patients of Somalian descent (Gahr 2014). The effect of the anti-vaccination groups is considerable and sobering.

Parents who are uneducated on the value of vaccines are easily led to believe that natural immunity is best. Acquiring natural immunity means allowing the child to be infected and letting the disease run its course in order to stimulate the immune system. From the point of view of these parents, they would rather their children have measles for a week than live with autism for the rest of their lives. While there have been communities around the globe that historically used natural immunity, it is comparatively more dangerous and risky than modern vaccines. The example that comes to mind is how exposure to cowpox granted smallpox

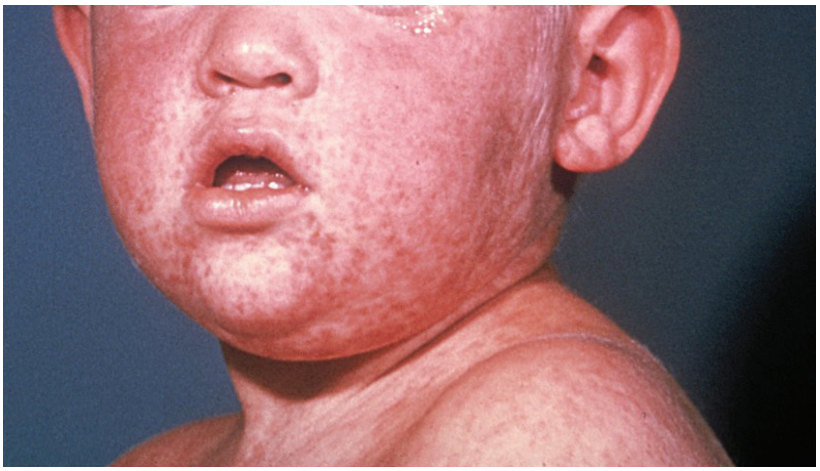

Figure 3. A boy on the third day of his measles infection. Image from CDC 2019.

immunity to many farmers and milkmaids in the 18th century. However, they were risking lifelong brain damage and other unpleasant side effects. Parents led by this ideology may be putting their children at severe risk of impairment and even death.

With the rise of vaccine hesitancy, there are significant implications regarding the clinical side of healthcare. The growing amount of distrust in science poses a new dilemma for doctors. Physicians must find new ways to talk to patients that will allow them to feel comfortable. Many clinicians today do not have the training needed to keep up with the shifting religious and social concerns of their patients. As a result, it is just as important to teach clinicians specific patient-centered communication skills as it is to teach scientific literacy to patients (Lorini 2018).

In closing, it is clear that a rise in vaccine hesitancy is causing an uptick in preventable diseases such as measles. Moving forward, the burden of teaching the public about the importance of vaccination and about the downstream consequences of vaccine refusal falls upon healthcare professionals. Nonetheless, the overall causes of vaccine hesitancy are due to religious exemptions, anti-vaccination group propaganda, and parental refusal. ❧

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A cross-cultural examination of spiritual or religious captivation and schizophrenia

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With the human population on earth nearing eight billion, it is no surprise that variation exists both biologically and culturally. However, humans actually share 99.9 percent of the same DNA, and we are far more similar than we may think. Although a seemingly small percentage, that 0.1 percent of genetic diversity is enough to create a baseline for the development of both advantageous and deleterious variants in physiology as well as behavior (National Human Genome Research Institute, 2018). Nonetheless, genetics aren't everything, because research has shown that our experiences can greatly influence the pathology of diseases and our overall biology. Culture emerges from our environments, and spirituality is a quintessential example of how human practice can influence physiological and psychological health.

Belief in higher powers or supernatural forces has been the foundation of many societies. Through the influence of governmental structures, social morals, and artistic expression, spiritual practices remain recognizable across centuries and continents. Many faiths feature stories of chosen ones hearing the voices of deities, important messages that offer universal truths, and the listener is encouraged to take up the helm of a spiritual prophet and spread these ideas to the rest of humanity. These disseminators, however, are often subject to backlash or oppression, as the sacred teachings they propagate often contradict and clash with the faith, culture, and societal status quo of different regions and times. Despite this, many of these individuals emerge as celebrate symbols of their faith– some of whom are later venerated as martyrs because their persecution was fatal. But what about those whose visions and beliefs are not from pious devotion, but from chemical and physical distortions in the brain that lead to delusions and multimodality hallucinations?

Schizophrenia is a complicated, debilitating, and chronic psychiatric illness that is characterized by a combination of positive and negative symptoms that respectively represent an excess or absence in cognitive function. The most archetypal positive symptoms include hallucinations, lack of insight, and delusions whereas the most common negative symptoms are social isolation, lack of motivation, impaired memory, diminished cognitive function, as well as reduced and incoherent speech (Picchioni, 2007). Diagnosed in approximately 5 out of every 1,000 people in the United States (Wu, 2011), this multifactorial mental disorder often presents either in late adolescence or during early adulthood. In addition to men being one and a half times more likely than women to be diagnosed with the condition, their symptoms have an earlier onset, are of greater severity, and they are less likely to recover (Picchioni, 2007). Like many other mental disorders, genetics influences the risk of developing schizophrenia. The probability of developing this condition increases to about 10 percent for first-degree relatives (i.e. offspring of an affected individual) and to nearly 50 percent for a monozygotic twin with an affected sibling (Patel, 2014). Environmental factors, such as childhood trauma, in-utero malnutrition, familial dysfunction, and psychotropic drug abuse, may also contribute to its development, particularly in those who are already genetically predisposed.

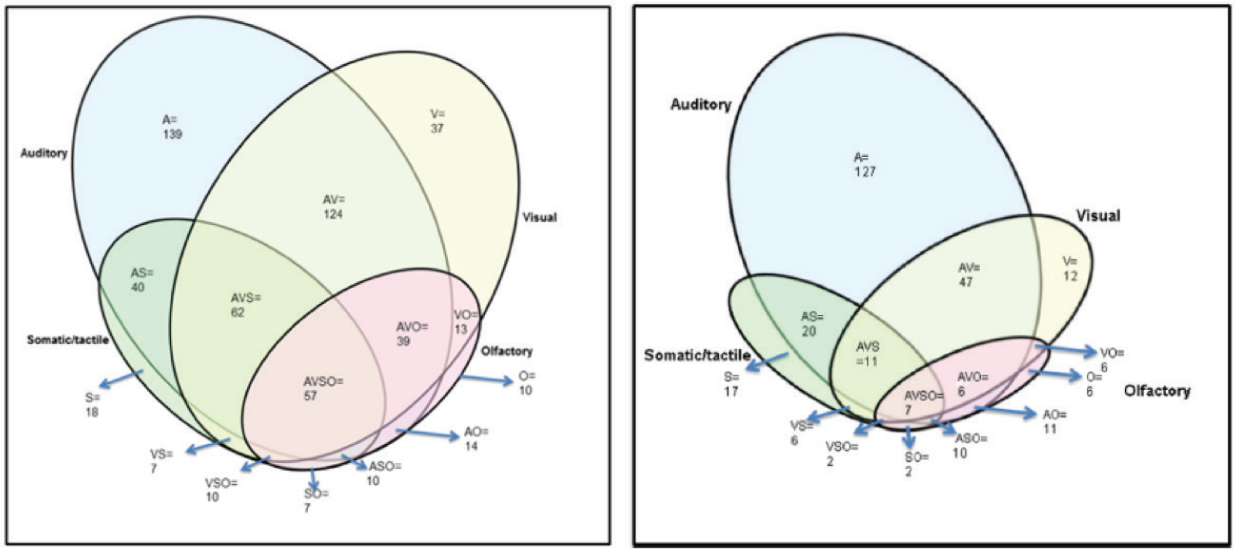
Hallucinations are a compelling and epochal for the diagnosis of schizophrenia; however, some modalities are more likely to be altered than others. Epidemiological research has shown that ethnicity and socioeconomic status aside, the auditory system is by far the most often consistently distorted among populations, fol-

