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ACADEMIC JOURNAL

March Issue

Issue 25

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Bacteriophage Use as a Living Therapy and Alternative to Antibiotics in The Dawn of Multi Drug Resistance By Mosi Jones

Abstract

Living in a world filled with bacteria is truly a remarkable thing. Microbes are microscopic creatures that are not visible with the naked eye. They are responsible for things such as fermentation, decomposition, and aspects of growth and evolution. Without microbes, society as we know it just wouldn't function. Unfortunately some microbial bacteria and viruses are pathogenic, meaning that they can be harmful to the host organism by causing disease and illness. They rely on the downfall of hosts to survive, leaving said hosts in a weakened state that could potentially lead to death. Lucky for patients, antibiotics have been an effective way to eliminate these pathogens, and have increasingly been used to treat pathogenic infection. It is this increased use and reliance on antibiotics that has led to an ever-encroaching issue. These bacteria and viruses are becoming resistant to these treatments, and are evolving into super bugs that pose more of a threat in a field where treatments are slowly running out. By looking at the evolution patterns and growth of bacterial persisters (meaning any bacteria that are able to survive after attempted eradication with a method of treatment), we can find new, innovative, effective, and efficient ways of treating them. And the rise of bacteriophages as a living therapy just may be the solution scientists are asking for.

Introduction

Exposure to bacterial and viral agents is inevitable, so the likelihood of contracting an illness at some point in one's life is almost guaranteed. But imagine if that illness was completely antibiotic resistant, and would continue to reproduce until the host was overrun with a severe pathogen such as MRSA (*Methicillin Resistant Staphylococcus Aureus*), MDR (multidrug resistant) *Mycobacterium tuberculosis* (MDR-TB), or even *Escherichia coli* (*E. coli*). That is the present issue: the rise of antibiotic resistance of extremely dangerous pathogens. This paper will discuss how the ascent of bacteriophage therapies may be the key to unlocking the secrets to resolving the threat of MDR infections and bacteria. This concept will be investigated from several different angles including the anatomy and physiology of phages, the medical application of phage therapies, the potential drawbacks of aforementioned therapies, and future

bacteriophage discovery. All with the goal of reinforcing the stability of bacteriophage therapies serving as a supplement or alternative to antibiotics when combating multidrug resistant bacterial infections.

The Anatomy and Physiology of Bacteriophages and Drug Resistance

Antibiotic resistance is a rising risk in the world, as antibiotic exposure gradually increases, so too does the population of pathogenic populations with antibiotic resistant genes. This serves as a serious problem as drug resistant bacteria can easily become a worldwide pandemic issue. Drug resistance occurs when a pathogen is able to persist even after being treated with antibiotics or other clinical drugs. This can happen through exposure and adaptation (vertical transference) or lateral transference from other species [1].

MDR bacteria and viruses can be seen in patients that don't finish their prescriptions, cases of repeatedly prescribed antimicrobial medications, and in many hospitals (in part due to the heavy concentration of pathogens, and access to medications). Examples of these infections include Pneumonia, MRSA, and yeast infections [16].

Bacteriophages are not living organisms, rather they themselves are viruses, which reproduce by engaging in biological subterfuge to take over bacterial and viral cells rather than eukaryotic cells needed within the human body and environment (mostly the human body in this instance). There are an untold number of different phages on Earth, each with its own specific set of receptors used to detect and identify specific bacteria (Fig. 1) [2]. The specificity of phages to their bacterial host could make phages extremely effective at targeting specific pathogens within the body without damaging the rest of the microbiome, a microscopic world of coexisting microbes [2].

The typical *myoviridae* phage consists of about 2 sections, that being the capsid head and the tail. The protein coated capsid head is located at the top of the phage and is responsible for containing the phage's DNA (Fig. 1). The head is affixed at the collar with tail support from whisker fibers to the main tail structure, which consists of many specific parts and is relatively more complex in anatomy as compared to the head. The tail consists of a delivery tube spanning from the head all the way to the central spike. This tube serves as a delivery system that allows the double stranded DNA to travel to the central tail spike for injection. This tube is covered by a contractile sheath that allows for successful injection of DNA into the host pathogen. The

baseplate consists of a wedge and a hub, which when combined serve as a supportive structure that allow for the connection of the short and long tail fibers. These tail fibers provide support and stability to the central tail spike, which is responsible for penetrating the pathogen's cellular membrane (Fig. 1) [39].

While phages themselves are considered viruses they differ from what would generally come to mind when one mentions the word “virus”. This is because phages do not infect eukaryotic cells, rather they tend to go for prokaryotic cells such as bacteria. Phages also differ in structure and physiology when compared to other types of virus in the sense that they have varying morphological differences and variation within their populations,with their main differing physical feature being their tails for which they are typically known for [39].

There are many different types of phages, each with their own set of special features. Some phages have double stranded DNA, such as the *siphoviridae* and *myoviridae* while others like the *inoviridae* and *microviridae* have single strand DNA. Structures can also vary, as in the case with heads, which can have a varying number of sides, as well as tails which differ in length, contractibility, and function. The phage depicted in figure 1 is that of the *myoviridae* family, as it is typically considered the most well known and studied [40].

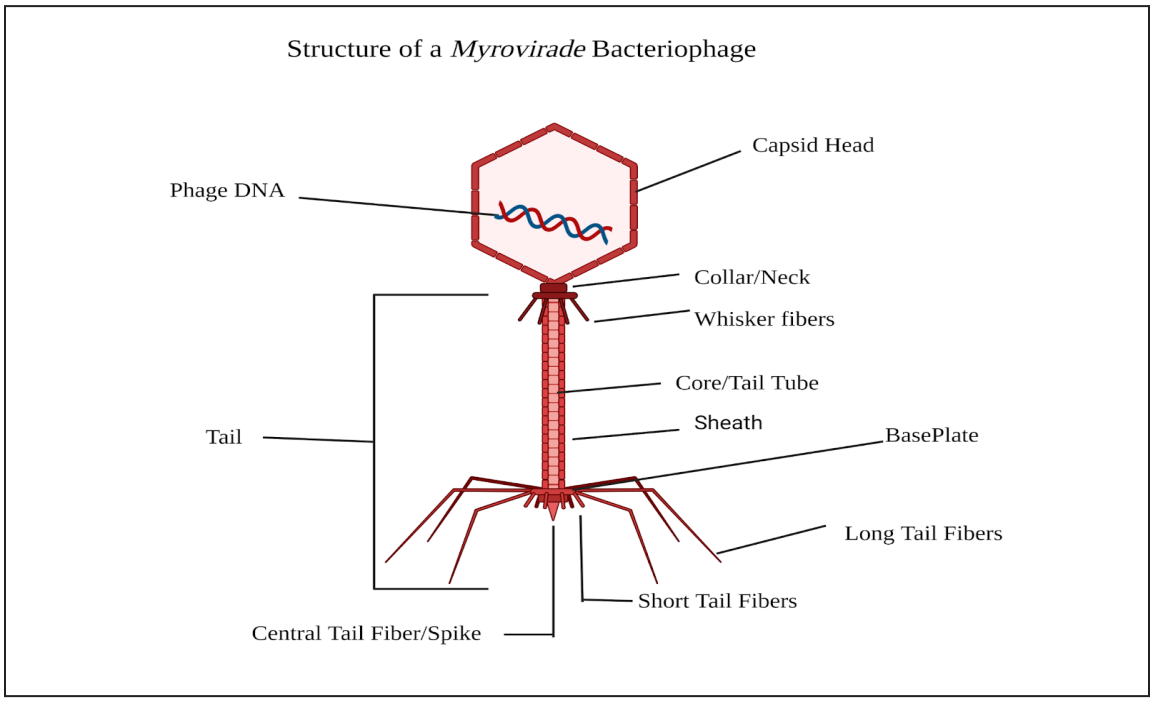

Fig. 1. An anatomical diagram labeling the main structures of the *myoviridae* phage. (Created in Biorender)

The replication cycle of these bacteriophages can either be lysogenic or lytic (Fig 2.). But the lytic phages are the most useful within the context of fighting drug resistance. When a host cell is identified via the specialized bacterial receptors connected to the phage, it begins the process of biological subterfuge. It implants its viral genetic DNA into the host pathogen by binding to cell receptors, which in turn begins to rewire the cell to replicate the phages DNA [3]. Because phages replicate lytically, the host cell eventually begins to lyse and bursts. This releases the newly created virions into the environment, where they can then infect new pathogenic host cells. This is important in the context of the emergence of multidrug resistant (MDR) bacteria, as the entire purpose of phage therapy is to eliminate the pathogen afflicting the host, whereas in a lysogenic cycle, the cell would not lyse and instead would simply replicate itself while still holding phage DNA in the daughter cells [4].

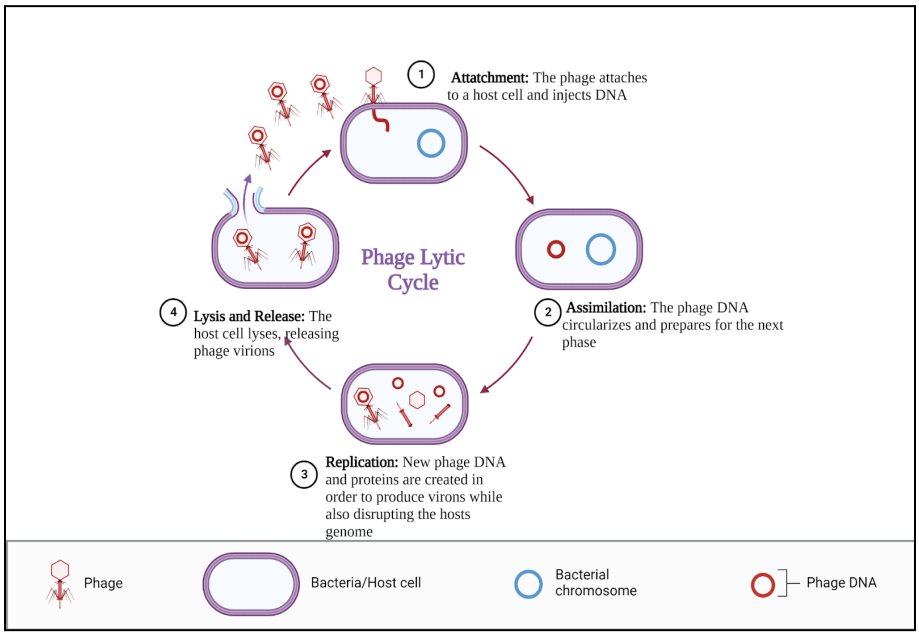

Fig. 2. Illustration of the lytic life cycle of a typical phage. Each step of the lytic replication process is numbered and shows the process starting with infection in step one and ending with lysis and release in step four. (Created in Biorender)

Medical Application and The Future Of Phage

There have already been groundbreaking discoveries for treatments in the world of medicine using phage therapy.The application of these therapies has allowed for the effective eradication of pathogen biofilms in patients. It is currently being used to treat patients with many

types of infections including respiratory illness, *C. difficile* (*Clostridioides difficile)* [15], MRSA (*methicillin resistant staphylococcus aureus*), and other hospital acquired infection; also referred to as nosocomial infections, which have been known to cause severe and lifelong impairments. Phage are being used to treat these pathogens because they show extreme efficacy while also completely avoiding the cause of damage to any other living microorganisms that may be essential to the microbiome [17]. They also seem to work better than antibiotics because they are able to bypass the pathogenic biofilms defensive extracellular polymer matrix which serves as a shield for the biofilm that many antibiotics are not able to pass through effectively by using enzymes (polysaccharide polymerase) that dissolve the polymer matrix substance [18]. All the while the lytic processes of the phages only increase their numbers as time goes on, improving chances of efficacy via higher concentrations of phage. Phages can be considered a "dynamic" treatment of sorts (pharmacodynamics and pharmacokinetics being the adaptability and functionality of treatment [34]) due to its ability to adapt concentration and dosage levels *in vivo*. This is in part due to the replication cycle of phages being dependent on the availability of bacterial hosts, as well as the absorbability and efficacy of the phages themselves [35].
In some nosocomial cases of MDR MRSA infection the use of *Myoviridae* phages such as SA012, K, and 812; have a larger capsid head which more phage DNA, and have been shown to be more effective at eliminating MDR MRSA biofilms in patients [5]. When tested topically (with a concentration of about 5 x 10^6 plaque forming unit (pfu)/mL) in mice models with 3rd degree injuries and skin wounds, the mice were shown to heal faster and more efficiently while also staving off MRSA infection. Mice with this topical phage therapy also had a 100% survival rate as compared to the 34% rate of mice without phage treatment [19].

This efficacy can also be seen within the context of other infections such as the bacterium *C. Difficile*. *C. difficile* is gram negative meaning it has a double layered membraneIt thrives in anaerobic (without oxygen) spaces such as the gastrointestinal (G.I) tract. This bacteria is responsible for a severe nosocomial illness that can cause diarrhea and inflammation of the colon. This bacterial infection is also common for those that take oral antibiotics, as the medication rids all microbial flora in the G.I tract, which allows for opportunistic bacteria like *C. difficile* to take over the microbiome. Treatments for *C. difficile* are difficult as they usually have already been exposed to an antibiotic, meaning that there is a great likelihood for these bacteria to present MDR infection. Other antibiotics such as vancomycin and fidaxomicin can be used to

eliminate most of the microbial spores and living *C. difficile* bacteria, but are usually unable to completely eradicate full traces of the bacteria. Not only that but these antibiotics are also becoming more and more useless to ease this particular ailment, which leads us into new territories of treatment, such as phage therapy. Specific phages typically in the families of either *Myoviridae* or *Siphoviridae* under the order of *Caudovirales* have tails and a more geometrically complex head with about 20 sides, and are known to be phages inclined to infecting *C. difficile* and are currently being studied and tested for combatting *C. difficile* bacteria within imbalanced microbiomes [6].

In a particular study conducted by *Prazak et al.*, the use of aerosolized phage cocktails (a mixture of phages that could improve efficacy in eliminating a specific pathogen) [20], referred to as "aerophages" were used to study whether MRSA based pneumonia infection could be eradicated in mouse models. The study demonstrated that the bacteriophages remained active *in vivo* and *in vitro*, remained local and did not spread to other organs. The phages were able to be retrieved at 93% of phages being recovered, and they did not activate any immune response or inflammation, and when combined with IV phages; increased recovery and curability to a staggering 91%, compared to the original 53% efficacy of the IV phage treatment alone. Not only that, but the repetitive use of IV phage was shown to cause immune system inflammation, while the aforementioned combo treatment did not . Thereby reducing mortality of the MRSA pneumonia infections tested. On the other hand, not all of the MRSA colonies were removed from some of the mice, but were not due to phage resistance [21]. And in other studies conducted by Forti. *et al.*[22] and Vahedi *et al*. [23] (respectively) showed extreme efficacy in treating a variety of bacterial biofilms ranging from *Acinetobacter baumannii* to *E. coli*, treating these pathogens with great results in mice.