...a correlational relationship between having a definitive sense of spirituality in one's daily life and the prevalence of religious themes in schizophrenic delusions...

lowed by the visual system (Bauer, 2011). Although all subjects in the study (Bauer, 2011) reported hallucinations that consisted of at least one modality, it is not uncommon for multiple sensory systems to be concurrently affected in a single psychotic episode. For instance, one study (Lim, 2016) showed that after examining the lifetime prevalence of unimodal and bimodal hallucinations in 603 patients with schizophrenia-spectrum disorders, a majority reported experiencing bimodal hallucinations. 77 percent of these patients were men, and it was found that audio-visual hallucinations were the most commonly reported bimodal combination. There doesn't appear to be a correlation between biological sex and sensory modality in hallucinations; the larger number of male patients in this study may simply be a reflection of the greater prevalence of male schizophrenics in general. In addition to examining lifetime prevalence, the researchers also performed a CASH (Comprehensive Assessment of Symptoms and History) screening to examine the current status of these schizophrenia-spectrum patients at the time of entry into the study. Fig. 1b shows that of the 285 patients that had hallucinations within the month prior, almost half of the patients experienced unimodal (auditory) hallucinations; furthermore, of those who reported bimodal hallucinations, audio-visual was still the most common variation (Lim, 2016). This discrepancy in reporting results confirms that the prevalence and nature of multimodal hallucinations are not well understood or documented. Even though the data in Fig. 1b shows that unimodal auditory hallucinations are the most prevalent, patients screened for lifetime prevalence of hallucinations more often report bimodal or trimodal hallucinations. This difference could be due to the fact that multimodal hallucinations are more memorable and harder to ignore because they engage more senses, occur less frequently and can even be traumatic. Thus, these kinds of hallucinations would be more consistently reported in answer to questions about one's history of hallucinations.

...the nature of having schizophrenia and religious or spiritual affiliations are independent of one another...

A study of patients in India with diagnosed schizophrenia and verifiable hallucinations showed that over 50 percent of visual hallucinations consisted of seeing "God," "Devils," or "Spirits," as denoted by Figure 2 (De Sousa, 2016). That same study showed that about 15 percent of subjects recalled the identity of the speaker in their auditory hallucinations as "God," while approximately 55 percent could not name the speaker. India is a predominantly religious and spiritual country, with prayers



Figures 1a (left) & 1b (right): The top schematic portrays the lifetime sensory modality distribution in 750 schizophrenic subjects, while the bottom schematic shows the same kind of distribution but for the one month prior to the screening. Both diagrams show that there is variance in not only which modalities are affected, but also the number. Image from Lim 2016.

and religious symbolism being common attributes in colloquial communication, pop culture, and architecture. As a result, there may be a predisposition for Indians to feel that God would communicate with them, whether or not the person has schizophrenia. This correlation is not specific only to India; there are many countries or societies that still exist today in which spirituality is a predominant feature in everyday life.

Visual Hallucinations		Schizophrenic patients (n = 48)	Percentage
Nature	Scenic	4	8.33%
	Bizzare	14	29.17%
	Sexual	2	4.17%
	Flashes of Light	2	4.17%
	God	16	33.33%
	Devils/Spirits	10	20.83%
Other Features	Past experiences	10	20.83%
	Continuity	11	22.92%
Time of the day	Day	4	8.33%
	Night	5	10.42%
	Both	39	81.25%

Figure 2. Based on the reported visual hallucinations of 48 schizophrenic patients, the most common themes are of supernatural or spiritual beings, as noted by the "God" and "Devils/ Spirits" categories. Image from De Sousa 2007.

The correlation between a religion's dominance in society and the prevalence of spiritual/ supernatural delusions is further confirmed in a transcultural study conducted on 430 schizophrenic patients of either South Korean, Taiwanese, or Chinese descent. The South Korean and Taiwanese subjects demonstrated greater religious affiliations, 42.7 percent and 62.9 percent respectively, when compared to the Chinese patients, of whom only 4.1 percent showed religious affiliation. The researchers theorized that this greater religiosity in South Korea and Taiwan was due to China's anti-religious and communist governmental regime in the mid-20th century (Kim, 2001). These patients were all individually interviewed: a psychiatrist asked each patient nineteen questions regarding the nature of their delusions. Afterwards, the screenings were analyzed by the interviewer, and the themes of the reported delusions were classified into the twenty-one categories, such as "family," "love/ affair," "superpower/hypnotism," "religion/supernatural," "possession," "I am god/Jesus/Buddha/ heavenly being." In terms of frequency of delusions within the given categories, the data show that the South Korean and Taiwanese patients more commonly reported supernatural or religious delusions, 47.1 percent and 41.0 percent respectively, whereas only 7.9 percent of the more secular Chinese patients reported such themes. When asked about delusions regarding persecution, 23.5 percent of the South Korean patients and 17.3 percent of the Taiwanese patients reported the persecutor as a religious or supernatural figure; only 3.6 percent of their Chinese counterparts reported such religious persecutors in their delusions. Although not causational, there does appear to be a correlational relationship between having a definitive sense of spirituality in one's daily life and the prevalence of religious themes in schizophrenic delusions.

There has been research that specifically compared the contextual nature of delusions between western and eastern societies. These investigations have particularly demonstrated that the variations in content may be due to differences in spiritual affiliation among societies. After all, there are a number of distinctions between Christianity and Islam, as well as Shintoism and Buddhism. In two comparative studies that examined the differences in delusions between patients of Germanic and Japanese descent, as well as Austrian and Pakistani descent, it was found that the Western patients of Germany and Austria had greater prevalence of religious delusions - particularly those surrounding guilt and committing sin - than their Pakistani and Japanese counterparts. These differences perhaps again signal the influence of regional differences in culture and religious denomination on supernatural delusions. Western European countries have a greater prevalence of Christian values, while Pakistan is majority Islam and Japan Shinto and Buddhist (Stompe, 1999; Tateyama, 1993).

Aside from religious and spiritual affiliation, another factor worth considering when addressing the prevalence of spiritual delusions and hallucinations across communities is the

Table 4 Significant changes in the relative proportion of certain religious symptoms across the 11 time segments of the study (proportions are out of the 632 files with religious symptoms, not the entire patient population)

	1975–76 N = 50	1977–78 N = 79	1979–80 N = 124	1981–82 N = 57	1983–84 N = 60	1985–86 N = 16	1987–88 N = 41	1989–90 N = 77	1991–92 N = 37	1993–94 N = 46	1995–96 N = 45
God ($P < 0.01$)	22%	38%	44%	39%	32%	50%	24%	51%	27%	20%	33%
Religious Behaviors											
Increased talking/ preaching ($P < 0.01$)	2%	15%	27%	32%	18%	19%	20%	25%	35%	17%	11%
Increased reading of religious texts ($P < 0.02$)	6%	9%	21%	12%	23%	13%	15%	13%	16%	7%	2%
Religious places (churches, mosques, etc) ($P < 0.01$)	6%	8.9%	18.5%	5.3%	20%	25%	31.7%	20.8%	16.2%	15.2%	11.1%
Joining religious groups ($P < 0.01$)	2%	2.5%	7.3%	3.5%	6.7%	18.8%	0%	11.7%	0%	2.2%	0%
Supernatural or frightening themes											
Cursed by Black Magic ($P < 0.05$)	16%	10%	11%	18%	27%	6%	12%	10%	14%	28%	18%
Possessed by an evil spirit ($P < 0.02$)	0%	4%	3%	2%	12%	6%	3%	13%	11%	7%	4%
Ginn ($P < 0.01$)	4%	0%	2%	5%	3%	6%	5%	13%	8%	15%	4%
Religious hallucinations											
Auditory hallucinations ($P < 0.01$)	16%	25%	22%	9%	12%	13%	15%	35%	30%	17%	31%
Visual hallucinations ($P < 0.05$)	10%	27%	15%	14%	12%	0%	10%	21%	24%	11%	24%

Figure 3. Over the course of two decades, the religious nature of Egyptian inpatients with psychotic disorders changed immensely; more specifically, the prevalence of hallucinations across subjects increased as well as religious behaviors like preaching of religious ideas and visitations to religious institutions like churches or mosques. Image from Atallah 2001.

socio-political climate of each respective society at the time of data collection. For instance, in an Egyptian study conducted on 632 patients with religious themes in their psychosis, Figure 3 shows that the content of their hallucinations and delusions (i.e. the figures, events, and practices) changed in relation to a social shift away from Islam towards Christianity over the course of the mid-1970s to mid-1990s. For instance, from the start of data collection in 1975 and to its end in 1996, auditory and visual hallucination prevalence across subjects approximately doubled. It is unclear whether or not this increase in religious behavior and psychosis is due to the religious shift being towards Christianity or the societal consequences of groups in the population diverging from the pre-existing, Islam-influenced cultural practices. Ultimately, this societal change corresponded to greater prevalence of psychosis in the communities as well.

Whether it is a product of the illness or cultural influence, faith serves many functions in the lives of individuals - with or without schizophrenia. For many, religiosity and spirituality give a sense of purpose and direction in life, an explanation for both positive and negative life events, a common ground for developing a sense of community, as well as a coping mechanism in times of distress. Although present research has shown that more devout schizophrenics are more likely to have spiritual-religious content in their psychotic episodes, it is also important to recognize the shortcomings of these studies. Aside from the challenges that can arise in screening these patients, this research was conducted on a complicated illness that is heavily stigmatized and still relatively unknown in its origins and development. Furthermore, it is important to recognize that the nature of having schizophrenia and religious or spiritual affiliations are independent of one another, yet it is when they coexist that we can possibly see the intersection where one influences an individual's experience of the other. ❧

AUTHOR BIO

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Trial by fire: the Ebola vaccine

Figure 1. Doctors prepare themselves to treat Ebola patients. Image from CDC.

DEANNA ALTOMARA
Staff Writer

It's a bloody death. Vomiting. Diarrhea. Bruising. Ebola is an unforgiving virus, killing half of its victims. But in the midst of the second-largest Ebola outbreak the world has ever seen, a promising vaccine is offering hope to end the suffering.

The Ebola virus was first discovered in 1976 near its namesake river in the Democratic Republic of Congo, formerly called Zaire ("What is Ebola Virus Disease?" n.d.). For years it was a rare and neglected disease and attracted little attention from the global community. That all changed as Ebola burst into the public eye in December 2013, when a toddler suddenly fell sick, possibly infected by the fecal matter of a local fruit bat in an impoverished Guinea village. Two days later, the toddler was dead, but the damage had just begun ("Ground Zero in Guinea," n.d.). The world's largest outbreak of Ebola infected 28,700 people and killed more than 11,300 ("Researching Ebola in Africa," n.d.). It was a time of unbridled fear, distrust, and miscommunication that left deep scars across the affected regions. Ebola was a knife to the heart of many distressed communities, disrupting trusted social systems, igniting controversy over traditional religious burials, and slashing all agricultural and economic activities. After the outbreak ended in 2015, people prayed that this disease would never arise again. But more than forty years after the first reports of Ebola, the virus has engulfed the Congo in a new epidemic.

But in the midst of the second-largest Ebola outbreak the world has ever seen, a promising vaccine is offering hope to end the suffering.

Ebola is a part of the ebolavirus family, which contains several different species. Ebola usually only affects monkeys and nonhuman primates, but four species in particular (Bundibugyo ebolavirus, Reston ebolavirus, Sudan ebolavirus, and Tai forest ebolavirus) have the ability to cause infections in humans (Mathebula et al., 2019). Harbored by bats and other small animals, Ebola is a highly contagious disease that spreads through bodily fluids ("What is Ebola Virus Disease?" n.d.). Once the virus infects a host, it begins replicating and spreading to organs like the liver and the spleen. Protected by a fatty coat that allows Ebola to directly infect immune cells, the virus sets off a cascade of toxic effects. Up to 90 percent of patients may die from this disease (Mathebula et al., 2019).

There are currently no licensed vaccines for Ebola, but several candidates are being tested in the Congo and other parts of Africa ("Ebola Vaccines," n.d.). One of the main contestants is rVSV-ZEBOV, a vaccine developed using a type of virus primarily found in cattle. This virus is structurally similar to Ebola but is harmless to humans. Using genetic engineering, scientists have attached an Ebola protein to the harmless virus, effectively allowing the virus to wear Ebola's name tag, and teach other cells to recognize what Ebola looks like. That way, when a vaccinated person's immune system encounters the real Ebola, it can immediate-

ly identify the virus and destroy it ("Ebola Vaccines," n.d.).

The vaccine was originally developed by scientists at the Public Health Agency of Canada and is now licensed to Merck, a leading pharmaceutical company ("Ebola Vaccines," n.d.). The vaccine worked as early as 2003, but since Ebola was not considered a high-priority pathogen, it remained untested. Development floundered until the United States named Ebola as a possible agent of bioterrorism, meaning the virus could be used to purposely infect American targets (Pinchin, 2019). Still, progress was slow, severely delaying the vaccine's deployment. It wasn't until 2014 that Merck decided to start testing the vaccine, during the first major Ebola epidemic (Pinchin, 2019). The first shipment of the vaccine was successfully deployed by Merck to Guinea in 2015 ("Second Ebola vaccine," 2019).

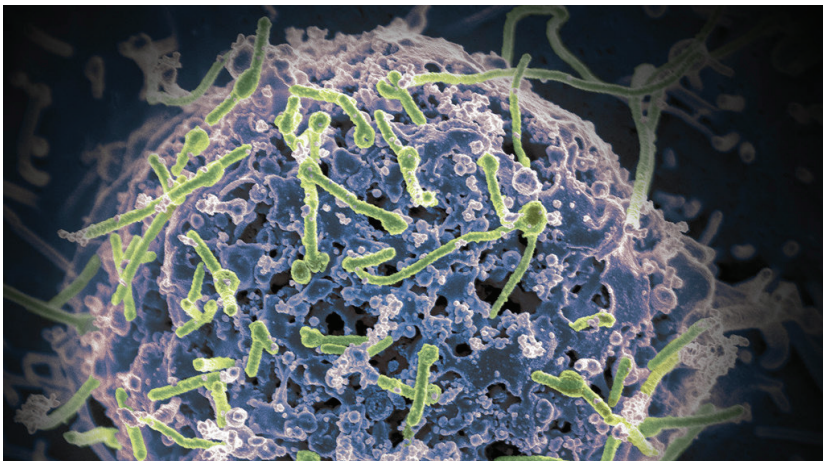

Figure 2. The Ebola virus on the surface of an infected cell. Image from NIH.

In most cases, a potential medication will go through several stages of testing and evaluation before it is declared safe to use. However, with Ebola there is simply no time. But is it ethical to give people a vaccine that hasn't been tested, with unknown efficacy and side effects? On the other hand, how can researchers withhold the only hope people have? The vaccine has been approved for "compassionate use," which allows companies and countries to bypass the usual drug licensing process when no other medical treatments are available for a certain condition ("Why is a new Ebola vaccine so controversial?" 2019).

But is it ethical to give people a vaccine that hasn't been tested, with unknown efficacy and side effects?