Phage therapy is a highly intriguing and new way of targeting pathogenic microbes as it introduces a concept of a "living therapy". While the phages themselves are not alive, they do evolve in order to adapt to the host environment and can pass genetic information through lateral transfer (a type of gene transfer that occurs between 2 different species in already existing cells) (Fig. 2). This allows for them to function as a sort of self programming intelligence that can coexist and adapt to its environment and the native microbiome [1]. This concept can be taken even further into a subject referred to as the Red Queen Hypothesis (RQH) (Fig. 3). RQH states that as the environment evolves, so do the organisms within it. It is optimal for survival, and in

doing so allows for the organisms to survive and reproduce. When a microbiome is introduced to an antibiotic drug, the bacteria within it that persist will typically carry more genetic information to code for resistance in order to protect their lineage as a species creating an adaptive zone where evolution can occur. It is exactly this evolution that then sparks a line of changes in the microbiome that then allow for homeostasis and stability to be restored. The concept of coevolution is brought into thought at this point, and creates a perspective in which the RQH has high relevance to MDR bacteria and microbiota in pertinence to coevolutionary patterns (Fig. 3) [7].

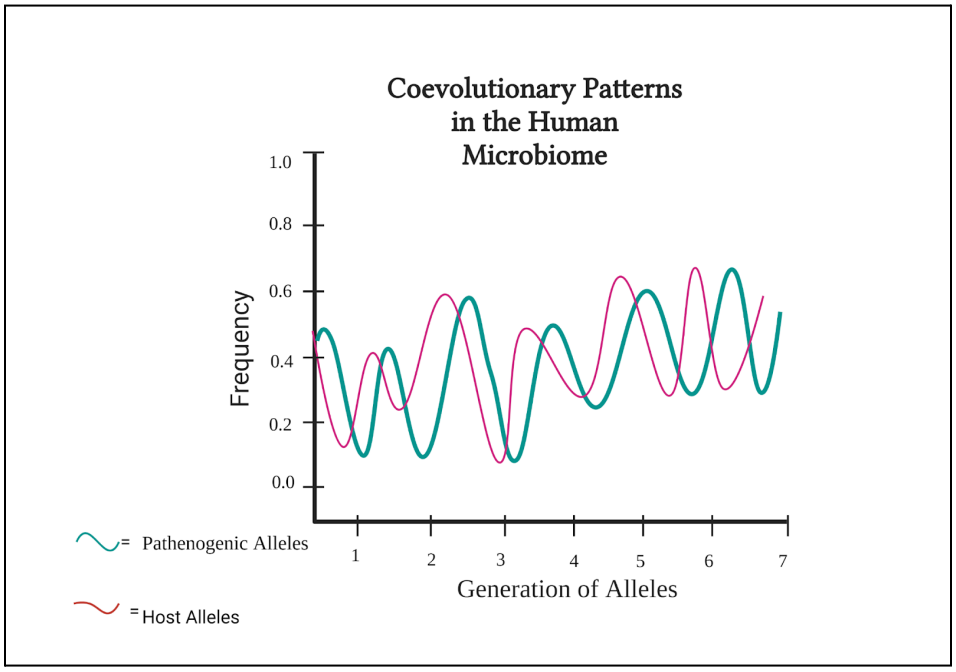

Fig. 3. A diagram showing the physical representation of the Red Queen Hypothesis. X-axis shows the alleles per generation, the y-axis shows the frequency of alleles within the population. A frequency of 1 suggests that the entire population has a given allele, a frequency of 0 indicates that none of the population has a given allele. The pathogenic and host alleles both adapt with each other and create a movement in which one is always just one step behind the other in terms

Questions Concerning Drawbacks and Discovery

While phage therapy definitely seems to be successful in eliminating drug resistant bacteria within medical settings, there are remaining questions and concerns attached as well. Limitations on the storage, application, maintenance, and the like still pose issues to the current

application of phage therapies. These limitations are particularly relevant when discussing temperature and pH. There are many types of phages, each with its own set of environmental preferences. In one particular study viral particles degraded at temperatures higher than 4°C.[8] And in another study most phages do not function properly in acidic environments below the pH of 3 [9], with some phages with higher pH resistant stability such as phiHN10 and phiHN50 that were able to withstand a pH within the 5-11 range, spanning through neutral and basic environments [10]. But by creating a properly balanced environment that allows the phages to survive and succeed within microbiomes such as the acidic environment of the human stomach, it is possible to extend the range of bacteriophages habitats with minor interference. Most phages are either stored in saline or buffered solutions and refrigerated, spray dried, or encapsulated [33]. These methods can extend the shelf life of phages for up to several years depending on the strain of phage or phages being handled [32]. But in general phages do not need -80 storage and most seem to do well in the 4- 8°C range, some being stable in -20°C [33].

Some pathogens may contain endotoxins. Endotoxins are pathogenic substances usually found in infectious agents, and they typically elicit a varying level of immune responses. These substances are usually referred to as Lipopolysaccharides or LPS for short [29], and can usually be removed with trichloroacetic acid or phenol-water in order to neutralize the proteins in the endotoxin via filtration [30]. Phage concentrations may contain LPS as they can attach to bacteria containing LPS. The lysates can undergo a "purification process" in which they are sterilized using filtration to remove any residual endotoxins, but in doing so may lower some aspects of efficacy [31]. We have treatments for endotoxins, so even if a phage were to lyse a cell and release endotoxins, there are existing treatment options such as anti-LPS antigens and protein neutralizers [36]. While anti-LPS antigens work to actively eradicate the endotoxin and protein neutralizers replace vital proteins in the endotoxin to inhibit function, both are effective at successfully eliminating the presence of LPS endotoxins and thereby preventing sepsis [37, 38].

Unfortunately the emergence of phage resistance and CRISPR genes in bacteria may serve as a roadblock for phage therapies, TheseCRISPR genes cause a plethora of problems that could prevent the transference of genetic material from phages to microbes[11]. These genes can make it a lot more difficult for phages to properly do their jobs in combating these bacteria, as said bacteria become resistant to the phages themselves. This is a biological response tied to the

RQH, demonstrating that these pathogenic microbes are still able to adapt to their surroundings by coding for CRISPR-Cas proteins that restrict the abilities of the phage subterfuge (Fig 3). Though this resistance is not as pervasive as the drug resistance issue we are currently facing in the modern medical world, there is still hope as phages are compensating for this by creating defenses that target and immobilize these proteins [12]. The use of a wide variety of phages in a phage cocktail can combat the issue of phage resistance in bacterial pathogens. By administering a mixture of phages, the likelihood of the bacteria to survive is rather low, meaning that the biofilm (or MDR bacterial pathogen) can be successfully eliminated without worrying about rapid adaptation and further resistance. This is because the pathogen would need to evolve several different mechanisms to block all of the phages and their modes of infection in a timely manner that it would most likely not be able to execute successfully [24]. Phage resistant strains of *Campylobacter jejuni* bacterial infection in chickens also showed signs of reduced aggression and competitiveness when compared to the original non-resistant strain. This demonstrates that even though phage resistance may occur, it still inflicts the functionality of the pathogen that it is targeting in certain bacterial strains and colonies [25].

However phage resistance and CRISPR genes do not limit the potential of phage's future progression to a detrimental extent. Phages are special because they exist naturally within the environment and can be used for a variety of purposes. One such purpose can be traced to agricultural use. The protein interactions associated with phages are especially important in an agricultural setting when they can be used to fight against microbial pests that target agricultural crops by creating biological antigens that work against pathogenesis; the development of pathogens[13]. Specifically, phages can be used to identify plant proteins that can bind to the coating proteins in crops, which can also be used to reduce protein folding and inhibit virality [26]. In a particular case conducted by *K.K Pasumarthy et al.*, AC3 proteins (replication enhancement for viral bodies) were used to lure in phages which were then able to identify the pathogen and allowed for a deeper understanding of reduced gene expression and gene silencing [27]. Another example of agricultural phage use would be the roles they play in preventing foodborne illness in foods such as lettuce, cheese, and meats via introduction to agricultural products as a bactericide [41].

Tying back into biology, phages are essential in the field of CRISPR and genetic editing. The CRISPR-Cas protein is being used to edit the DNA of microbiota, such is the case when

treating MDR resistant bacteria. The phage is able to act as a vector that can successfully deliver the CRISPR-Cas protein into the pathogenic cell by storing the protein within the capsid head [14]. Examples of this can be found in studies that focused on eliminating *Staphylococcus aureus* skin infections in mice using CRISPR-Cas9 protein carrying phages, showing efficacy in eliminating the pathogen without disturbing non-drug resistant bacteria [28].

Conclusion

The world of bacteriophage therapies has proven to be quite a useful one. In a world where MDR bacteria are becoming increasingly common, new solutions are needed in order to solve these rising problems. Phage therapy is an answer that medicine has been looking for: a living therapy in which the treatment can adapt and work with the patient in order to successfully treat antibiotic and drug resistant infection. The efficacy and future use of phages is proving to be rather efficient at eradicating pathogens that would otherwise harm the world's populations. Antibiotic and drug resistant bacteria will continue to be a problem in medicine until further research and action is taken, such as with the aforementioned MRSA and C.diff cases and many other MDR nosocomial infections (including but not limited to Pneumonia and *Candida* yeast infections) . As we continue into a new age of medical science we look to new innovative ways of adapting to the challenges of existence; as the rise of phage therapies can aid us further into the future than stagnant methodologies such as antibiotics could.

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Review of Nanoparticle-Based Drug Delivery Methods in Conjunction With Antisense Oligonucleotide for the Treatment of Spinal Muscular Atrophy By Ansh Patel

Introduction

Recent studies, experiments, and marketed treatments have brought about the vast benefits of nanotechnology and the hope it brings with it. With rare diseases increasing at an alarming rate, in both the number of diseases and their prevalence, now more than ever, effective treatments are needed to combat this unyielding battle. Nanotechnology provides practical solutions to lingering obstacles in the healthcare industry, enabling further progress in treating rare diseases.

Despite recent advancements in the field, nanotechnology is considered relatively new, with modern nanotechnology emerging in 1981, especially in medicine. A common consensus, nonetheless, is that despite sparse knowledge of the field, nanomedicine offers a surplus of benefits that have the potential to revolutionize the field of medicine. This work aims to review and summarize some of the most promising nanotechnology applications in the medical domain of rare diseases, specifically Spinal Muscular Atrophy (SMA).

Benefits in Medicine

Nanomedicine comprises devices and nanostructures for diagnosing, curing, mitigating, and treating diseases [1]. However, the most crucial aspect of nanomedicine is that nanoparticles can reach once-thought-inaccessible places of different biological systems, including the central nervous system (CNS), due to their smaller size.

As the name implies, nanomedicine works at a molecular level through various methods, the most effective being nanoparticle-based drug delivery systems. Nanoparticles (NPs) are chemically engineered organic or inorganic particles, also considered nanomaterials. They work by interacting, through the exploitation of their outer surfaces, with the molecular biological environments around them to perform nanoscale processes that accomplish the task at hand [1]. In the case of NP-based drug delivery systems, in most applications, NPs encapsulate the drug, are directed towards the targeted cells and deliver the drug to the targeted site with the controlled release [1]. These features alone make NPs a suitable medium for drug-delivery systems. Aside from drug-delivery systems, nanomedicine can accurately diagnose diseases, repair damaged

tissues, conduct gene therapy, and provide immunity (e.g., vaccines) [1]. Nanomaterials have an advantage when it comes to diagnosis over current methods. Through non-viral administration, they can provide more accurate diagnoses through an environmental sensor. NPs modified with an environmental sensor relay the patient's inner body to the outside environment (e.g., MRIs), a task that invasively-administered methods of diagnosis cannot entirely achieve. Nanodevices can repair targeted tissues and cells without negatively impacting the surrounding biological environment (e.g., tissue nanotransfections). Along with tissue repair, nanomedicine also provides genetic treatments through chemically-modified nanoparticles. One such example is CRISPR, a chemically-modified protein whose original purpose by one's cells is to help form RNA transcripts and was repurposed for genetic editing. Nanoparticles have also been implemented into vaccines because of their advantages as a drug-delivery system. Their profound ability, in this case, is their protection of RNA from nuclease degradation, a focus of this review. Nanoparticles have been implemented within vaccines and administered on a global scale; the Pfizer and Moderna SARS-CoV2 or Covid-19 vaccines are manufactured with lipid-nanoparticles (LNPs) for RNA protection from nuclease degradation and increased immunity [2, 3].

Types of Nanoparticles

Nanoparticles have an extensive database comprising two categories: organic and inorganic NPs. Organic NPs originate from within a biological system, such as protein-nanoparticles (PNPs), while inorganic NPs are particles originating from external elements such as gold nanoparticles (AuNPs). While the studies have shown the usage of inorganic NPs to report better overall efficacy over organic NPs, cytotoxicity due to metallic poisoning and low biocompatibility/biodegradability seems to be the primary factor limiting their usage. After reviewing multiple studies, it can be concluded that organic NPs are the better choice due to their low cytotoxicity, higher biocompatibility and biodegradability, and efficiency, despite their lower efficacy.

There are multiple types of organic NPs, including, but not limited to, polymer NPs, LNPs, PNPs, peptide NPs, liposomes, polymerases, exosomes, and dendrimers [4]. Each nanoparticle has its trade-offs and nuances for specific use cases, and multiple in-vitro/in-vivo studies have been conducted with these NPs. The most prominently studied organic NPs have

been LNPs, peptide NPs, and PNPs. In terms of efficiency and efficacy, specifically in CNS-focused drug-delivery systems, polymer NPs, peptide NPs, and exosomes appear to be the best choices.

NP-based drug-delivery systems are created so that NPs would act as a carrier that makes up for the weaknesses of the drug, such as low solubility, poor cellular uptake, or intercellular trafficking, and increase its effectiveness. They are also advantageous for their protection from nuclease degradation, controlled drug release, site targeting specificity, and intercellular delivery. However, NPs can also overcome a significant deficiency of modern pharmaceuticals - accessing the CNS. Only 1% of modern pharmaceuticals can reach the CNS because of their inability to cross the blood-brain barrier (BBB) and brain-cerebrospinal fluid (BSCFB).

The BBB and BSCFB are biochemical membranes in the brain that are tightly packed endothelial cells with neuron pericytes and astrocytes [4]. These membranes allow nutrients and small lipid-soluble molecules to pass through while blocking almost everything else [5]. The difference, however, between these membranes and cell membranes is that these have tight junctions, specific transport and carrier proteins, and low rates of fluid-phase endocytosis [6]. NPs, such as the ones listed above, can break through these membranes and effectively deliver pharmaceuticals to the CNS without any chemical changes being done to the drug itself, which could affect its therapeutic effect.

As mentioned before, polymer NPs, peptide NPs, and exosomes are the best options for crossing the BBB and accessing the CNS due to their specific qualities.

Polymers are substances containing large sequences of macromolecules joined together, both natural and synthetic. Synthetic polymers originate from labs, including polyester, nylon, and Teflon, while natural polymers include nucleic acids, proteins, lipids, and carbohydrates. Polymer NPs are natural polymers that originate from living organisms and possess significant advantages in creating an effective drug-delivery system. One specific advantage is the versatility of their properties. They have varying natural compositions, as mentioned above, different releases and degradation abilities, and easy manipulation of their outer surface. They offer long blood-circulation time, controlled release of pharmaceuticals, and good loading capacity [7, 8]. In addition, when modified with GLUT1-ligands (Glucose), they are very effective in permeating across the BBB due to the GLUT1 receptor proteins on its membrane [9].