Unfortunately, just because a vaccine is available does not mean it is ready to start saving lives. There are simply not enough doses of the vaccine for the entire at-risk population. To solve this problem, epidemiologists are using ring vaccination, a strategy used to help eradicate smallpox in the 1970's. Instead of vaccinating everyone, officials only vaccinate those who have come in contact with an Ebola victim or their body fluids in the last 21 days. This strategy effectively protects the people who are at greatest risk of contracting the disease. By late September 2019, 223,000 people had been given the vaccine ("Second Ebola vaccine," 2019). That month, the US Food and Drug Administration also announced that a half-dose of the vaccine was proven to be just as effective as a full dose. Upon hearing the good news, Merck pledged to make 400,000 doses. However, this would still not be enough if another large outbreak were to occur (Pinchin, 2019).

The success of rVSV-ZEBOV has encouraged Johnson and Johnson to develop its own version of the vaccine, which was deployed to affected areas in mid-October ("Second Ebola vaccine," 2019). But some officials fear that using two different vaccines will only confuse people, feeding into the general atmosphere of mistrust. Some locals believe that the vaccine could cause mental illness, infertility, or increase the risk of contracting Ebola itself ("Vaccinating against Ebola," 2019). After a landmark study confirmed that the vaccine was 100% effective, the United States Food and Drug Administration officially approved it under the brand name Ervebo.

The initial strategy of using local government to spread information about Ebola backfired, as many communities do not know or trust state authorities. Many government structures are associated with varying degrees of corruption. Corruption and general poverty drain public health efforts—often, healthcare sys-

Figure 3. Doctors from the UK are dressed in protective equipment to keep them safe while exposed to Ebola. Image from DFID.

tems are underfunded and simply do not have the resources to treat dangerous and highly contagious diseases such as Ebola. Some people argue that if it weren't for the political and economic instability that weakened many African public health systems, Ebola would not have caused such a widespread outbreak in the first place (Pinchin, 2019). In fact, one of the most effective health communication campaigns during the Ebola epidemic was ultimately headed not by a government or international organization, but by a Liberian rapper's music video that discouraged risky behavior like shaking hands or eating bushmeat that might harbor the virus (Gyenes, 2019). While more effective than many of the other strategies employed, confusion and uncertainty still reign as many people are still torn over who they can believe. People are unsure as to whether they can trust the advice of family and friends (who might advise eating kola nuts or taking a hot salt bath as effective Ebola remedies), or the Western doctors who promise healing in closed-off treatment facilities from which many never return.

There is also a cultural stigma attached to Ebola, and those infected are sometimes seen as contaminated, dangerous, or even deserving of infection. Some survivors have been attacked, isolated, or completely abandoned by their communities (Bortel et al., 2016) Wary of the stigma, some people are afraid to be seen getting the vaccine, for fear that their neighbors will think that they have been exposed. Pop-up clinics have helped to deliver the vaccines anonymously, and have also provided an extra layer of protection in areas where violent conflict can erupt at a moment's notice ("Second Ebola vaccine," 2019). In locations where there has already been high exposure, vaccinations are offered to everyone in the neighborhood. About 90 percent of the populace typically choose to accept the vaccine. The WHO and its partners have also focused on recruiting locals to serve on vaccination teams, thereby fostering community acceptance and eventual self-reliance ("Second Ebola vaccine," 2019).

The Ebola vaccine is a revolutionary development, but alone, it is not enough to resolve the epidemic. The outbreak has been driven by a complex combination of structural instability, miscommunication, and mistrust. Stronger public health systems are needed in developing countries, health systems that can treat and prevent conditions that predispose people to disease. But with further research, investment, and community partnership, there is hope for an end to the Ebola epidemic. ❧

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Growing antibiotic resistance and the path to the superbug

VYAS MURALIDHARAN
Staff Writer

Since the discovery of penicillin in 1928 by Alexander Fleming, the world has progressively become more and more lackadaisical with the use of antibiotics, whether it be regarding a small sinus infection or the common cold (for which antibiotics are entirely useless). Years of misuse are leading to a massive public health crisis. The growing trend of antibiotic resistance can be linked directly to the overuse of these drugs. Modes of transmission vary from the water we drink to the food we eat. As the crisis worsens, scientists are looking to build a completely new drug framework. One option they have turned to are bacteriophages.

Antibiotic actions today are built upon a few basic biochemical (Satyanarayana 2018). A large plurality of antibiotics utilize a beta-lactam molecule to disrupt the cell wall of a bacteria, preventing it from rebuilding and in effect, killing the bacteria. Other antibiotics attempt to damage nucleic acid macromolecules. The quinolone class of antibiotics, for example, target topoisomerase enzymes, whose functions are related directly to the supercoiling of DNA. By trapping and disabling these enzymes, the strands are unable to be rejoined. As a result, the bacteria will trigger a DNA stress response, eventually leading to cell death. As effective as these frameworks have been in the past, they have their limitations. Overuse of antibiotics have resulted in the evolution and spread of bacterial genes that are immune to their effects.

Overuse of antibiotics have resulted in the evolution and spread of bacterial genes...

Despite the many warnings issued regarding the rising usage of antibiotics, there has been a sharp increase in the usage of antibiotic drugs globally. A joint study between Johns Hopkins University, Princeton University, the Center for Disease Control, the University of Antwerp, and other European institutions showed that antibiotic resistance had gone up by 65 percent between 2000 and 2015 (Klein 2018). The rapid modernization and increased availability of drugs in Low and Middle Income Countries (LMICs) such as India and Turkey are major contributors. Antibiotic consumption increased by 114 percent in LMICs, from 11.4 to 24.5 billion daily defined doses, while the prescription rate increased by 71 percent.

Despite the relatively stable

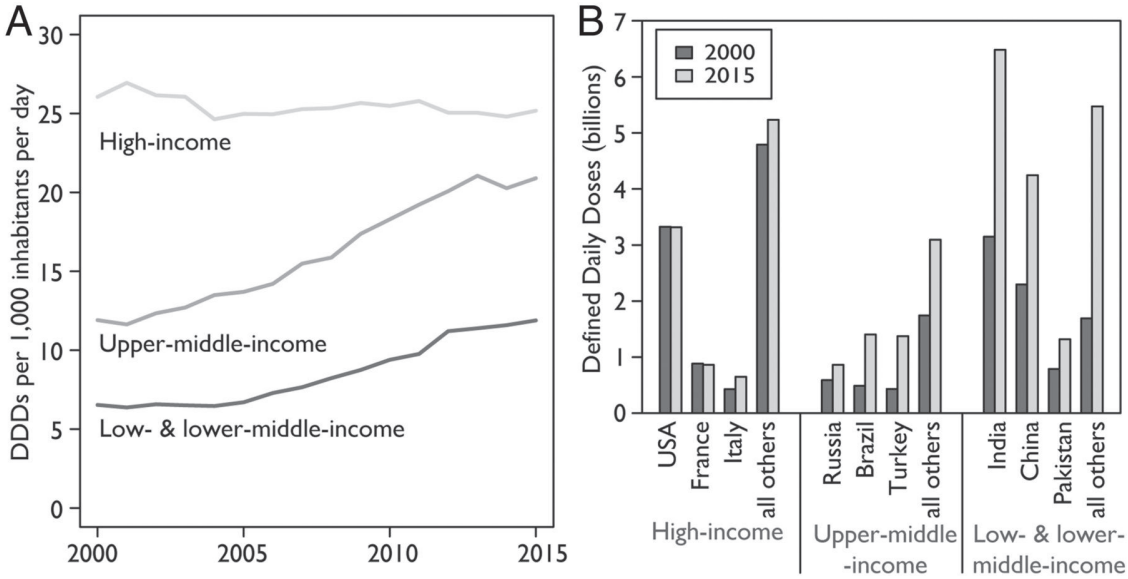

Figure 1. These graphs show the change in drug consumption over time using Daily Defined Doses. Drug consumption in high income countries has stabilized; however, consumption in low income countries have been steadily increasing. Image from Klein 2018.