Exosomes are derived from extracellular vesicles from cells used for cellular communication and the transportation of materials. Due to this, exosomes are incredibly effective in transporting pharmaceuticals between and in cells. Their specific advantages are their easily manageable surfaces, high biocompatibility and biodegradability, complete non-cytotoxicity, and originating solely from cells. As a carrier, exosomes show the most potential in carrying most pharmaceuticals, primarily due to their ability to resist nuclease degradation, penetrate the BBB, and deliver the drug with site-specific precision. Targeting moieties can be modified upon the surface of exosomes and have been shown to increase mRNA delivery into the BBB to suppress tumors [10].

Peptide NPs are amino acids that are bonded together by covalent peptide bonds. Peptides are molecules made up of amino acids joined through dehydration synthesis and helped to form ribosomes. They are an efficient delivery system due to their size, low cytotoxicity, high ability to reach the targeted sites, and transcapillary delivery of bio-cargoes [11]. Peptide NPs have shown high efficiency in crossing the BBB, and studies have shown tumor-suppressing functions in brain gliomas. Chemical modifications can be made upon the surface of peptide NPs with ligands to perform vital communication (through signals) with cellular membranes.

Nanoparticles serve as excellent potential candidates for NP-based drug delivery systems.

Strengths of organic NP-based drug delivery systems

One of the most significant advantages of NP-based drug delivery systems is that they are non-invasive. Most drugs designed for neurodegenerative diseases are administered through invasive methods, usually requiring intracranial or intrathecal injections, both of which can present severe limitations to patients and weaken them. Patients present numerous side effects, such as infection, edema, and neuronal damage [12]. Though these invasive methods are effective, non-invasive methods can offer equal or even better effectiveness without the excess burden on the patients and lessen the chances of adverse side effects.

Besides acting as a more effective vessel in medicinal delivery, NPs are incredibly advantageous in making up for the weaknesses the drug themselves lack. They have high malleability, which makes it easier to load the drug into NP, resulting in the ease of manufacturing. Chemical modifications increase the productivity and strength of the nanoparticle, and its small size acts as a natural carrier that escorts the drug to nearly inaccessible

places to reach, such as the CNS [13]. Along with this, they have high biocompatibility with biological systems, high biodegradability, flow density, cellular penetration and uptake, and make up for solubility— all desirable properties in the context of drug delivery. Additionally, they outperform conventional drug delivery mechanisms with their ability to restore cytoarchitecture and connection patterns in CNS disorders. Nanocarriers exhibit the ability to absorb proteins, interacting with the BBB endothelial cell receptors, allowing them to cross the BBB without harming the barrier itself. Nanocarriers have significant potential concerning their efficiency as an NP-based drug delivery system, specifically towards their positive effects on pharmaceuticals [4, 10, 14].

Toxicology

While nanoparticles possess properties that are significant towards providing effective solutions to ongoing treatment problems, there are still questionable concerns that plague its progress.

Nanoparticles are abundant in every part of the human body. Nanoparticles are cells, vesicles, proteins, and nucleic material. On the other hand, Engineered nanoparticles align more with the definition of "nanotechnology." Despite nanoparticles' non-toxic properties within our living organisms, once engineered, they can exhibit toxic properties and be cytotoxic in living organisms.

As aforementioned, nanotechnology is a novel platform, and there is limited research and knowledge, resulting in several unknowns which need to be explored before utilizing it widely in medicine. The concerns of nanotechnology are the potential for toxicity, atypical immune responses, and the implications of the cost and manufacturing processes. Organic NPs engineered in a lab, usually through chemical modification, have raised toxicity concerns, despite originating from biological systems. The click-down within this realm of research suggests that cationic charges on NPs are toxic, while neutral and ionic NPs show little to no toxicity. Cationic NPs, especially LNPs (regardless of charges), have been shown to activate inflammatory responses and aggravate immune responses [1, 14]. LNPs and organic NPs can biodegrade, which means that side effects and toxicity might usually exist for a finite amount of time. Currently, inorganic NPs pose the most significant threat to biological systems due to the high toxicity presented in studies. With high cytotoxicity, inorganic NPs have little

biodegradability, despite showing biocompatibility (usually due to chemical modifications), meaning that they will continue to exist within biological systems without degrading, which is an incredible danger to one's health.

Applications

Antisense Oligonucleotides (ASOs) are a form of gene therapy that inhibit the viral reproduction of genes [15]. ASOs as potential gene therapies may be a relatively new drug class, but not the concept, as drugs like Fomivirsen were first released in 1998 [16]. ASOs work by penetrating cellular membranes, reaching the pre-RNA, transcribing specific genes to include exons to be transcribed into the RNA, and eventually into mRNA, which is then used to create proteins. Its innovation alone makes it an already highly sought gene therapy. However, when paired with its other strengths, its applications seem limitless in providing potential treatment options for genetic disorders. Some of ASOs' applications include (1) cryptic splicing mutations, which could prove effective in β-thalassemia, breast cancer, and cystic fibrosis [17]. Cryptic splicing refers to splice sites not used in pre-mRNA but spliced due to their mutations in genes. Through their ability to perform this function, ASOs provide a therapeutic effect by cleaving transcriptions consisting of genetic mutations that might otherwise be obscured or left undiscovered. (2) Therapeutic potential for inflammatory diseases, dystrophy, atrophy, anti-apoptosis, and cancers by switching between alternative splicing isoforms [17]. Alternative splicing is a cellular process in which exons in transcribed pre-mRNA are included or excluded to generate mature mRNA transcriptions. (3) Inducing exon inclusion for cancers, spinal muscular atrophy, and Duchenne muscular dystrophy [17]. The induction of exons is significant in acting as a suitable form of treatment for diseases, as they can increase the production of vital proteins lost due to mutations. (4) Correcting the reading frame to allow the production of internally deleted partially functional proteins in Duchenne muscular dystrophy, spinal muscular atrophy, and dystrophic epidermolysis bullosa [17]. The internally deleted partially functional proteins refer to poorly synthesized vital proteins due to genes incapable of transcribing fully functioning proteins. (5) Induction of reading-frame disruptions to achieve partial protein knockdown in, for example, atherosclerosis and cancer [17]. Similar to correcting reading frames for synthesizing functioning proteins, this application of ASOs enables them to replace naturally degrading, partially-functioning proteins with fully functioning ones.

Strengths & Weaknesses of ASOs

ASOs have tremendous potential as gene therapy; however, they are still considered a new drug with even newer technology. As such, they may have the potential to offer beneficial and effective genetic treatment options, but one needs to acknowledge their limitations which may result in low efficacy and effectiveness inside biological environments. Considering the cost of the released ASOs, which will be further discussed in the coming sections, ASOs' limitations could curb their potential as a prospective treatment for genetic disorders.

The strengths of ASOs include (1) High target specificity. ASOs can accurately reach a targeted site through specific conjugations of targeting ligands while exhibiting low toxicity and systemic exposure. Systemic exposure refers to the amount of time that a drug can exist within a biological system before being retained by the immune system. (2) Longer half-life dosing. Through higher circulation within the body, ASOs exhibit longevity in their gene-splicing processes resulting in effective therapeutic effects. Prolonged half-life dosing also results in a lower dose and dosage, which can be especially beneficial cost-wise. (3) Exhibit multiple methods of treatments for the specific downregulation of disease-relevant genes. Due to their several applications, ASOs can be used for many disorders and purposes, and through this, they have efficient gene knockdown and precise gene-splicing. (4) The most significant strength of ASOs is that their effects are reversible [12]. Reversible effects are an attribute not previously demonstrated in most other genetic therapies, and it sets ASOs apart from the rest. This attribute is vital because permanent effects upon the pre-mRNA can result in irreversible side effects and burden upon patients due to their permanent alterations in pre-mRNA.

Despite these strengths, the limitations of ASOs must be acknowledged and weighed against the benefit before considering them as a candidate for gene therapy. (1) Unconjugated ASOs exhibit poor cellular uptake and intracellular trafficking. Cellular uptake refers to molecules interacting with plasma membranes or, in other words, poor cellular permeability. Without this crucial property, ASOs' ability to cross into cells is not guaranteed, meaning they cannot splice pre-mRNA if it cannot reach the proper site. Intracellular trafficking refers to the ability of a drug to travel in the cytoplasm of cells. Without the property of intracellular trafficking, ASOs cannot reach the nucleus to splice pre-mRNA, posing the same access issue. (2) Poor BBB crossing. Most genetic disorders are neurodegenerative disorders, so it is essential

that ASOs can reach the CNS, if needed, and access neuronal cells. Poor BBB crossing is not just due to the poor cellular uptake of ASOs but is associated with the strength and extreme selectivity that properties of the BBB have compared to regular specialized cells. (3) Poor endosomal escape. Endosomes are vesicles that transport proteins, lipids, and other materials from the plasma membrane to organelles in the cytoplasm and vice versa. Related to ASOs, they must use endosomes to reach the cytoplasm to reach the pre-mRNA in the nucleus; however, if they cannot influence chemical changes in the endosomes to escape, it results in the ASOs being secreted back outside of the cell. (4) Nuclease degradation, The biggest weakness of ASOs is nuclease degradation. Nuclease degradation refers to the degradation of foreign genetic material through the immune system. Unlike the weaknesses mentioned above, the ASOs can still reach the targeted site. However, through nuclease degradation, ASOs might be degraded through white blood cells before exhibiting proper retention in blood circulation and reaching the targeted site [10, 12, 15].

In terms of efficacy and efficiency, ASOs exhibit subpar results due to their weaknesses that generally outweigh their strengths. At the same time, there is still the indubitable fact that the weaknesses of unconjugated ASOs act as a liability towards the overall performance of ASOs. However, their reversible effects and alternative splicing concept continue to set them apart from modern genetic therapies.

ASOs in Duchenne Muscular Dystrophy and Spinal Muscular Atrophy

While listing out applications of ASOs, its therapeutic effects were most evidently shown upon muscular disorders such as Duchenne Muscular Dystrophy (DMD) and Spinal Muscular Atrophy (SMA). These two disorders are perhaps the most common rare genetic disorders exhibited in infants, with SMA being the leading cause of genetic mortality in infants. The fatality rate of these two disorders is incredibly high relative to the prevalence of the disorders, and the lifespan of the patients is limited to around two years in infants. Due to their status as rare diseases, finding an effective treatment for them can be incredibly difficult, but new treatment avenues have opened due to new technology leveraging ASOs.

Two treatments, Nusinersen and Eteplirsen, were released for SMA and DMD, respectively. While specific weaknesses do plague the overall efficacy of the unconjugated ASOs, they serve as suitable candidates for these muscular disorders. Despite having two

different genetic targets, their treatment processes are nearly identical: antisense-mediated exon-skipping therapies. SMA and DMD patients experience genetic mutations that induce partial functioning proteins; SMA is the lack of survival motor neuron proteins that inhibits muscular growth. DMD is the lack of dystrophin proteins while strengthening muscle fibers and protecting them from injury through muscular contractions. Antisense-mediated exon-skipping therapies refer to the ability of ASOs to skip (exclusion) or induce exons in pre-mRNA before translation into mRNA, which is used in the Endoplasmic Reticulum (ER) to synthesize proteins. Exons refer to specific parts of a gene that can help the gene synthesize partially or fully functioning proteins through its inclusion or skipping. Nusinersen and Eteplirsen work in this manner. The gene that Nusinersen targets is the copy of the survival motor gene, SMN2, due to a mutation that causes the loss of the original survival motor gene, SMN1, which transcribes fully functioning SMN proteins. Research and studies have shown that including exon 7 within SMN2 increases the full functioning that it transcribes. As such, Nusinersen splice-splits the inclusion of exon 7 with the pre-mRNA transcript before its maturation. Unlike SMA, DMD's gene referred to as the DMD gene, inclusion of exon 51 into the mRNA transcript results in the partial functioning of dystrophin proteins, resulting in a progressive muscular loss. As such, Eteplirsen split-splices the exclusion or skips exon 51 of the pre-mRNA before its maturation resulting in a greater production of functioning dystrophin proteins [11, 12, 15, 17].

Studies have shown positive results in the production of fully functioning SMN or dystrophin proteins has increased; however, there are still side effects and burdens that need to be addressed. As aforementioned, their reversible effects lighten the concern of their side effects, but not patient burdens, as they assure patients and examiners that they will not last for long.

Rare Diseases

Despite their deceptive name, rare diseases affect over 300 million people worldwide, with approximately 7,000 diseases existing today, of which 80% percent is genetic. Compounded with the fact that they are difficult to quantify at scale, the severity of rare diseases is also typically underestimated. Rare diseases are challenging to treat for multiple reasons: they are difficult to diagnose, they cannot be classified objectively, and there is a sparse understanding of pathology and progression [18]. The biggest issue concerning rare diseases is their frequently changing and geographically-varying classification criteria. Each country has its guidelines that

are relative to its population size. For example, the United States, with a population of 356 million people, has stated that any disease with a total prevalence of fewer than 200,000 cases is considered rare. However, the United Kingdom, with a population of approximately 37 million people, has set any disease with a total prevalence of fewer than 33,000 cases as a rare disease. This stark contrast in "prevalence limits" will subside numerous diseases considered rare in the United States as to their classification in the United Kingdom. As a result, it is difficult to find universal cures, studies, or research on the most prevalent rare diseases. In addition, finding a cure/treatment for rare diseases is extremely difficult due to: low prevalence, patient isolation, limited research literature, and lack of financial motivation for pharmaceutical companies [18]. Low prevalence is the most significant obstacle in finding effective treatments for rare diseases since it results in patient isolation, limited understanding, and low financial contributions toward them. Patient isolation refers to patients feeling isolated from their long diagnostic processes and lack of understanding/support from scientists and the public. The limited knowledge stems from low prevalence, lack of studies, and improper diagnostics of these diseases. Additionally, such a wide breadth of rare diseases makes it difficult for scientists to understand any one disease deeply.

Focus on rare diseases began to increase attention when President Reagan, in 1983, signed the Orphan Drug Act in response to a lack of medical research and attention to rare diseases. Orphan drugs are pharmaceuticals produced to treat rare medical conditions in which the lack of prevalence would cause the drug to be unprofitable. This act was a significant milestone in the rare disease treatment market as it incentivized the private sector to increase research in rare disease treatments by offering government assistance. Since its approval, 600 orphan drugs have been released over the past 40 years, including ASO drugs such as Nusinersen and Eteplirsen [18]. Moreover, the government established the National Organization for Rare Disease (NORD) as a platform for research and information into rare diseases. The US National Institute of Health (NIT) and Food and Drug Administration regulate the training and guidance to improve the quality and marketing of NIH-funded rare disease orphan drugs. Over the recent decade, the rare disease treatment market (RDTM) has been exponentially increasing. As of 2019, the RDTM has exceeded $144.3 billion and is expected to grow by at least 12% over the coming years, with the US spending the most on treatments. Despite no cure, these efforts have not gone to waste, especially with the rise of orally-administered treatments. With a market share

of $80 billion in the RDTM in 2019, orally-administered treatments are becoming the preferred medium of administration for rare disease treatments [18]. Their significance compared to invasively administered treatments is becoming more recognized. Such benefits include, but are not limited to, increased safety, higher patient compliance, ease of ingestion, and significantly lowered chances of pain. Scientists have already developed an effective orally-administered treatment for Fabry disease, a rare genetic disease, that has proven to exhibit both high efficiency and efficacy in treatment.