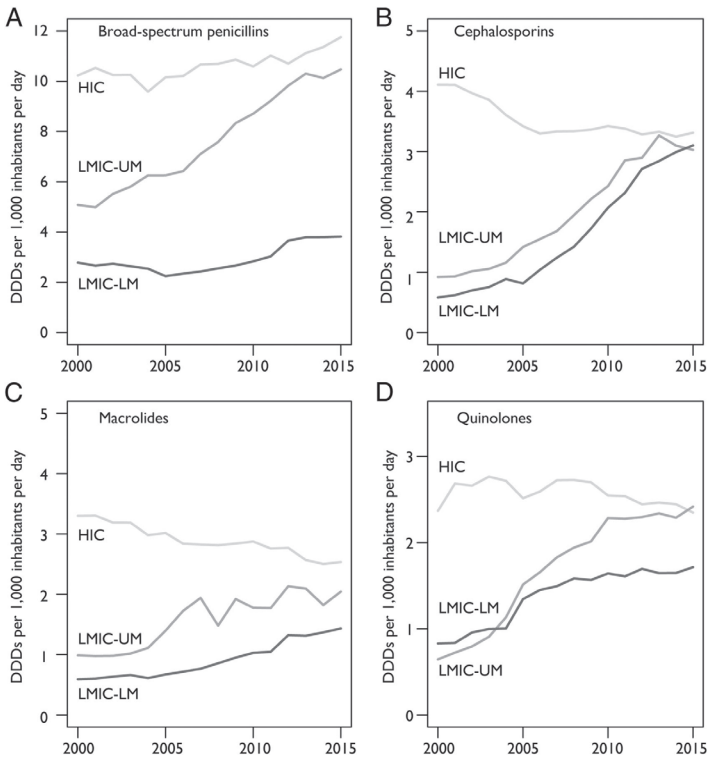

Figure 2. These graphs showcase certain classes of antibiotics that have seen increased usage over time. Both low and high income countries are approaching similar rates of usage, potentially leading to increased antibiotic resistance, including in antibiotics defined as "last resort." Image from Parker 2016.

overall usage of antibiotics in high income countries such as the United States, France, and the United Kingdom, the number of deaths due to antibiotic resistant bacteria has escalated. Total consumption of antibiotics increased by only 6 percent in the 15 year period the study was conducted (Klein 2018). However, in 2013, the CDC issued an alarming report stating that nearly 2,000,000 Americans were infected with antibiotic resistant bacteria in just that year, with more than 23,000 of those cases dying annually.

As resistance to normal use antibiotics grows, more doctors are starting to turn to what are commonly known as last resort drugs, some of the most potent antibiotics ever created. Examples include colistin, aminoglycosides, and carbanapem. These drugs are called last-resort because of their potency at small dosages and because they are only used when all other treatment options have failed. However, these drugs come with their own risks; colistin, for example, is seldom used due to its kidney toxicity, while aminoglycosides have the additional effect of causing sensorineural hearing loss as well as permanent balancing issues. The joint study showed an increase in the usage of last resort drugs across all countries from 2000. Although a slight decrease in the rate in high income countries in recent years indicates an interest in resolving the issue, the number is significantly higher compared to that of 2000 (Klein 2018). In addition, low and medium income countries are also converging to very high rates, exacerbating the crisis. One example of this phenomenon can be seen with Cephalosporins. As described earlier, the daily defined dosage for 1000 inhabitants per day is decreasing in high income countries, around three and four. Unfortunately, lower income countries have rapidly approached that same rate (Klein 2018).

...everyone is always at risk, all the time.

These increased rates of usage of last-resort drugs such carbapenem, colistin, glycylcyclines are leading to an increased number of bacteria that can resist antibiotics. In 2013, the head of the CDC, Thomas Frieden, warned of a growing number of carbapenem-resistant Enterobacteria. These colonies can potentially lead to septic shock, which entails widespread organ failure. In an increasingly connected, globalized world, one mutation found in one hospital can spread beyond the confines of the hospital. In fact, several states in India, such as Haryana and Tamil Nadu, reported the spread of the NDM1 gene through the drinking water supply and sewage waste (Kumaraswamy 2010). The gene encodes for an enzyme that can block the activity of nearly every antibiotic, including the highly regarded carbapenem. The same NDM1 gene began to pop up in the United Kingdom after the patients had just traveled to India.

Antibiotic usage in agriculture is another contributor to the crisis. In 2015, China reported the rise of bacterial resistance to

colistin, a drug that was seldom ever used outside of a hospital setting (McKenna 2013). Beef producers in China had been giving their cattle large swaths of colistin in order to make the meat healthy for consumption. If just one unit turned out to be resistant, it would spread to the rest of the cattle. These plasmids spread rapidly, not just between cows, but between all species of animals. Colistin resistance is primarily encoded on two different genes: mcr-1 and mcr-2. To determine just how widespread the problem had become, researchers in China took fecal swabs from a variety of farm animals in different intensive feeding farms in the Jiangsu province. The mcr-1 in colistin resistant E. coli bacteria from pigs, chickens, and cattle was 68.86 percent, 87.58 percent, and 71.43 percent, respectively (Zhang 2019). The mcr-2 was present in 46.82 percent of pigs, 14.90 percent of chickens, and 19.05 percent percent of cattle. As traditional antibiotic resistance builds, doctors resort to last-resort drugs, which also builds up resistance in a cycle of negative feedback. It's a vicious cycle. The problem with bacteria is that one gene found on one plasmid can transfer so quickly and so easily between different individual units. In an increasingly globalized world, there is no such thing as an isolated case: everyone is always at risk, all the time. For example, any individuals exposed to an affected water system become carriers for that bacterial gene. And everyone you meet has the potential to be a carrier.

The existing framework simply doesn't work anymore. Tweaking methods only work for so long, and they're failing. Each framework has its limitations, as bacteria have evolved mechanisms to disable the molecules used by antibiotics. We can only outmaneuver so much; it's time to think a little outside the box.

A potential option includes the use of bacteriophages as an alternative to antibiotics by injecting viruses to fight off a bacterial infection. Bacteriophages are a class of viruses that parasitizes a bacterium for its own reproduction. It hijacks the bacteria to make more of itself, and in the process, kills it. Certain bacteriophages are tailored to specific types of bacteria, meaning any sort of resistance would be more contained and isolated.

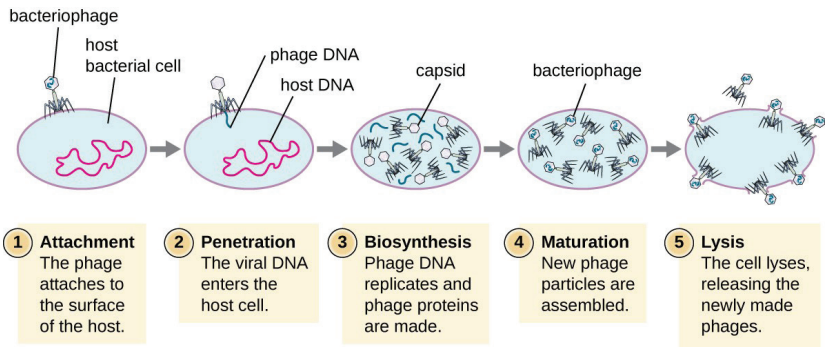

Figure 3. The lytic cycle, where the bacteriophage uses the bacterial machinery to replicate itself then lyses the cell. Image from Muralidharan 2019.

Phage therapy was an idea discussed in 1930s Soviet Russia before the antibiotic revolution. However, it has recently been used as something of a Hail Mary, when even last resort drugs have failed. One such example of this in recent years occurred in 2016. Dr. Steffanie Strathdee at the University of California-San Diego successfully used a cocktail of bacteriophages to cure her husband of a multidrug resistant infection, one that led him into a coma for nearly 3 months and nearly to a state of total organ failure (Mertz 2019). A phage cocktail would consist of multiple phages proven to be effective against the pathogen in question. One phage on its own simply wouldn't be enough.

There are certainly some attractive qualities of phage therapy, such as its specificity. Moreover, just as bacteria evolve to combat phages, the phages evolve naturally as well. Though the CDC and other western health agencies haven't officially sanctioned major trials, phages have been used in Eastern Europe over the years. For example, in 1987, a phage therapy was able to reduce typhoid fever incidence fivefold when compared to the placebo (Górski 2018). Beyond simply allowing for targeted therapy, phage therapy may allow for antibiotics to regain their potency. Pseudomonas aeruginosa is an example of a multidrug resistant bacteria. OMKO1, its targeted bacteriophage, attacks the efflux pump of the bacteria. Efflux pumps

maintain the chemical concentrations of bacteria and play a key role in antibiotic resistance—as resistance grows, the pumps can recognize antibiotics. However, in fighting off the OMKO1 bacteriophage, P. aeruginosa had to make a huge evolutionary trade-off: by protecting itself from bacteriophage targeting, the bacteria became vulnerable to antibiotics that it had previously been resistant to (Chan 2016).

Phage therapy is a fairly new method. Further research needs to be done to determine the total safety of the procedure. Whatever the future may hold, one thing is certain: the current trajectory is not sustainable. Soon, we may live in a world where even something as small as strep may require the use of the most potent antibiotics without the confidence that they will cure the infection. However, some treatments provide hope and direction for further research to be done. ❧

AUTHOR BIO

Vyas is a third year majoring in Quantitative Sciences with a concentration in Neuroscience & Behavioral Biology alongside English. His favorite place in the world is his bed and once slept 22 hours uninterrupted.

Edited by Sarah Kim, Bushra Rahman and Dr. Tyler Cymet
Placed by Michael Namer

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Acupuncture as a potential rehabilitation therapy for post-stroke paralysis

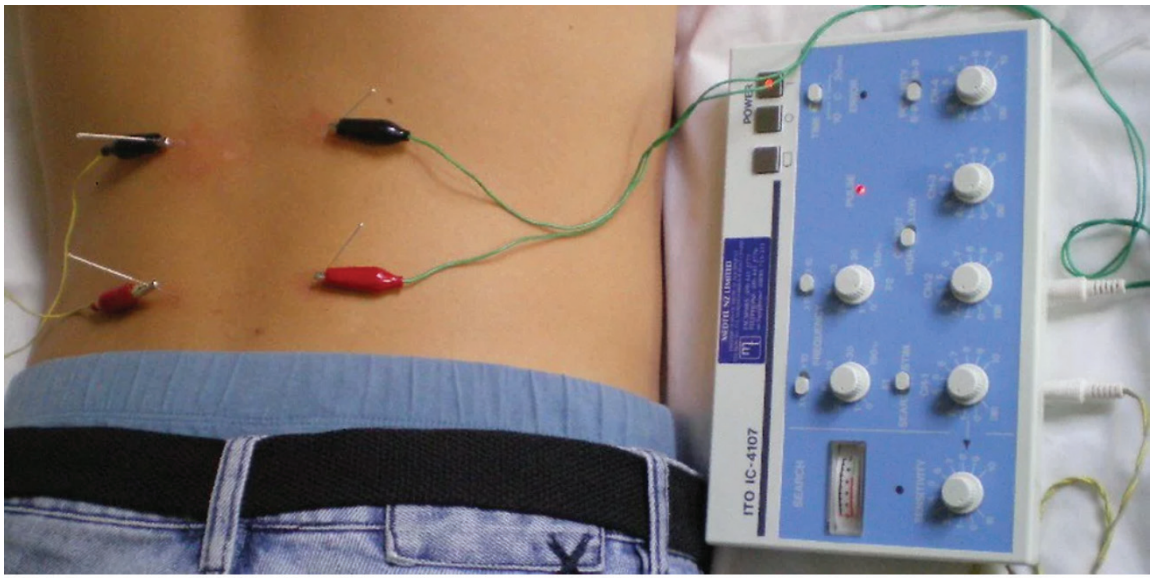

Figure 1. Demonstration of electroacupuncture. Needles are placed at acupoints and then stimulated with pulses of electric current. This needle manipulation is supposed to increase the efficacy of acupuncture therapy. Image from Sacred Lotus Acupuncture 2017.

ALAINA WATERS
First-Year Liaison

CARISSA WU
First-Year Liaison

Within the past few years, acupuncture has garnered significant interest in the West as a form of alternative medicine for various ailments. A millennium-old technique, acupuncture has been widely used in China to treat both mild and severe medical conditions, including post-stroke paralysis. In the West, acupuncture medicine has been under stringent review for its potential as an alternative or complementary treatment for general motor impairment in patients. General motor impairment is often a symptom of stroke. This article will analyze current research on the efficacy of acupuncture treatment in rehabilitating ischemic stroke patients.

Acupuncture is one of the main treatments used in traditional Chinese medicine (TCM) to treat disruptions to the normal circulation of "qi", the TCM concept of vital energy, and blood throughout the body (Dharmananda, 1996). TCM is based on the concept that a body contains a system of meridians, paths through which qi circulates. When there is a blockage or disturbance within a meridian, the disruption of circulating qi creates an imbalance in the body, which leads to disease (Dharmananda, 1996). Several decades ago, TCM practitioners opted to use electronic instruments to measure meridian electrical conductance (MED) to identify blockages of qi. The meridians are illustrated in Figure 2 for further reference.

This article will analyze current research on the efficacy of acupuncture treatment in rehabilitating ischemic stroke patients.

Acupuncture therapy involves the insertion of fine needles into specific acupoints along meridian lines to reduce a build-up of qi at blockages and to prevent disease. In recent years, studies have related the locations of these acupoints to areas of high nerve concentrations (Chavez et al., 2017) and have shown that acupuncture stimulates signaling systems and biochemical production (Dharmananda, 1996).

An ischemic stroke is a life-threatening disease in which blood flow to the brain is restricted due to a blood clot or fatty buildup. The restricted