However, even with all these efforts, 70% of all rare disorders remain without treatment. Effective treatment is desperately needed, with most rare disorders classified as fatal and approximately 60% developed in childhood [18].

SMA Background

Spinal Muscular Atrophy (SMA) is a rare autosomal recessive genetic muscular disease. It is considered the leading cause of genetic infant mortality rates worldwide and the 7th most common rare disease in a survey of 100,000 people worldwide [19]. SMA is a highly severe disease with a moderately high prevalence, mostly in children. SMA has four types defined by motor milestones patients can achieve [20, 21]. Types I - III are the ones that will be discussed within this article, as they are the deadliest and affect the more significant population.
SMA Type I is the most common type of SMA and the most fatal. With a prevalence of 1 in 6,000 to 10,000 neonates, type I has the highest mortality rate and primarily affects infants at birth. Type I patients display overall muscular weakness and hypotonia, low limb movements, lack of tendon reflexes, fasciculations, swallowing and feeding difficulties, and impaired breathing around 6 months of age. They never gain the ability to sit upright by themselves, and for most of their life, they are situated with a respirator. Their expected lifespan is less than 2 years, though modern clinical care has improved this statistic. Some cases have shown SMA type I exceeding this age and reaching ages up to 5, but it is rare without treatment. Eventually, most infants with type I SMA die due to their rapid progression of muscular weakness, leading to respiratory failure [20].

SMA Type II still mainly develops within infants, with onset around 6-18 months after birth. While prevalence is not as high as type I, the expected lifespan remains short and has a high mortality rate. Patients will still experience respiratory difficulties and may require

ventilation, but they can sit upright without support from others. Most patients have a lifespan into young adulthood/adolescence [20].

SMA Type III is developed in children after 18 months of birth, but patients usually retain the ability to walk independently. However, most other milestones cannot be achieved adequately without support, including running, standing up, or climbing, since leg muscles are affected first. Multiple complications often accompany this disease, including scoliosis, joint problems, muscular weaknesses, and respiratory infections. However, most patients can expect an average lifespan [20].

SMA patients all lack a common attribute: the survival motor neuron gene (SMN1). This gene provides transcriptions to synthesize survival motor neuron proteins (SMN), which are responsible for maintaining motor neurons. Without proper expression of the SMN1 gene, the body, mainly in the spinal cord, lacks functioning SMN proteins leading to the degeneration of motor neurons and poor motor movement. Though all SMA patients have an identical copy of SMN1, known as SMN2, its transcript results in poorly synthesized SMN proteins, with only about 10% fully functioning. As a result, SMN2 cannot synthesize enough proteins needed for normal motor neural movement resulting in SMA. Researchers and studies have shown that splicing pre-mRNA transcripts to include exon 7 within the SMN2 genes increases the output of fully functioning SMN proteins by approximately 50-60%, serving as the basis for treatments for SMA [11, 20, 21 22].

SMA Diagnostic Methods

SMA is a rare disease, but despite its low prevalence, multiple methods exist to diagnose one with SMA, including the PCR-RFLP method, blood tests, genetic testing, nerve conduction testing, and muscle biopsies. PCR-RFLP stands for polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method— it works by digesting the PCR based on the digestion of PCR amplicons with appropriate restriction enzymes to produce distinct polymorphic fragments used as markers for species identification [23]. Along with this method, blood tests are accurate enough to act as a marker for SMA. Blood tests pick up samples of proteins and enzymes and check for creatine kinase. Deteriorating muscles release this chemical, acting as a marker for muscular disorders. However, this chemical merely indicates muscular disorders, whereas other methods are more accurate in diagnosing one definitively with SMA.

Lastly, genetic testing is a blood test specifically focused on nucleic acids. With its 95% overall efficiency, genetic testing can find mutations, deletions, or alterations with the SMN1 gene [20]. The nerve conduction test is an electromyogram that directly scans the nerves within muscles. The test measures neural activity, and, as such, lower neural activity within muscles indicates SMA. Muscular biopsies are periodic tests in which examiners remove a tiny piece of muscle and have a lab analyze the sample for any muscle loss or atrophy. In almost all cases, except for muscular biopsies, the cost is not a significant issue for these tests, and they are easily accessible [24]. In addition, genetic testing, with an average efficiency of 95%, confirms SMA diagnosis and, in some states, is part of the routine screening process for newborns.

Treatments

Besides Nusinersen, two other treatments have recently been released since Nusinersen's release in 2016. Besides the performance of the drug itself, the main problem is the costs. Ridisplasm, the first non-viral administered treatment of SMA, Zolgensma, a one-time dose invasively-administered Adeno-Associated Virus drug, and Nusinersen, a multiple-dose ASO invasively-administered drug. It is hard to differentiate the effectiveness of each drug due to limited studies of each one, which primarily stems from these drugs being set at an inaccessible price. In terms of material the treatments are made up of, ASOs seem to be the most promising. Nusinersen seems to have a tremendous impact mainly on SMA types I and II, as they are the deadliest forms of SMA, but they can still be used to treat all forms of SMA. The FDA approved Nusinersen in 2016, however, it remains to be determined how cost-effective the treatment is. Due to the low prevalence of SMA and the cost of manufacturing, Nusinersen is priced extremely high and must be priced lower in order to have a more significant impact on the population of individuals who suffer from SMA, it must be priced lower. Currently, 4 doses are required for the first year, costing a total of $750,000. Afterward, a maintenance dose is required every 4-8 months till the patient's death, which is $375,000 per dose [12, 20, 21]. Zolgensma was released in 2019, and though significantly cheaper than Nusinersen (in terms of the overall cost) and intravenously administered, its high cost still needs to be justified. The one-time dose will cost the patient $2.1 million, with results of improvement not completely guaranteed [25]. Lastly, Risdiplam, the first at-home, orally-administered treatment of SMA, is cheaper and has demonstrated strong potential since its 2021 US FDA approval. Despite being incredibly

expensive compared to most drugs, Risdiplam still maintains the lowest cost of all current SMA drugs on the market, at an annual price of approximately $100,000 and a maximum annual price of $340,000 (cost varies upon weight) [26]. However, progress is being made. Aetna, a private healthcare insurance company, has recently launched a new program with full coverage for these three genetic therapies, significantly lowering the burden of these high prices. Without effective healthcare, people affected by SMA may not be able to access any of these therapies, leaving them to rely solely on clinical care.

Despite the cost-effectiveness of these drugs being justified, from a company standpoint, their impact will be limited to specific populations without lower prices. Through speculation, nanotechnology cannot only increase the efficacy of these drugs but increase their cost-effectiveness. By offering non-invasive methods of administration (Nusinersen and Zolgensma), intrathecal and intracranial injections would no longer be necessary and would offer hope to patients who cannot afford high-cost treatments. In addition, nanotechnology provides reassurance for increased effectiveness of the drugs with fewer and milder side effects and greater access to biological systems (CNS) that are crucial for treating SMA.

Strengths

Organic nanocarriers are excellent drug delivery systems for ASOs, especially for treating SMA. NPs can protect ASOs from harsh biological environments and nuclear degradation while improving biocompatibility, cellular permeability, and uptake [10]. The purpose of ASOs is to splice pre-mRNA to transcribe higher levels of fully functional proteins. In turn, ideal NPs should provide safer transport to the cells and make up for the weaknesses that ASOs exhibit. The most vital aspect of NPs is their ability to better ASOs in terms of efficiency. Their attribution of targeted delivery and controlled release allows for greater distribution of ASOs with increased accuracy of the drug. Due to their small size, nanocarriers can also act as effective transports within cells, increasing their ability to reach the nucleus.

Another significant advantage is that NP-based drug delivery systems can reach the CNS, allowing for non-invasive methods of delivery for ASOs into the patient's body. The need for current treatments to employ invasive administration methods is to access the CNS, primarily blocked by the BBB. Nusinersen, which employs invasive administration through intrathecal bolus injections through a lumbar puncture needle, has reported severe side effects, primarily due

to the method of administration [12]. These adverse side effects include headaches, vomiting, pyrexia, respiratory infection, and upper respiratory tract infection, but they vary depending on the type of SMA the patient is diagnosed with [12]. Converting the method of administration to non-invasive would be incredibly beneficial towards the efficacy of the ASO itself and eliminate a significant burden upon patients.

As aforementioned, nanoparticles that show these strengths include exosomes, peptides, and polymers. All three have a common factor: their ability to penetrate through the BBB and access the CNS [7, 10, 11]. Exosomes have shown great potential due to their intercellular trafficking ability, cellular permeability, and effectiveness in crossing the BBB. In addition, they demonstrate high biocompatibility and biodegradability, with targeted delivery and controlled release, which could help to prove exosomes as the most effective organic NPs for drug-delivery systems, not just for ASOs.

Aside from exosomes, peptide NPs exhibit similar potential and, unlike exosomes, have shown efficacy as NP-based drug delivery systems for ASOs. Br-ApoE (K→A) is a form of peptide NPs, considered conjugated P-PMOs, which have been identified as a candidate for NP-based drug delivery systems for Nusinersen. Despite the in-vivo study being conducted on adult mice with SMA, they serve as an effective marker of the significant potential of nanoparticles to benefit, in terms of efficacy, Nusinersen [11]. Evaluation of Br-ApoE (K→A)-PMO resulted in a significant increase in the median survival of the SMA mouse pups from 78 days to two mice surviving to 282 and 290 days, respectively [11]. In addition, Br-ApoE (K→A)-PMO-treated mice exhibited numerous markers of increased health, including increased weight gain and higher muscle strength [11].

Polymer NPs are highly advantageous in chemical modification due to their varying natural compositions, different releases and degradation abilities, and easy manipulation of their outer surface. They have high blood circulation retention, controlled drug release, good loading capacity, and high BBB crossing. Despite all of these strengths, NP-based drug delivery systems, as a whole, exhibit considerable weaknesses.

Limitations

While the overall advantages of NP-based drug delivery systems outweigh the current and other systems, their weaknesses should still be assessed. The primary concerns are

cytotoxicity and provoked immune responses. It should also be noted that there needs to be more knowledge, mainly due to the lack of in-vivo studies on humans concerning their weaknesses [27]. The full scope of these weaknesses is yet to be understood entirely.

According to current research, organic NPs exhibit cytotoxicity, such as cationic NPs, as aforementioned. However, the effect on one's immune system is yet to be learned. Scientists understand that, especially when carrying foreign nucleic material, including mRNA, it is more than likely that without proper "stealth," an immune response is inevitable. Stealth relates to the ability to remain undetected by white blood cells (WBCs) within an organism through cellular membranes. This property can also be seen within studies conducted for nanoparticles, regardless of whether they are organic or inorganic. Particles that exhibit high retention (not due to low biodegradability) within the blood circulation also have higher properties of stealth [4]. Without stealth properties, nanoparticles will attract an inflammatory and aggravate immune response for the NPs to be eliminated from one's body through the kidneys.

The real issue arises from the side effects of such aggravated immune responses, especially in patients exhibiting SMA, and the burden, if any, on the patients. Despite the low prevalence of this property exhibited within organic NPs, the possibility continues to exist. Another weakness is poor endosomal escape. Though not exhibited within all nanoparticles, it is highly plausible that without proper endosomal escape, similar to that of ASOs, NPs cannot escape vesicles transporting them to reach the cytosol and reach the nucleus to release ASOs. LNPs and exosomes have been shown to combat this weakness heavily, improve endosomal escape within ASOs and increase intracellular trafficking.

In-Vivo/In-Vitro in Animal Models

Due to nanomedicine being a new technology, in-vivo studies have been sparse or inconclusive, and there has been a greater prevalence of in-vitro studies. While in-vivo studies consisting of nanoparticles have been conducted with more than promising results, they have mainly been tested on mice or other rodents. Such actions imply that these results may be inaccurate for humans as well. Such as any organism, humans' anatomical structure varies significantly from that of rodents. With such vast anatomical differences, it is to be expected that the results of in-vivo studies on rodents will vary for humans, meaning that nanoparticles that have shown effective BBB crossing in rodents, may not exhibit that same property in humans

[27]. The significance of this could be misleading of nanoparticle efficacy and efficiency in humans. To validate the beneficial nature of nanoparticles for treating diseases, elements, such as the one mentioned, must first be studied in detail [27].

That being said, LNPs have recently undergone mass production in vaccinations, becoming the first instance of an mRNA-LNP vaccine. Moderna and Pfizer's SARS-Cov19 (COVID-19) mRNA vaccinations are constructed with LNPs to protect the Covid-19 mRNA from nuclease degradation and increase the vaccine's overall effectiveness against the infectious disease [2, 3].

LNPs were chosen as a drug-delivery system for the mRNA due to their ability to protect the mRNA from nuclease degradation, assist with intracellular trafficking and endosomal escape, and aid in prolonged retention within the bloodstream. LNPs within the vaccines were constructed with a mixture of phospholipids, cholesterol, PEGylated lipids, and cationic or ionizable lipids [3]. These materials act to stabilize and provide structure to the nanoparticle. In addition, LNPs exhibit fusogenic compatible properties, allowing them to fuse with cellular lipid membranes. LNPs can fuse with target cells and effectively release their cargo into the cell cytosol [28].

While this may be the first in-vivo LNP study, liposomes have been used to deliver mRNA cargoes to mice in vivo since as early as the 1990s. Lipidic-delivering agents, such as Lipofectamine, Stemfect, and TransIT-mRNA, were released to assist in in-vitro cell transfection of nucleic materials [15].

The LNPs have proven incredibly effective as natural protectants for mRNA in vaccines; however, side effects have been presented. Though some were mild and others more severe, the exact cause of these side effects is yet to be determined. No studies have been conducted to determine the cause of these local and systemic side effects. Some insist that immunogenic material within the vaccine induces an inflammatory response within the respiratory system, resulting in side effects. However, others claim that introducing LNPs aggravates the immune response, provoking a robust inflammatory response and causing the observed side effects [2].

Cost-Effectiveness

Regarding negative implications, NP-based drug delivery may offer a speculative solution to a critical problem with Nusinersen: cost. Despite justified cost-effectiveness for

patients, high costs still heavily plague the overall impact of Nusinersen. At approximately $750,000 for the first year of dosage, following annual maintenance doses at $375,000, Biogen claims that this pricing is reasonable due to its classification as an "ultra-orphan drug" and the other due to the rarity of the disease and its sought-out effectiveness. Many orphan drugs have been priced around $500,000, but most insurance companies will not provide coverage due to their high prices (except for Aetna HealthCare), rendering the treatment inaccessible to specific populations [29]. However, there is some hope for lowering their cost.