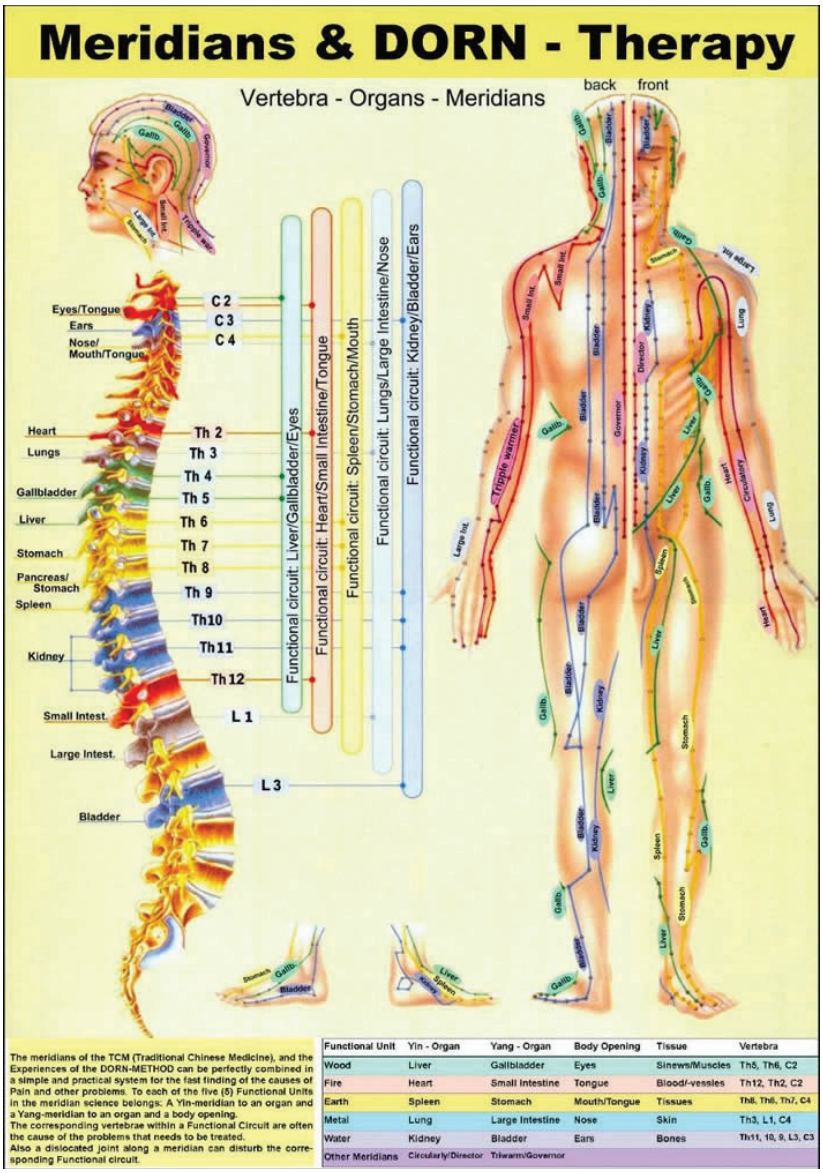

Figure 2. Diagram of meridians. Image from Koch & Steinhauser.

blood flow can result in permanent brain damage, which often manifests physically in stroke patients as motor and cognitive impairments. According to TCM theory, strokes occur due to "'Blood stasis,' 'Wind,' 'Phlegm,' 'Qi deficiency,' 'Fire-heat,' and 'Yin deficiency with Yang hyperactivity'" (Chang et al., 2019). These different factors disrupt the normal flow of qi through the meridians to different degrees. A 2019 study conducted in Taiwan shows a clear correlation between meridian electrical conductance (MEC), a measurement of qi, and hemiparesis (paralysis on one side of the body). In this study, 102 subjects suffering from acute ischemic stroke had MEC measurements taken using the meridian energy analysis device (MEAD). MEC measurements in limbs with limited or absent motor function were found to be significantly higher than in limbs with full motor function, suggesting a consistency in diagnosis and technology used for ischemic stroke (Chang et al., 2019).

In recent years, researchers have begun to explore acupuncture therapy and its biological effect on the human body. Studies focusing on acupuncture treatment for ischemic stroke propose that acupuncture can modulate processes related to brain tissue regrowth (Chavez et al., 2017). According to an in-depth literature review conducted by Chavez et al., acupuncture has shown to be effective in improving recovery from ischemic stroke by encouraging neurogenesis (production of neurons) in brain tissue, modulating blood flow and preventing apoptosis (cell death triggered by the cell itself) in the ischemic area. Figure 3, retrieved from this same study, shows the areas of the brain affected by the acupuncture therapy.

According to this same study, one of the most effective forms of acupuncture is electroacupuncture (EA), a technique in which needles are first inserted at acupoints and then are charged with small amounts of electricity. Performing EA led to a reported rise in concentrations of specific proteins and growth factors (Chavez et al., 2017). These biomolecules are involved in a number of processes that further increase neurogenesis and angiogenesis (production of red blood cells), especially in ischemic areas of

All of these effects help to counteract or repair damage from the initial cell death and vessel damage caused by an ischemic stroke.

the brain. Other notable effects of EA include an elevated quantity of neuroblasts (precursor to a neuron) in the hippocampus and subventricular zone, as well as the upregulation of anti-apoptotic factors (Chavez et al., 2017). All of these effects help to counteract or repair damage from the initial cell death and vessel damage caused by an ischemic stroke.

There are currently limited thorough and large-scale research studies available on the use of acupuncture as a therapy for paralysis post-ischemic stroke. Therefore, there are inconclusive results regarding the effectiveness of acupuncture. However, a large collection of small studies from varying countries and cultures, both Western and Eastern, show promising results and encourage further investigation of acupuncture remedies.

For our research, we looked at both individual studies and meta-analyses with articles in each of these categories coming from both western and eastern researchers. Many of the individual studies, such as those conducted by Naeser et al., Zhang et al., and Li et al. report positive results; acupuncture was found to be an effective therapy for patients suffering from post-stroke paralysis. These studies report statistically significant increases in function when acupuncture was used and minor lesions caused the paralysis. The study conducted by Naeser et al. had a total of only 16 subjects used for statistical analyses (1992) while the study from Li et al. reported the outcomes of just one patient (2017). While the findings of these studies should not be disregarded, they do not provide a large enough sample size to yield generalizable evidence supporting acupuncture for treatment of ischemic stroke patient paralysis.

A meta-analysis conducted by Wu et al. shows potential for the use of acupuncture as a standard practice. This study compiled a large group of studies and found an 80 percent rate of overall effectivity for acupuncture following ischemic stroke. However, the authors hesitate to draw firm conclusions due to study limitations, such as small sample sizes, research and publication bias, and flaws in study design, including a lack of consensus on what constitutes a control group or control procedure for an acupuncture study (Wu et al., 2010). On the other hand, another meta-analysis conducted by Sze et al. concludes that acupuncture is not effective in improving motor function in patients who suffer from post-stroke paralysis. However, acupuncture may be effective in improving the quality of life for patients by decreasing their level of disability, meaning that patients are better able to function in their daily lives despite their impairment stemming from the paralysis (Sze et al., 2002).

Nevertheless, the meta-analyses themselves may risk a lowered level of credibility due to the bias for affirmative results in Chinese medical journals (Wu et al., 2010). Chinese medical journals tend not to publish research that yields results contrary to the hypothesis– in this case, results that would signify a low efficacy of acupuncture. This means that it is highly likely that there is a higher proportion of positive results available in Chinese publications than is representative of the actual efficacy of the technique, resulting in meta-analyses which are inherently flawed and biased.

None of the studies examined in this article are both conclusive and positive, but the results of these studies warrant further investigation into the use of acupuncture as a therapy for paralysis. Given the general efficacy of acupuncture in the literature currently available, it is important to continue investigating acupuncture as a potential therapy.

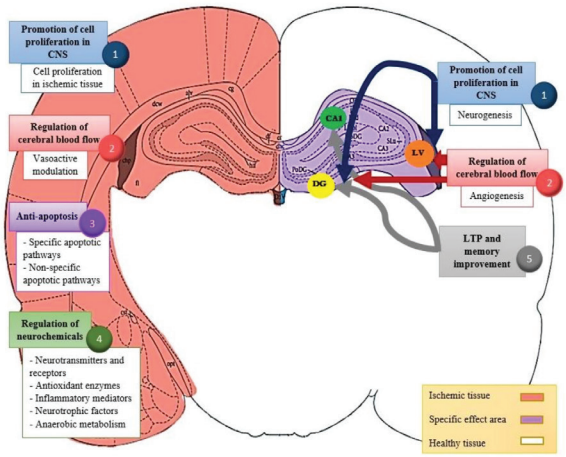

Figure 3. Different researched effects of acupuncture on the brain, particularly structures and mechanisms related to ischemic stroke. Image from Chavez et. al. 2017.

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AUTHOR BIOS

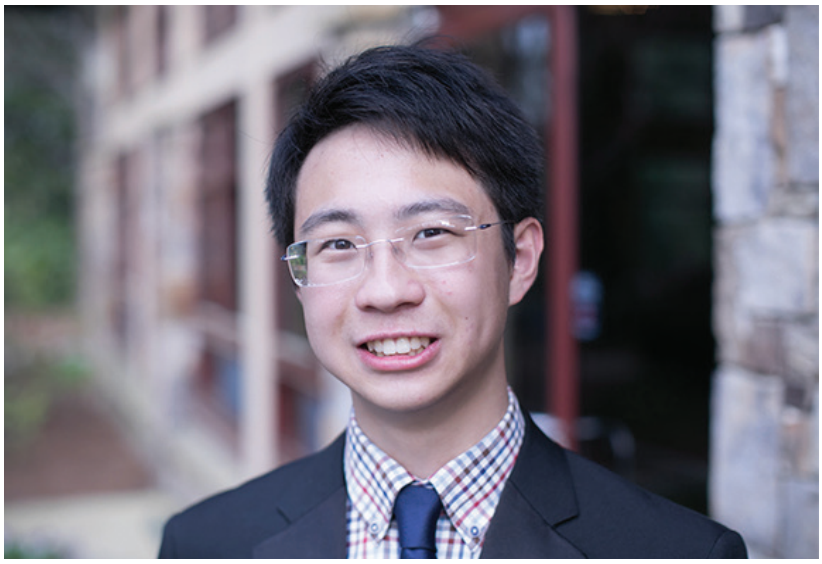
Carissa Wu is a first year Biology major. An interesting fact is that she has visited countries in five different continents.

Alaina Waters is a first year student planning to study Biology with a minor in Mathematics. In her free time, she enjoys embroidering her own personal designs.

Edited by Anna Farrell, Preethi Reddi and Dr. Sarah Blanton

Placed by Rachel Xue

Memoriam



Earlier this year, the Emory Undergraduate Medical Review was saddened by the loss of Albert Zhang, a second-year Emory student. Albert previously served as treasurer of EUMR and wrote and edited articles for the journal in Spring 2019. In May of 2019, he was elected to take on the role of copy editor-in-chief. Outside of EUMR, Albert was involved in the Emory Wheel, College Council, Media Council, and the Emory Journal of Asian Studies. In addition to his many involvements, Albert was known for keeping a running list of ways to improve Emory. During his time in our organization, he was able to act upon his ideas and worked tirelessly to improve EUMR.

Albert was known for his late night phone calls to ensure that articles and tasks would not only be completed on time, but would also exceed the expectations of the tasks he was provided. Albert maintained confidence that the articles he was assigned would be completed, even offering to co-author himself on one which was behind schedule. As a first-year student, he eagerly took on the role of treasurer mid-year and worked actively with Media Council in order to ensure that EUMR would maintain its charter and funding. He negotiated and collaborated with other organizations to ensure that funding was allocated appropriately and fairly following budget cuts to Media Council. Upon taking on the copy editor-in-chief role, Albert made a promise to expand and grow EUMR's presence and involvement with other student organizations. Albert played a large role in the growth of EUMR's online presence through our blog. This past year, interest in EUMR has grown tremendously, in large part due to Albert. The quality and content of this year's publication is an attestation to the work Albert was able to accomplish. We are beyond grateful to have been a part of Albert's legacy at Emory.

ADVISORY BOARD

MICHAEL CRUTCHER Ph.D.

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).

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

MUHAMMAD AZEEM

Medical doctorate in Child Psychiatry at Yale University

Dr. Azeem's primary clinical and research interests include Autism Spectrum Disorders, ADHD, child and adolescent psychiatry training, global mental health, and looking into innovative ways in reducing seclusions and restraints in inpatient child and adolescent settings.

TYLER CYMET

Medical doctorate from Nova Southeastern University College of Osteopathic Medicine

Dr. Cymet is an internist with research interests in joints and the musculoskeletal system. He discovered a new syndrome in 2006 which was named for him called the Erondu-Cymet syndrome. He now serves as the chief of clinical education for the American Association of Colleges of Osteopathic Medicine.

ARRI EISEN

Doctorate in Biochemistry from the University of Washington

Dr. Eisen is a professor of pedagogy at the Center for Ethics at Emory University. He aims to engage undergraduate students in the exploration of science and its applications in broad contexts. He has led the Emory-Tibet Science Initiative since 2005 and continues to be involved in many projects at Emory.

LAWRENCE MARKS

Doctorate from Harvard University

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.

LYNN O'NEILL

Medical doctorate from Vanderbilt University School of Medicine

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.

MOHAMMED SHAHAIT

Medical doctorate from the Jordanian University of Science and Technology

Dr. Shahait is an attending urologist who also teaches at the Perelman School of Medicine at the University of Pennsylvania. His research focuses on the use of robot-assisted radical prostatectomy as a method of treating prostate cancer.

KIM TRAN

Medical doctorate from the University of Medicine and Pharmacy at Ho-ChiMinh City, Vietnam and doctorate in Medical Sciences from Hamamatsu University School of Medicine

Dr. Tran is a professor of physiology and pharmacology at Des Moines University. His research interests include cardiovascular pathobiology and therapeutics, especially the role of GPCRs in disorders such as menopause, heart failure and hypertension.

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.

SARAH BLANTON

Clinical doctorate in physical therapy from Emory University

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.

JESSE SOODALTER

Medical doctorate from the Warren Alpert Medical School of Brown University

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

DAISY LI

Editor in Chief

Daisy is a second year pursuing a bachelor of science 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 potential. That aside, there is nothing she loves more than a day with no agenda spent on all sorts of creative endeavors.

NATHAN JACOB

Secretary

Nathan is a second year majoring in Biology with a minor in Philosophy. He began as first-year liaison and now as secretary, he does a little bit of everything to ensure that all aspects of the club run smoothly. Outside of EUMR, he is also involved in organizations such as club tennis and Remote Area Medical. 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!

ANIRUDH PIDUGU

Treasurer

Anirudh is a fourth year majoring in Neuroscience and Behavioral Biology with a minor in Predictive Health. As treasurer, he works on budgeting for all the event committees and the club's dealings with SGS. Outside of EUMR, he is also involved in SAHI and The Emory Wheel. In his free time, he enjoys basketball and chess.

JINNY YOO

Managing Editor

Jinny is a fourth year majoring in Anthropology & Human Biology and looking forward to medical school in the fall. She has been a writer in EUMR since her second year at Emory and took on the role of Managing Editor for EUMR Open Access (formerly the blog) over the past two years. Outside of EUMR, she has also been involved in Emory Bioethics Society. She "peaked" three years ago when she ran a half marathon.

ANNA FARRELL

Events Chair

Anna is a fourth year majoring in Neuroscience and Behavioral Biology. She started EUMR as a first-year liaison, and founded the Emotive Arts Series, a medical humanities conference which is now hosted by EUMR each year. Later on, she advanced into the roles of Copy Editor and Events Chair. Outside of EUMR, she spent a summer working as a science writer composing Wikipedia articles for the military.

PREETHI REDDI

Senior Advisor

Preethi is a fourth year majoring in Biology. She has been involved with EUMR ever since she joined as a first-year liaison. She was one of the founders of the Emotive Arts Series and last year, served as Copy Editor-in-Chief. This year she is currently working on her honor's thesis with the Grady Trauma Project, covering topics such as traumatic brain injury, Post-Traumatic Stress Disorder and sex differences.

Editorial Board

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Aditya is a third year majoring in Neuroscience and Behavioral Biology and minoring in Quantitative Sciences.

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Aidan is a second year double majoring in Chemistry and Environmental Science. He has an identical twin.

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Alexa is a fourth year double majoring in Anthropology & Human Biology and Biology. She works in the Lindo Lab.

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Lauren is a third year double majoring in Anthropology and Neuroscience. She grew up in France.

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Lesley is a third year majoring in Biology and minoring in Music. She is fascinated by Russian music and culture.

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

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