NP-based drug delivery systems, when conjugated with ASOs, can lower the frequency of doses and the dosage amount while providing a form of non-invasive administration. Through speculation, this could prove evidence of the ability of NP-based drug delivery systems to lower the cost of Nusinersen, though how much is unknown. Effectively, lowering the frequency of doses could potentially result in overall annual deductions of the drug without altering the cost of a single dose. In addition, lowering the amount of dosage required would lower the cost of manufacturing Nusinersen for a single dose, hence decreasing the cost of the drug. Lastly, preliminary evidence could provide a link between non-invasive administration and lower costs. Despite being a different type of drug, Risdiplam employs oral administration through a liquid form and is priced at a significantly lower cost than all current SMA therapies at an annual cost of ~$100,000-400,000 [26]. Extrapolating this trend further, if Nusinersen were to employ oral or non-invasive administration methods, it could result in a significantly lower cost, essentially eliminating the currently operated methods of administration which are both expensive and risky. As such, the probability that NPs will be conjugated within drugs for mass production can be reasonably assumed to be within the near future, in which, afterward, cost-effectiveness can be measured.

Conclusion

Nanotechnology is an up-and-coming technology with seemingly limitless applications in medicine. The most prominent of its applications lie within nanoparticle-based drug delivery systems for traditional pharmaceuticals, especially for neurological and rare diseases. Spinal Muscular Atrophy, and diseases similar to it, can all benefit from its usage within existing treatments. NP-based drug delivery systems have the potential to provide, in simple terms, protection, increased efficiency and efficacy, access to the CNS, increased dispersion of the drug,

and specific targeting. NP-based drug delivery systems have many applications but potentially serve most effectively as mediums for genetic therapies, such as ASOs. A commercial joint venture between ASOs and NPs could potentially prove incredibly beneficial in treating SMA, not just in terms of efficiency but lowering costs and making it safer for the consumers. Nanoparticles, however, face obstacles in achieving mass industrialization of joint ventures with pharmaceuticals: the limited knowledge about them and their potential effects on humans. Regardless, some nanoparticles have already been released to the public for use as drug-delivery systems, as seen in the recent SARS-CoV-2 vaccine released by Moderna and Pfizer. Nanoparticles can apply for their benefits in various methods that could revolutionize current medical treatments and technology. In addition, they potentially serve to effectively provide or innovate upon current treatment for illnesses such as cancer, ALS, Alzheimer's, cardiac diseases, and much more. Nanotechnology can offer plenty of medicine, but until medical researchers fully understand its full extent, it may be some time till they are commercially introduced to the medical market.

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Easing the Transition from Single-use Products to Sustainable Products to Reduce the Impact of Microplastics on Public Health By Ines Hwang

Abstract

Plastic pollution, due to the usage of single-use products, is a growing concern for public health. Microplastics cause inflammatory, reproductive system, or liver damage as well as diminishing appetite. There are unique sustainable alternatives to those single-use products that are not broadly known to the public. The majority of people do consider that sustainability is important, however, the alternative options are less well-known and single-use products are more convenient for consumers. There were attempts to be more sustainable such as banning plastic bags, so we may go further in using sustainable food containers, straws, bins, and so on. Thus, this review paper compiles the most effective ways to persuade people to use sustainable alternatives.

Introduction

Plastics have become one of the major concerns in our society and have been for awhile. Plastic originally means “pliable and easy to shape” (sciencehistory.org). They are strong, flexible, light, and convenient and thus popular with consumers. The first plastic was invented by John Wesley Hyatt in 1869. It was able to be shaped to imitate natural resources and so it was a revolutionary invention to replace many natural resources and fulfill human needs. In 1907, Leo Baekeland invented Bakelite, the first fully synthetic plastic. Since then, World War II has greatly expanded plastics to a point where now plastics are used everywhere by everyone (sciencehistory.org).

Today, there are 7 types of plastics categorized by their chemical components which determine their different uses as Figure 1 exhibits. The information on types of plastic is indicated on all plastic products produced. Though all of these kinds can be harmful when exposed to extreme heat, the safer options are (1), (2), and (5). Also, the only recyclable plastics are (1), and (2). (plasticoceans.org) Among our 17 Sustainable Development Goals shown in Figure 2, plastics are a big problem for goals #6, 7, 11, 12, 13, 14, and 15 which exhibit how many problems plastics are involved with and the significant negative impacts of it. Moreover, it is a growing environmental concern now as it takes them hundreds of years to biodegrade (savemonkeycarbon.com).

As plastics grew into a bigger business for many powerful companies, the Government has restricted a lot of them. For example, stores are banned from giving out plastic bags to customers in states like New Jersey. However, there are also a lot of economic or political players involved, so companies often lobby the government to be able to sell and promote their products.

Thus, this paper is going to explain the toxic impact of plastics on the environment and human health as well as introduce alternatives and ways to change human habits or behaviors in order to lessen the amount of plastic consumed.

Plastic Is A Problem For Our Environment

To achieve the Sustainable Development Goals (SDGs) by 2030, the usage of single-use plastics should decline to transform us from a plastic society to a sustainable society. The usage of plastics vastly increased since the 1950s. Humans have produced 8.4 billion tons of plastics in the past six decades and most of them are in landfills or our environment. Global production has risen exponentially and the massive amount of plastics has become a severe problem for our environment (A. Nagi, R. Kuti).

Single-use plastics are used in our lives every day, and most of these types of plastics (#3-7) are non-recyclable and non-biodegradable. It is known that only 9% of the plastic we use is recyclable (greenpeace.org). Plastic products such as utensils, bottles, bags, cups, and so on are seen every day and are wasted every day even in unnecessary circumstances. Though often people do not recognize that the negative impacts of disposed plastics on the environment are also linked to human health.

It concretely affects our environment as the plastics end up in the landfills or ocean and negatively impact terrestrial and marine animals. In 2004, large amounts of microplastics were first found in the world's oceans (wasserdreinull.de). This initially presented the danger of non-biodegradable products, since plastics will not go away on their own. Just because we cannot see them near us doesn’t mean that the plastics aren’t impacting our health and environment. Moreover, it’s not only the big chunks of plastics that harm our environment through compiling the nonrecyclable trash and physically tangling the marine animals, but small plastic particles are consumed by both animals and humans.

In 2020, The Proceedings of the Royal Society published a study investigating the effect of microplastics on soil fauna. This study exhibits the negative impacts of microplastics on terrestrial animals. Microplastics reduced the number of species living below the surface, like mites, larvae, and other small organisms that enrich or preserve the fertility of the soil. It is extremely toxic as chlorinated plastics release dangerous chemicals into the land that are absorbed by groundwater and more water sources, which may later impact the whole ecosystem (unep.org). Although plastic pollution starts in our environment, it eventually endangers human health as well.

Microplastics on Human Health

Animal consumption of toxic plastic particles places plastic in our food chain. What animals consume or water sources absorb are microplastics. The definition of microplastics is as follows: “Microplastics describes the entirety of all synthetic plastics and their products, which are smaller than 5 mm in size and which are either released directly into the environment or formed indirectly in the environment” (NOAA). Therefore, microplastics are created by degradation after used plastics are disposed of in the environment. Microplastics are a threat to the environment and animals as they are constantly consumed. Toxic micropollutants like residues of plasticizers, heavy metals, PFOS, or pharmaceuticals may be attached to the microplastics as well (Dr. Doyle Pruitt). The consumption leads to microplastics persisting in the food chain which eventually comes back to us, humans.

Dick Vethaak, an ecotoxicologist at Vrije Universiteit Amsterdam in the Netherlands, did a study on plastic detection in human blood. His experiment found Polyethylene terephthalate (PET) in 50% of the donors and Polystyrene (PS) in about 36% of the donors. PET is commonly found in disposable water bottles and PS is commonly found in food packaging (Osborne). When plastic is exposed to extreme heat, such as the sun, it ultimately becomes dangerous as the plastic particles move into the products inside (National Geographic). This is concerning since plastic particles could travel through our bloodstream and be transported throughout the whole body.

Researchers hypothesized that human exposure to microplastics may lead to several health problems including oxidative stress, DNA damage, inflammation, and so on. When inflammation becomes persistent, it can lead to consequential health problems. But the potentially harmful factors aren’t simply plastics. Microplastics were also found to carry human

pathogens on their surface. Human pathogens cohere exceptionally strongly to plastic waste rather than to natural surfaces. In 2016, a study published found that Vibrio cholera, a human pathogen that causes cholera in humans, is attached to microplastics taken from the North and Baltic Seas (plastichealthcoalition.org). In addition, plastics are non-biodegradable, so they can travel long distances in the aquatic environment. Therefore, it has been speculated that plastics may be contributing to the spread of diseases, especially near environments with high plastic pollution and low sanitation.

In 2019, scientists estimated that an average American citizen consumes between 74,000 and 121,000 plastic particles (Human consumption of microplastics - ACS publications) though it is surely an underestimation due to only 15% of consumed food being assessed. This study also revealed that bottled waters are the highest source of microplastic consumption for humans as water bottles contain approximately 100 microplastics per liter. Additionally, other research conducted reveals that plastic tea bags and baby bottles may release over millions of microplastics (Plastic teabags release billions of microparticles - ACS publications; nature.com). All these data warn about the intake of plastics in our bodies and the toxic chemicals that may remain in our bodies for an unknown amount of time. More questions are yet to be answered, such as whether these plastic particles will ever leave the human body, but it is already clear that we need to take action now.

People Habitually Purchasing Plastics

The wide availability of plastics makes it easy for people to purchase and use plastics. Its massive production has made it very available to humans as it is definitely convenient to use these products once and then throw them away.

According to The Organization for Economic Co-operation and Development's (OECD) first Global Plastics Outlook, the growing population and income is increasing the amount of plastic used and thrown away, and the policies to prevent leaks into the environment are inadequate. Plastic consumption has quadrupled in the past 30 years, driven by developments in emerging markets. From 2000 to 2019, Global plastics production doubled to 460 million tonnes. "Plastics account for 3.4% of global greenhouse gas emissions" (OECD). While the number of recycled products only grows by thousands, the number of disposed plastics increases by tens of

thousands as exhibited in Figure 3. These data illustrate the severe scale of the problems that plastics are causing.

Plastics are found everywhere. Vinyl is a plastic material, meaning all those bags used in stores, trash bins, and packaging are all plastic. Also, wrappers, disposable food containers, furniture, and so on all involve plastics. Its availability is seemingly infinite. Moreover, people unconsciously use excessive amounts of them. For example, in 2018, the containers and packaging category of plastics had the most plastic tonnage with over 14.5 million tons (United States Environmental Protection Agency). Every day, and especially with the pandemic, there are 59 million parcels delivered per day according to the Parcel Delivery Index 2021, many of which contain plastic packaging for food, drinks, and boxes. For instance, Washington Post Reports that according to the environmental group 'Oceana', due to the pandemic in 2020, Amazon.com, Inc. generated 599 million pounds of plastic packaging waste, a 29% increase compared to the previous year. Societal issues impact plastic production as well. Amazon is one of the world's largest e-commerce websites, but the real problem is that this is only one example of many. It is simply one part unveiled. Attempting to replace all plastics can be viewed as impossible for our society at the moment. Thus, it needs to be a societal change, not altering the components of a few products.

Surprisingly, even clear office tapes are made of plastic elements. The countless amounts of plastics wasted are inevitable when these everyday materials are made of plastics, and sometimes people use them unknowingly. Therefore, 'knowing' is extremely important. Changing the eyes upon daily plastic usage and growing awareness of the amount of plastic we use may be the step that should be taken to really reduce the number of plastics to make a change for our environment.

The convenience of using disposable plastic products makes it difficult for people to switch to more sustainable products. We are vulnerable to convenience and friendliness. The habits are what stop us from taking action. "The consumer oftentimes has little choice to refuse plastic, " said Trent Hodges, Plastic Pollution Manager for the Surfrider Foundation. "And because it's so ubiquitous and such a common item, it becomes a force of habit" (projectplanetid.com). Its commodity and use become a habit for people and this unstoppable use of plastics is a social problem that leads to environmental and public health problems. In this case, when attempting to stop the usage of plastics, it is important to introduce the people to

alternative options rather than continuously reminding them of the problems that the majority of the people already are informed of. Therefore, introductions to new products are necessary and may serve as a solution to the growing toxicity of plastics.

Alternatives to Plastics.

There are various alternatives to plastics that are not widely known to the public. As plastics are so widely available, the introduction of alternatives is necessary. As mentioned, packaging is one of the most common reasons for plastic production. There are food wraps made of Beeswax that are reusable and do a better job compared to normal plastic wraps or bags. First of all, it is easy to use. When it is reusable, people often think that it is inconvenient to wash them and use them again. However, these beeswax wraps only require a quick rinse with water, or if needed a mild amount of dish soap can be applied. Second, it is better for your food. When using these wraps, you apply the warmth of your hands and mold them over the food or the edge of a bowl. The seal that these wraps make helps the food stay fresh for a longer amount of time. Lastly, and most importantly, beeswax wraps are 100% biodegradable as they are only made of non-toxic ingredients. Ingredients are as follows: cotton fabric, beeswax, tree resin, and jojoba oil (true.earth).

Beeswax packagings cost $20 for 3 different sizes of them in one pack. It definitely is more expensive, about 3 to 4 times, than regular Ziploc food wraps. However, when looking at the long term usage it is cheaper as it is reused while the disposable products get thrown away after using them once. The plastic product is also vulnerable to tears and therefore has less ability to keep the food fresh. Also, beeswax alternatives may be even more convenient than disposable food wraps because it does not pile up in the trash can.

Surprisingly, seaweed is a good material for packaging. As seaweed is a constantly growing plant, we have an abundant amount of it that can be used. It is said that 0.03% of brown seaweeds can replace all the PET bottles used annually. Most importantly, seaweed packaging is biodegradable. It may only take around 4 weeks to biodegrade in soil, and certain products are edible, which makes it an extremely beneficial alternative to disposable plastics. Seaweed-based products can replace plastic bags, cups, wraps, and more. For example, seaweed-based edible energy drink “bubbles” were introduced at a London Marathon to be tested in 2019. It was successful and the same company has also been testing seaweed sauce sachets as well.

There are companies like Evoware, Loliware, and Skipping Rocks Lab. They have been developing seaweed-based products for a while as shown in Figure 4 and Loliware is currently working on alternatives to plastic straws while Skipping Rocks Lab is working on wholly removing plastic water bottles.

The next product is made up of milk. Before the 1960s, people used to use milk instead of acrylic paints. It sounds strange, however, when milk is heated and combined with acids, like vinegar, casein is produced. Casein is a protein that is fast-drying and a water-soluble medium to carry pigments. Acrylic paints contain plastics, but Casein does not. As it is composed of milk, it is edible, biodegradable, and a good alternative to plastics. Discovered in 1897 by Galalith, Casein is a great option for an eco-friendly material for packaging. Now Lacptips, a French Company, is trying to use casein as a water-soluble plastic alternative by applying to our needs in the 21st century, such as high delivery packaging demands (rts.com).

Mushrooms, or mycelium, are considered a possible alternative to plastics. Mushrooms are an organic material grown without chemicals and can be grown to specific dimensions for any given use. Specialties of mushroom products are that they are thermally insulated and water-resistant while also being biodegradable. It may be seen as a fitting alternative for Polystyrene (#6) packaging that is commonly used for delicate items such as electronics, glass, or more. Brands like Bowers & Wilkins, Hudson Hemp, and Openly Human are currently growing custom-molded mycelium products.

Lastly, bamboo is also a great recyclable material for making utensils, toothbrushes, cutting boards, and more. Bamboo is not only biodegradable but also has antibacterial and antifungal properties. Moreover, they are abundant and easy to use as they grow without fertilizers or pesticides. They can regrow to adult size in 3 to 5 years so they almost never need to be replanted, can be grown in various environments, produce 35% more oxygen compared to other similar plants, can rebuild eroded soil, require little water and care, and most importantly produce an exceptionally durable material (householdwonders.com). Thus, products made of bamboo are durable, healthy, and water resistant too. Isshah bamboo toothbrushes are known to be manufactured under the guidance of dentists and are more mold resistant than plastic toothbrushes. This means that using these alternative products is often not only good for the environment but for us as well. The prices of sustainable alternatives are usually similar or

cheaper when considering their long-term usage, and they are much healthier without toxic chemical components.

Human Habits

Consumption of anything but especially plastics comes from a psychological factor. It is human habits that make people choose the more convenient option. Figure 5 shows the habit cycle. People regularly take actions and this is stimulated by internal or external triggers depending on your location, time, emotional state, surroundings, or last action. In our case, it would be pulling out a plastic bottle or bag as the more convenient choice. Nonetheless, the impacts of our choices are not always valuable or positive but can be negative. Although plastic products are convenient, they come with harsh environmental impacts and monetary loss. Despite knowing the toxic impacts of plastics, these habits are hard to change. In order to persuade the public to change to plastic alternatives, it will be beneficial to offer equal convenience without the negative impacts. All products and companies target consumers to be addicted to their products, and thus without individual willpower, nothing can change. Thus, change can only happen with individual willpower or by having small rewards or punishments. In other words, the internal or external trigger needs to change. This can happen in many other ways depending on different individual situations but here are some suggestions from this paper, as it introduced alternatives to plastics. Switching from plastic-based products to more sustainable alternatives is a win-win situation both for our environment surrounding our society, as well as individuals consuming the products for their own health and benefits. As Herbert Lui says “you should pre-decide the best choices in your life, and make those decisions more convenient” rather than habitually choosing convenience when they are often negative to your life. Thus, making decisions before the event occurs is important. As Archilochus, a Greek lyric poet, wrote “We don’t rise to the level of our expectations, we fall to the level of our training” (medium.com).

Another way is setting rewards and punishments. Think about the punishments that would occur, like deteriorating health and the environment, not only for yourself but for the community, society, and the world. As mentioned, there are societal, environmental, medical, and economic rewards to using alternative products. So the individual willpower needs to strengthen and start the change, away from the previous habits to newly set habits (psychcentral.com).

Conclusion

The convenience of plastics or disposable products is understood but needs transformation. So, alternatives are listed for a wide range of products, including packaging, utensils, or even toothbrushes. Using these alternatives will be vital. If plastic consumption increases without bounds, it will come back to harm us in the future. As mentioned earlier, it does not only hurt the environment and marine or terrestrial animals but us humans. Unless we want plastics to consume our Earth, we need to make changes in our daily choices. Soon, it will be irreversible and uncontrollable by humans. The scale of it doesn't matter, if you replace your whole house plastic-free or simply start using reusable bags and water bottles, big and little steps are urgently needed right now.

A sudden decrease in plastic usage is not expected. However, if any individual changes their choices to use alternative products rather than plastic products, the goal of this paper is fulfilled. In society, one influences the other and this cycle will loop. There are already people who have been taking action but this paper will hopefully create a new common habitual loop in general to use non-disposable products.

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What is the Association Between Schizophrenia and Addiction at a Neuronal and Socio-Cognitive Level? By Deren Bulut

Introduction

Through many years and cases, researchers observed that substance abuse disorder, commonly referred to as substance addiction, goes hand in hand with schizophrenia. According to the Epidemiological Catchment Area study, 47% of patients diagnosed with schizophrenia have critical problems with drug or alcohol abuse throughout their lifetime compared to 16% of the overall population. Specific substances such as tobacco, alcohol, cannabis and cocaine use disorders occur three times more frequently in schizophrenia patients than in the general population (Mueser et al. 1990). The association between these two disorders does not have one single explanation, yet it can be studied by looking at the different places where they interfere. This paper will discuss "Why there is a correlation between drug abuse and schizophrenia in patients" and further dive into the three main aspects of human psychology: how they overlap in neuronal, cognitive and social levels in the patients by reviewing current literature. We will look at the research studies done to enlighten the neuronal systems responsible for both substance addiction and schizophrenia and discuss if there is any point where they interfere or overlap. In the cognitive part, the paper will discuss similarities and differences in the symptoms and reveal any relevant association. While it is crucial to look at the individual level, such as neuronal and cognitive, social aspects of these two disorders and how they might be triggering each other simultaneously, such as the attitudes they get from society, the treatment costs, and the social consequences. The social part will be the last aspect of human psychology discussed in this essay. Finishing with the discussions of the treatments used for each and potential future avenues to pursue treatment-wise, this paper aims for the readers to understand the significance of how substance addiction is a potential threat and possibility for many diagnosed patients, starting with schizophrenia.

Before starting with the neuronal aspect, a brief introduction to these two disorders are necessary because they are heavily misrepresented by today's leading source of communication, the media. According to the American Psychological Association (APA), schizophrenia is a psychiatric condition characterised by incoherent or illogical thoughts, disorganised behaviour and speech, and delusions or hallucinations, such as hearing voices. The onset age of this

disorder can vary between late teens to early thirties, affecting almost 0.32% of the population, equivalent to 1 in 300 people (WHO 2022). Substance use disorders, on the other hand, vary significantly in symptoms or what type of substance they use. However, it is well known that when a substance's use becomes compulsive despite its negative consequences, such as health risks, social issues, etc., a person can be identified as "addicted" to a substance.

Neural Aspect

By starting with the neuronal aspect, it is vital to look into the brain and come up with neuropsychological outcomes because these two disorders are proven to manipulate the chemical levels or systems—first, schizophrenia in the brain. We will discuss three hypotheses hypothesised to be responsible for schizophrenic symptoms and are used today for treatment purposes. These hypotheses can not be used to explain the disorder alone but are essential for the future of drug treatments.

A. Dopamine Hypothesis

The dopamine hypothesis is the oldest hypothesis that was put forward. *Dopamine* is a neurotransmitter involved in memory, movement, motivation, mood, attention and more (APA). This hypothesis originates from the research that suggested that in schizophrenic patients, the dopamine levels were higher than usual in the region called the striatum, which is responsible for the positive symptoms (delusions, hallucinations, etc.) and the dopamine levels in the prefrontal cortex, which is responsible for the executive functions such as organising, judging, and planning, were relatively low (Matthyse 1973). One evidence supporting this hypothesis is that the antipsychotics used for treatment showed a clear correlation between their binding affinity to the postsynaptic dopamine receptors (Seeman et al., 1976). To justify why this might be the causing the symptoms, an elevation in the presynaptic dopamine release in the absence of appropriate stimuli causes the patient to associate the irrelevant stimuli to the temporal increase in the dopamine levels, which comes off as perplexing to the individual. Dopamine levels randomly increasing in such cases can lead to the symptoms of paranoia and delusions since the conscious brain tries to explain the experience of the instant dopamine release caused by the dysfunctioning of the dopamine system with irrelevant stimuli (Kapur 2003).

B. Glutamate Hypothesis

Glutamate is an excitatory neurotransmitter. The genes implicated in schizophrenia in GWAS (genome-wide association studies) involve glutamate synapses and signalling (Jia et al. 2010). Further evidence for the involvement of the glutamate system in schizophrenia comes from blocking the glutamate receptors with drugs such as ketamine, which mimics psychosis. The glutamate hypothesis suggests that hypofunction of the glutamate system is involved in schizophrenia. Connecting with the dopamine hypothesis, blocking these receptors also increases dopamine. In contrast to the dopamine hypothesis carrying a more significant proportion in treatment processes, it is found that there are more genes implicated by GWAS studies that are associated with glutamate but not as much with dopamine in schizophrenia patients. One explanation suggested was that the changes to the glutamate system occur upstream of the dopamine system meaning glutamate over-functioning may result in dopamine hyperfunction.

C. Neurodevelopmental Hypothesis

Genetic predisposition of schizophrenia is often observed to combine with environmental factors such as stress, critical brain events and psychoactive drugs. This hypothesis very initially originated from the idea of "brain plasticity" and how the onset of schizophrenia may be heavily affected by the events and stimuli throughout our neurodevelopmental stages because the usual age of onset of schizophrenia is around the early twenties, as mentioned. There are also neuropathological findings such as lack of gliosis or neurodegeneration, altered cell positioning, packing density and size in patients (Pino et al. 2014).

By moving on to substance addiction, two main findings support what happens inside the brain. The first one is that the substances used act directly on the brain's reward system, which is the dopamine system associated with schizophrenia and substance addiction overlap. The brain also weakens the activity in the prefrontal cortex resulting in impaired judgement and decision-making skills while under the influence of drugs (Perry 2015).

The dopamine system is the reward centre of humankind. Humans tend to seek things, stimuli that bring us pleasure which is, in other words, "dopamine firing", and this level of "seeking" may turn into "needing" in schizophrenic patients due to their fluctuations of elevations and depression of these neurotransmitter levels. Patients with schizophrenia may be "self-medicating" themselves with the substances when they are "deprived" of dopamine since the substances act directly on the dopamine system (Green et al. 1999). While this might be the case, since it is a two-way road, "the diathesis-stress model" suggests that a neurobiological

vulnerability, a genetic disposition such as having the genes that affect the glutamate receptors as mentioned, interacting with an environmental stressor which in this case is the substance use can lead to schizophrenia, trigger the what is already there but may not be our in that time interval, or ever (Fowles 1992).

Socio-Cognitive Aspect

As is the case for many other mental illnesses, schizophrenia is in heavy contact with the social life and environment of the patient, which also again reflects their substance abuse amounts. First of all, the common trend of diagnosed or undiagnosed patients having a higher susceptibility to developing an addiction to certain substances has to do with the way these substances, especially the ones we call “street substances”, are represented and portrayed as an escape mechanism to people who have little to no access to therapy of any kind from various reasons varying from social pressure to poverty. “The cumulative risk factor hypothesis” suggests that schizophrenic patients have an increased risk of developing a substance-related addiction because of the constant exposure to a combination of stressors such as poor cognitive, social, and educational conditions, which heavily occurs in the presence of poverty, victimisation and distorted social environments (Mueser et al. 1990). These stressors originate from the lack of awareness about this illness, worsening existing cases. The stereotypes associated with schizophrenia, such as that they are naturally violent and chaotic, which are already triggering as environmental factors, can lead to patients also internalising them themselves. As the social factors worsen the cases, the use of substances as an escape mechanism increases which worsens again, forming an actual paradox that can lead to suicide in some cases. It has been found that individuals with both the diagnosis of substance use disorder and schizophrenia have been reported as having higher positive and negative symptoms, being more likely to be not adapted to the medication treatment and depression, and also having higher suicide rates than those with patients with just a single diagnosis of schizophrenia (Chang 2021).

At this point, the major social stressors that cause the issues should be specified and elaborated more. Discussions on these stressors will also help with psychotherapy. By initiating the expectations of daily life being a struggle for schizophrenia patients, schizophrenia is associated with severe psychotic symptoms that harden daily functions. However, the only symptom DSM-5 requires of all cases is a deterioration (“progressive impairment or loss of basic

functions, such as emotional, judgmental, intellectual, muscular, and memory functions", according to APA) of social functioning. (Black 2016). Whether it is maintaining relationships and family dynamics, getting and keeping a job, or even going on with the flow of daily life in a society. Less than one-third of the diagnosed patients work daily. A small percentage of patients with schizophrenia marry, and when they do, it often ends in divorce (Behere 2011). These are statistics demonstrating the inability to function socially. The desire to seem like other people is the main factor that drives these people to some substance abuse. When schizophrenia is accompanied by the effects of certain substances that almost mimic the psychosis symptoms, the already impaired cognitive functions get even more damaged, which only causes a worsening of all these social dysfunctions.

Last but not least, the cost to society of the illness. Schizophrenia was ranked among the top 25 leading causes of disability worldwide in 2013. The World Health Organisation (WHO) estimated that the direct costs of schizophrenia in Western countries range from 1.6% to 2.6% of total healthcare expenditures, accounting for between 7% and 12% of the gross national product (GNP). Especially for the US, the economic load of schizophrenia is found to be more than $60 billion per year. Compared to its abundance, this enormous burden of the illness can be explained by the illness not having a "curable" nature and having an early onset age with continuing symptoms for a long time (Chong 2016). In addition, the annual economic burden of substance misuse is estimated to be $249 billion for alcohol misuse and $193 billion for illicit drug use. The numbers increase exponentially over the years when the combined outcomes of schizophrenia and substance abuse disorder occur (HHS).

Treatments

The exploration of the current treatment methods, discussing recommendations, and seeking future avenues to pursue are necessary to treat these disorders and prevent them, to some extent, from co-occurring in patients. Like the neuronal aspect part, each of the most common treatment methods for schizophrenia and substance abuse disorder will be discussed with their potential areas of development.

Schizophrenia requires consistent, in most cases, lifelong treatments even if the symptoms stop occurring. It is crucial to remember that there is always a chance of a relapse in the case of this illness, as there is for most mental disorders. Psychosocial treatment combined

with medications is observed to help manage the condition to a great extent; however, it is vital to keep in mind that in some severe cases, hospitalisation may be necessary (Mayo Clinic).

A. Medications:

The most common medication therapy used in schizophrenia is antipsychotics which act directly on the dopamine system, as mentioned before. The main aim of many medication treatments is to control the symptoms at the minimum possible dosage of the drug. There are many antipsychotics, like first/second-generation antipsychotics and long-acting injectable antipsychotics (Mayo Clinic). Some examples of these antipsychotics are risperidone (Risperdal), quetiapine (Seroquel), olanzapine (Zyprexa), ziprasidone (Zeldox), paliperidone (Invega), aripiprazole (Abilify) and clozapine (Clozaril) (CAMH). Other medications can be prescribed, too, such as antidepressants and anti-anxiety drugs. It is crucial to remember that medications such as these take a couple of weeks to show an effect.

B. Psychosocial Therapies

Antipsychotic medicine for schizophrenia has improved over the last couple of decades, reducing the burden of side effects. However, it is observed that medication alone is insufficient for recovery and adaptive adjustment. Thus, psychosocial therapy is necessary to achieve the maximum cognitive and physical repair level. The most used psychosocial therapies are social skills training, cognitive behavioural therapy (CBT), cognitive remediation, and social cognition training (Kern 2009). They all target different things. Thus, it is best to examine them each.

-*Social Skills Therapy:*

The main goal trying to be accomplished in social skills training targets the social and independent living skills of the patients. As mentioned, patients with schizophrenia show some social dysfunction in most cases, so it is crucial to get help for social living. The first applications of social skills therapy go back to a method called “token economy”, which American Psychological Association has defined as “in behaviour therapy, a program, sometimes conducted in an institutional setting (e.g., a hospital or classroom), in which desired behaviour is reinforced by offering tokens that can be exchanged for special foods, television time, passes, or other rewards”. The methods relied on direct tangible reinforcement or punishments but as more cases were observed it was found that others can also influence the patients and each other, what we call “observational learning”. These therapies can now be conducted individually or as a group, enabling an occasion for influence and observation. These therapies now primarily target

unique social skills such as finding a romantic partner, keeping a job, and other social skills that are extremely important for daily social functioning.

-Cognitive Behavioural Therapy (CBT):

Improved therapies are required to lessen the discomfort and functional impairment brought on by psychotic episodes in schizophrenia. CBT originated with targeting the positive symptoms (hallucinations, delusions, etc.), but in modern times, the focus shift has turned to the negative symptoms. Negative symptoms such as loss of interest and motivation in life and activities can be seen as "normal" accompanied by the positive symptoms but are equally crucial to target because the patient may become asocial, not be overloaded with shame or guilt, may lose, if they had any, any expectation for success and any achievement. In general, they are very highly susceptible to letting go of everything. CBT focuses on the self-beliefs that can lead to extreme levels of self-hatred, like "I am not good at anything" and "I am not capable of a future". Like the social skills training, these can be helped individually or as a group and have different stages: engagement and assessment, coping enhancement, helping them form a developed understanding of the psychosis they are experiencing, and working on delusions, hallucinations, and other symptoms.

-Cognitive Remediation:

Originating from neuroplasticity, cognitive remediation aims to enhance cognitive functioning by stimulating damaged areas of cognition like memory and attention; the official CRT treatment program takes 48 weeks to complete. Meetings can last anywhere from two to four hours and usually happen once a week on a different day. In other instances, clients are assigned weekly homework tasks that must be finished on time.

-Social Cognition Training

The term "social cognition" refers to a broad concept that describes the mental processes that underlie social interactions, including perception, interpretation, and response generation to the intents, dispositions, and emotions of others. This kind of psychosocial therapy also has an important place in the treatment process of schizophrenia.

C. Hospitalisation

Hospitalisation may be required to guarantee safety, necessary nutrition, and rest. Moreover, basic hygiene needs during crises or times of severe symptoms.

D. Electroconvulsive therapy

Electroconvulsive treatment (ECT) is a process in which tiny electric currents purposely cause a brief seizure in the brain under anaesthesia. ECT appears to alter brain chemistry to alleviate the signs and symptoms of several mental health problems. Electroconvulsive therapy (ECT) may be an option for patients who do not respond to medication therapy.
In the cases of substance abuse disorder, some of the main treatment methods include behavioural counselling, medication, medical applications used to treat withdrawal symptoms or deliver skills training, and treatment for mental health issues such as depression and anxiety, which in many cases, long-term process following to prevent relapse (NIDA 2019).
By knowing these, the discussion can lead to the common areas in the treatments for both overlaps, which can be counted as the main things to be considered when looking at the psychological and pharmacological treatments. In psychiatric disorders, only some treatments can be suitable for every patient. The treatment process should be designed individually to respond to the patient's needs. Medications should be guided and accompanied by behavioural therapy for maximum effect. Lastly, treatment should be available. One of the biggest obstacles in this process is the availability of treatment for all social groups, and there is still a long way to go till it gets there.

Future avenues to pursue in cases of treatment differ. For example, for medication treatments, the main goal is for the drugs to directly target the complex system in the brain rather than a more wide targeting to reduce the side effects to the minimum. For behavioural therapies, the process can be more consistent and followed through. Overall, as mentioned above, the main thing that can be focused on for development would be the accessibility and availability of therapies.

Conclusion

To summarise the findings, schizophrenia and substance abuse disorder coincide in many cases due to neuronal and socio-cognitive reasons and motives. The association between them can be observed through many specific experiences, whether cognitive, neuronal or social, like the similarities of their symptoms, their effects on the dopamine system, and the social effects and consequences. Both schizophrenia and substance abuse disorder are found to be among the most effective disorders in the light of social dysfunction; thus, therapy is a necessary process to have a deeper look. Whether behavioural or pharmacological, progress can be observed in many

cases, separately or in combination. This makes the further development of the treatment methods even more necessary. Both of these disorders are heavily stigmatised in today's world, making the patients' experiences even harder than they should be. A responsibility for non-diagnosed people is to help to break these stigmas and stereotypes and research both schizophrenia and substance abuse disorder from credible sources to have a greater understanding of the challenging experiences they go through daily.

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The Toxicology of African Medicinal Plants: Evaluating and Understanding the Benefits of using African Medicinal Plants for Treating the Body When Exposed to Toxins By

Ameerah Abayomi, Neha Gurram, Angelica Hernandez, Katie Hung, Adrija Jana, Subha Mahmud, Alana Powell

Abstract

This paper summarizes different versions of research done in various journals that were released about the effectiveness of herbs found across Africa, primarily focusing on the Northern and Western parts of the continent. The usage and benefits of these herbs as medicine has been traced back to the 3200 BC era and were utilised by ancient healers. Now, attributable to the power of modern chemistry and new research done in the field of toxicology, the presence of different compounds in these plants has been analyzed and if used well, they can help to discover new cures for exposure to toxins in the body. Therefore, this study is designed to highlight the hidden and proven benefits of African medicinal plants while supplying extensive summaries of the findings about its foundation, some chemical breakdowns, the diseases it has been scientifically shown to help as well as different limitations to the link between toxicology and African medicinal plants. Lastly, the study concludes with suggestions made about potential research that could be done to boost the benefits of the linkage between the two.

Introduction

Toxicology, coined in the 17th century, is the medicinal discipline which governs the adverse effects of chemical substances on living organisms. For ages, in the continent of Africa, the usage of medicinal plants has been an important factor in the health care sector. Many plants have been proven to be useful however, the remedies of traditional medicine in Africa are currently not regulated, under-researched and contain many controversies. Therefore, the field of toxicology is divided on whether African medicinal plants are efficient in treating the body when exposed to toxins. This body of research reviews and evaluates available data about and related to the usage and benefits of African medicinal plants in the treatment of toxins in the body, while delving into the past and future relationship African medicinal plants hold with toxicology.

History of the toxicology of African Medicinal plants

The benefit of African medicinal plants dates back to 3200 BC by ancient healers in early African civilisations, such as KMT (ancient Egypt), Nubia, Ethiopia and Songhai. Due to these plants' successful results, the healers in these civilizations were deemed to be the gods of medicine. Furthering their capabilities, mixtures to treat various diseases were started to be made of herbs, animal parts, and clay, but according to ancient medical books, a majority of these were made from plants, by the civilizations. In a newer era, medicinal plants were also noted to be used by slaves while they were held captive and forced to work on different plantations. Plants such as cotton roots were used as contraceptives and okra- a plant native to Africa was used because of its unique healing capabilities. Although currently due to deforestation and habitat loss, some medicinal plants have gone extinct, the history of these plants proves that they are beneficial to the body and have been used to treat toxins and viruses in the body for thousands of years.

Vital Chemicals found in African Medicinal plants

After analysis of useful chemicals found in African medicinal plants, they are usually classified into different groups according to their certain abilities of antibacterial properties, antimicrobial properties and anthelmintic properties. These properties characterize the benefits that the chemicals found in different African medicinal plants will bring to the human body.

The antibacterial properties allow plants to destroy bacteria and suppress their growth or their ability to reproduce. *Muzigadial A* is proven to have antibacterial properties when treating toxins. This chemical compound is obtained through the extracts of the plant *Warburgia salutaris,* known as the pepper-bark tree by the residents of South Africa, which is used as a topical medicine for sores and inflammation. *Vernodalin, vemolide* and *Sesquiterpene lactones* are other compounds obtained from the ethyl acetate extract of the leaves of *Vernonia colorata* that was also proven to have antibacterial properties. Furthermore, *Vernodalin* is known to have anti-tumour and anti-fungal activity. This information was screened and resulted in *V. colorata* as a medicine against bacteria-related diseases. *Sesquiterpene lactones,* this compound has been shown to possess anti-inflammatory properties. Of the compounds above, *Vemolide* is the least researched however it is known to have anti-parasitic and anti-inflammatory activities. In Nigeria, *Murrayaquinone A* was discovered in the plants *Murraya euchrestifolia and Murraya*

joenigii. The exhibition of its antibacterial agents was documented because of its apparent inhibition against the bacterial infections, *Escherichia coli* and *Staphylococcus aureus,* along with its anti-parasitical agent against *Trichomonas gallinae;* thus, proven the use of potential antibiotics of *Murrayaquinone A*.

Antimicrobial properties are defined according to the plant's defence mechanisms against predation by microorganisms, insects and herbivores. The research about the carbazole alkaloid of *Murraya koenigii* has been reported to show potent cytotoxic activity against human leukaemia cells, prostate cancer cell lines, and viral and clinical pathogens. Different compositions and extractions of the *Murraya koenigii* plant such as the monomeric and recently binary carbazoles have been indicated to be anti-oxidant, -tumour, -microbial, -inflammatory, -trypanocidal and mosquitocidal activities through further research and observations. Anthelmintic activities in plants are described as natural drugs used to treat parasitic worm infection, which usually infect humans, livestock and crops. The chemical compound, B-asarone in the *Acorus calamus* plant was ascertained to show anthelmintic properties, which led to the common use of *Acorus calamus* when treating intestinal-helminthic infections in countries such as South Africa and India instead of pharmaceuticals.

This listing of different chemicals in medicinal plants benefits our progression in medicinal toxicology of how they cure toxins and diseases of the human body. Even though there is an underlining risk of overdosing on chemicals causing chemical poison, which is still a factor in misusing medicinal plants. The lack of understanding and research on these African medicinal plants about their full potential is unsure and too complex for expanding the use of these plants. Hence, with more sufficient and thorough discoveries on traditional medicinal plants, they will become more beneficial in the medical field for the removal and treatment of toxins in the human body.

Toxic Diseases that Medicinal Plants have Proven to Help

Taken into account from studies that 34% of Africa's population lives in poor socio-economic conditions, the need for low-cost and accessible medicines to treat the wounded and sick is essential. Moreover, Africa is the home of rich medicinal plants that treat maladies such as diabetes mellitus, and heart-related diseases. The availability of these plants makes affording medicines attainable. Despite the richness and great advantages, some plants are toxic.

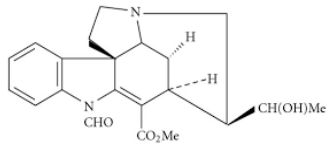
Strikingly, some of these toxic plants have favourable qualities and traits which have proved to aid in treatment.

It has been found out upon research and other scientific courses of action that African medicinal plants are said to have pancreatic beta cells regenerating insulin potential, hypoglycaemic effects, increasing insulin secretion, enhancing glucose uptake by adipose tissue or muscles and inhibiting glucose absorption from the intestine and glucose production from the liver. ***Clausena anisata*** is a popular plant to treat diseases such as gastrointestinal disorders, fever, pneumonia, headache, hypotension, sore throat and sinusitis, and venereal diseases, as an aphrodisiac and anthelmintic, as a tonic for pregnant women, and as a tonic for infants to prevent rickets and to control convulsions. *Clausena anisata* contains essential oils, especially in their leaves and fruits. It is identified by its strong aroma. That said, after extensive analysis, it has been found that the essential oils of this particular plant contain chemo-variants: (E)-anethole, methyl chavicol, (E)-foeniculin, β-pinene and other oils containing a large number of constituents varying in concentrations of 0.2% to 20%. It has been found that leaf powder and different leaf and root extracts showed signs of notable antifeedant activity against the stem borer *Helicoverpa armigera*. A methanol extract of the twigs showed moderate antiplasmodial activity against a chloroquine-sensitive strain of *Plasmodium falciparum* in vitro. Moreover, the leaf's essential oil exhibited significant antibacterial activity against *Salmonella typhimurium*, *Pseudomonas aeruginosa*, *Alcaligenes faecalis*, *Bacillus subtilis*, *Enterococcus faecalis*, *Flavobacterium suaveolens*, *Leuconostoc cremoris* and *Serratia marcescens*. Clausenol showed crucial activity against a range of Gram-positive and Gram-negative bacteria and fungi. The leaf oil also exhibited significant antifungal activity against *Alternaria alternata*, *Aspergillus parasiticus*, *Geotrichum candidum*, *Phytophthora palmivora* and *Penicillium citrinum*.

Another significant plant used in treatments for diseases such as malaria, yellow fever and *trypanosomiasis* is ***Morinda lucida.*** This plant is found in Senegal, Sudan, southern Angola and Zambia. The infusions or plasters of the root, bark and leaves are used to treat the diseases mentioned above. Moreover, it is also used to treat diabetes, hypertension, cerebral congestion, dysentery, stomach ache, ulcers, leprosy, and gonorrhoea. Its major constituents include various types of alkaloids and anthraquinones (C14H8O2). The two isolated compounds of this plant are Adewunmi and Adesogan as well as 10 anthraquinones from the stem of the plant. In addition to

that, Petroleum ether and DCM extracts of *M. lucida* have shown anti-inflammatory activity in COX-1 and COX-2 assays.

Commonly known as God's tree, ***Alstonia Boonei*** is scientifically proven to be useful traditionally for its antimalarial, aphrodisiac, antidiabetic, antimicrobial, and antipyretic activities. Despite that, the plant parts are rich in various bioactive compounds such as echitamidine, N*α*-formylechitamidine, boonein, loganin, lupeol, ursolic acid, and *β*-amyrin among which the alkaloids and triterpenoids form a significant portion. Regardless, The bark of the *Alstonia* tree is one of the viable analgesic herbs available in nature. A sweet decoction of the bark of A.Boonei can be used to treat: painful menstruation (dysmenorrhoea), and lower abdominal and pelvic congestion associated with pelvic gynaecological problems such as pelvic inflammatory diseases. It is also used to reduce the painful urethritis common with gonococcus or other microbial infections in men. Furthermore, Alstonia bark can be used to formulate herbal tinctures which can be used as a cogent antidote contra to rat, snake and scorpion poison.



Nα-formylechitamidine (3)

Adotey, JP et al., (2012, July 30). A Review of the Ethnobotany and Pharmacological Importance of Alstonia boonei De Wild (Apocynaceae). Europe PMC. https://europepmc.org/article/PMC/3413980

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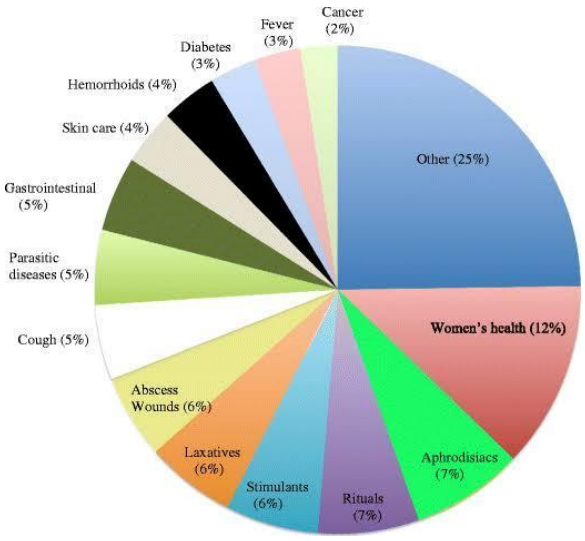
Discussion of Factors Affecting the Research

Inevitably, many factors limiting the value of research needed to thoroughly answer the research question were faced. These limitations stem from the lack of previous studies done to prove the benefits of the link between the two, that is; toxicology and African medicinal plants. Much of the data used to support the claims mentioned in many of the references are based on vitro screenings, which are conducted in lab equipment but Vivo screenings which are done in the body produce more accurate and better results. Therefore, the little access to Vivo screening is a limit to the data supplied to answer the question. Notably, another limit to the research conducted, is the major possibility that the effects of African medicinal plants on various person's immune systems are susceptible to change. This issue lies with not having enough variations in tests done as well as the types of tests conducted.



Andel, T. et al.; (2016, December 16) Most frequently mentioned disease categories, expressed as a percentage of the total number of plant species. Springer Link. https://link.springer.com/article/10.1007/s12231-016-9365-8#Fig3

Another limitation is the insufficient amount of evidence to prove how effective these medicinal plants are stated in the paper. This limits our research because we do not know which medical plants have a higher or lower percentage to improve a person’s overall health. Which can cause later problems since we would not be able to list what African medical plants people should use to improve their well-being. There are currently ongoing studies regarding what plants are just known to be healthy for the body and other plants that are known to heal. This limits research because we currently do not fully understand or know which plants are

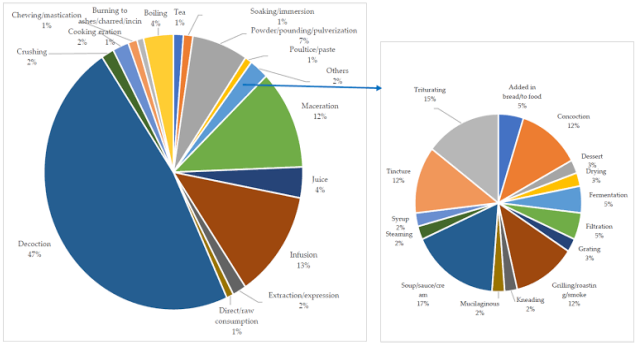
specifically better to heal an outer wound or scar and which plant is best to improve a person's overall health within themselves.

Potential Research to be Done on the Toxicology of African Medicinal Plants

In the past, "medicine," as we know it today, was unavailable causing people to depend on natural herbs to treat diseases. Africa is known as the original habitat of the human species, so presumably, the knowledge of using medicinal plants started disseminating from there itself. If we delve into this wealth of knowledge regarding the proper uses of African medicinal plants, it may be able to provide a direction as to how they can be used to treat exposure to toxins in the human body.

The idea of poisons or poisonous plants for a very long time is that they only cause harm. Outside of scientists, researchers and other personnel in this field, very few people are aware that poisons can be used to treat other toxins. Hence, exploring the question: 'are poisonous plants able to cure toxins?' could help expand the body of knowledge in this regard. Further research should also be applied to the area of infectious diseases and their vectors as they are hugely responsible for transmitting these pathogens. Evaluating if African medicinal plants can keep away these disease-spreading vectors along with the diseases themselves, would be a bonus in the medical field.

As the famous saying goes, "Prevention is better than cure." If we can prevent diseases from affecting us in the first place, there will be no need to worry about a cure. Analyzing if African medicinal plants can cure diseases is important, additionally, it would be helpful to try and discover if using them in small amounts regularly can also help in preventive purposes.



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Conclusion

Roughly 80% of the world's inhabitants continuously depend on herbal medicinal plants for the treatment of toxic diseases in the body. Each chemical found in these medicinal plants is divided into distinct groups according to certain abilities which include: antibacterial properties, antimicrobial properties and anthelmintic properties. Properties of certain plants have been tested and researched, yet the impactful results encountered are hardly being put to use. Therefore, ***legitimately*** utilizing these plants in the field of toxicology by treating exposure to toxins in the body should be further scrutinised and set into place. Moreover, the benefits of African medicinal plants precedes only helping with treatments of toxins in the body. Additional benefits confirmed through analysis include easy availability, affordability, accessibility, and promising effectiveness comparable to the often high cost and adverse effects of standard synthetic drug agents. This shows that the field of toxicology must start relying on the usage of African medicinal plants in the production and development of methods to treat toxins in the body, as it has been proven to be beneficial.

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Manipulating DNA Using CRISPR-Cas to Lessen Autism Symptoms in Juvenile Patients

by Arianna Pereira

Abstract

Clustered regularly interspaced short palindromic repeats, or more often referred to as CRISPR-Cas9, is a nobel winning technology that cuts DNA at a very specific site, directed by a supplied RNA. Then, endogenous repair mechanisms ideally insert a supplied DNA sequence as a replacement of genes in the genome. The two founding scientists from California, Emmanuelle Charpentier and Jennifer Doudna, discovered that a particular enzyme, Cas9, can be guided by a programmable RNA to translocate and bind to specific genetic sequences in most any organism. Cas9 then works as molecular scissors, snipping both strands of the DNA's double helix and allowing for scientists to manipulate the DNA.

CRISPR-Cas9 technology is being used to genetically edit mosquitos to reduce the spread of malaria, engineer agriculture to withstand the growing threat of climate change, andin human clinical trials to attend to an assortment of diseases, from cancer to transthyretin amyloidosis, a rare protein disorder that slowly progresses, attacking nerves and internal organs. In short, "It's a tool that scientists and clinicians around the world are using to understand our genetics, the genetics of all living things, and — most importantly — to intervene in genetic disease," Jennifer Doudna, PhD, a founding scientist of CRISPR-Cas9, stated during the annual meeting of The Association of American Medical Colleges.

Discussion

While a cure for genetically attained autism is far from tangible, researchers are setting their sights on gradual steps to make genome editing treatments for autism a reality. Researchers are now able to use CRISPR-Cas9 to narrow in on 10 of the 100 related genes that are most significant in the onset of genetic autism.

In addition to monogenic ASD, syndromic autism - caused by a sole genetic mutation - causes decreased protein efficiency. As a way of constructing more knowledge on particular ASD mutations, a more attainable goal has arised. Studies are being conducted to find treatments for single celled conditions that are closely related to the broad disorder of genetic autism. Along with the ASD mutation stated above, Rett syndrome, a syndrome categorized under the umbrella

of autism spectrum disorders, is the result of mutations on the X chromosome on a gene labeled MECP2. There are more than 900 different possible mutations found on the MECP2 gene making it challenging to diagnose Rett syndrome amidst the number of related disorders. The syndrome is often diagnosed in infants, ages 6 to 18 months, after key infant milestones are missed, such as responding to a given name or interacting with peers.

A condition related to ASD, named Fragile X Syndrome (FXS), is a result of mutations occurring in the FMR1 gene. FMR1 produces FMRP, a protein that aids in brain development. *[3]* Those with Fragile X Syndrome do not produce this fundamental protein. Fragile X Syndrome has attempted to be treated in mouse models using CRISPR-Cas9. A 2016 study led by pharmacologist David Hampson of the University of Toronto in Canada, observed mice with Fragile X syndrome before, during, and after, CRISPR-Cas9 treatment. CRISPR-Cas9 erased or reversed abnormal motor activity and anxiety problems that were obvious before the treatment was given.

Fragile X Syndrome is also being studied using transient gene therapy, a treatment that does not edit the genome; as opposed to permanent gene therapy. This method focuses on noncoding RNA (ncRNA), antisense oligonucleotides (ASOs), gene delivery, and RNA manipulation; antisense oligonucleotides being in advanced stages of development. Antisense oligonucleotides reduce the expression of a target gene by binding to the messenger RNA (mRNA), effectively silencing its protein product from being translated. They are being tested to target toxic CGG repeats in the FMR1 gene. A healthy human body contains 5-22 CGG repeats (CDC). CGG repeats upwards of 55 often causing Fragile X Syndrome symptoms while CGG repeats upwards of 200 caused the diagnosis of the syndrome itself.

In current methods of treatment, complementary DNA (cDNA) of the corresponding mutated gene is delivered using adeno-associated viral vectors (rAAVs) which silence transcription factors that do not allow for the expression of the target gene. Using RNA interference (RNAi) or Post-Transcriptional Gene Silencing (PTGS) to do this may also trigger an increase in protein production, lessening symptoms.

The link between ASD and Fragile X Syndrome is not as clear as it is with Rett syndrome though there are many commonalities. Rogers et al. noted that 33% of children, ages 21 to 48 months, with Fragile X Syndrome could not be differentiated behaviourally from children of the same age with ASD. Nonetheless, according to the Fragile X Foundation, many individuals

suffering from Fragile X Syndrome are often co-diagnosed with ASD. They note that this may be because the FMR1 gene mutation is the leading cause of ASD diagnosis.

As of 2022, strategies are still constantly being tested, reinvented, and ruled out. As an illustration, in 2018, *Complete Disruption of Autism-Susceptibility Genes by Gene Editing Predominantly Reduces Functional Connectivity of Isogenic Human Neurons* was published. The paper presented the observations of an experiment that included inserting a protein tag into premature termination sites, using CRISPR, on human DNA. DNA was collected via blood samples and/or skin biopsies. Using RNA sequencing, scientists discovered the convergence of several neuronal networks, resulting in a reduction of synaptic activity. The experiment was proven successful to silence the expression of ASD-relevant genes (AFF2/FMR2, ANOS1, ASTN2, ATRX, CACNA1C, CHD8, DLGAP2, KCNQ2, SCN2A, TENM1).
As an alternative, researchers injected CRISPR-Cas9 into the brains of infant and adolescent-aged mice, which counteracted the effects of the SCN2A mutation, a gene often linked to ASD, by homologous repair. Despite the fact that the experiment was successful, CRISPR-Cas9 can only create a double strand break (DSB) in DNA, limiting its abilities. A common myth surrounding the breakthrough technology is that CRISPR-Cas9 is able to replace base pair sequences, not only cut them. This is false; a double strand break caused by CRISPR-Cas can end in one of two ways. The first, homology directed repair (HDR), includes a homologous recombination that ends in an error free repair. The second, nonhomologous end joining (NHEJ), results in random insertions/deletions which cause gene disruption. Nonhomologous end joining has made insertion of non-threatening or even beneficial DNA a difficult feat on the large scale.

To truly make genome editing treatments for ASD in juvenile patients an attainable prospect, these treatment strategies need to be translated from rodents to humans. This will perhaps be the most demanding part of these treatments being accessible worldwide. The Massachusetts Institute of Technology (MIT) and the Chinese Academy of Sciences are working to perform CRISPR-Cas9 therapies for autism on primates. The hope is that lessening the differentiators between species will make the transfer to human patients slightly more straightforward. Differentiators include: pH level balance, release of antimicrobial peptides, anatomy, etc. Nevertheless, the bioethics of such procedures need to be discussed as the controversy is widespread.

Bioethical Concerns Surrounding CRISPR-Cas9 As A Treatment For ASD

CRISPR-Cas9 has caused an uproar of debate since its founding. Futuristic ideas of applications of CRISPR-Cas9, such as "designer" children, are not the only aspect of the technology that people question from an ethical standpoint. People all over the world are questioning who governs CRISPR-Cas9 and its uses. Bioethical concerns surrounding CRISPR-Cas9 treatments for ASD in juvenile patients are widespread and continuing to grow. The idea of one being neurotypical versus neurodivergent is often used while researching ASD. Scientists now determined that the central difference between neurotypical and neurodivergent people is the way one perceives the world. Often, people who are "neurodivergent" prefer the term "neurodiverse". Author of *Disability Discourse* and sociologist Judy Singer wrote, "For me, the key significance of the Autism Spectrum lies in its call for and anticipation of a politics of neurological diversity, or 'neurodiversity.' The neurologically different represent a new addition to the familiar political categories of class/gender/race and will augment the insights of the social model of disability."

Neurodiversity is a title that respects variations of the human nervous system regarding learning, mood, attention, sociability, as well as alternative cognitive functions. It does not consider these conditions abnormal or unhealthy. Neurodiversity also encompasses the understanding that ASD and related syndromes are disorders to be understood and may be treated using therapy. The label, coined by the people that claim it, largely rejects the medical model of disability. This terminology has aided ASD individuals to have a more fulfilled life according to the neurodiverse community.

On the other hand, there is the term "neurotypical" which arose when its counterpart, "neurodiverse", was first used. Neurotypical describes individuals who are more comfortable in social and communicational settings, learn and perform cognitive tasks at an average rate, and meet specific milestones in infant and adolescent development. The existence of people who categorize themselves as either neurodiverse or neurotypical creates neurodiversity across the globe. Treating individuals who may not agree they need treatment is a large part of the bioethical concerns surrounding CRISPR-Cas9 as a treatment/prevention technique for ASD. Another concern arises after the transfer from animals to humans has been made. In any one of the previously mentioned strategies, clinical trials may start on human embryos; as CRISPR-Cas9 is only effective at preventing ASD when an individual is single celled, and the

altered DNA can be confirmed before multi-celled development. This creates a divide regarding who should decide to implement CRISPR-Cas9 for the treatment of possible ASD. Unfortunately, there is no concrete answer to this common, and perhaps most important question.

It is also necessary to consider the consequences of such trials. Embryonic editing may cause severe side effects that would last for generations. The same can be seen with the embryonic editing study led by chinese scientist, He Jiankui, who used CRISPR-Cas9 targeting the CCR5 gene to initiate HIV resistance. CRISPR did not result in the deletion of the 32 nucleotides that caused the production of the CCR5 protein in either twin. The study led by Jiankui led to numerous experiments regarding strategic methods for delivering CRISPR-Cas. The experiment notified the field of the potential ethical misuses of CRISPR-Cas and caused a 5 year moratorium on CRISPR human research. This global mandatorium allowed discussions including the technical, medical, societal, ethical issues surrounding CRISPR-Cas in terms of germline editing. To address these concerns around germline editing, a new committee had been set up by the World Health Organization

Delivery

Although CRISPR-Cas9 can be administered on an embryo to make edits that will persist as the organism develops, CRISPR-Cas9 is difficult to administer to multiple cells all at once. However, various methods are being tested by scientists to make delivering CRISPR-Cas proteins and guide RNA simultaneously to multiple cells possible.

One method delivers CRISPR-Cas9 through a viral vector. This has been scrutinized due to the high chance of immunogenicity, and potential to provoke an immune reaction. Historically, CRISPR technology has been delivered by viral means through an adenovirus. In rare cases, this has caused organ failure due to the adenovirus vectors triggering a dangerous immune response, leukemia, and ultimately death. In the lab, the transfection of the adenovirus can be aided by electroporation, but would only be acceptable for *in vitro* methods, where the cells are removed from the organism and treated in culture. The high-voltage shock essential to permeabilize cell membranes may not only be toxic but may lead to lethal permeabilization of the treated cells. However, there is a newer alternative with promising outlooks to deliver CRISPR-Cas9 throughout the genome. Delivery can occur through the Cas9 protein and gRNA as a ribonucleoprotein (RNP) complex and would be delivered through an engineered

adeno-associated virus that does not contain the genes required to initiate the lytic cycle and harm the cells. While this is effective to some extent, adeno-associated virus is prone to off-target effects since it can react to many different types of cells and tissues. The problem of off-target effects can be mitigated via tissue specific promoters. These promoters prevent unwanted transgene expression because of DNA only being able to be transcribed within specific tissues that contain certain promoter cofactors. However, there is the problem of uneven distribution of Cas9 protein and gRNA due to local defusion near the site of injection. There is also the concern of organ accessibility. Only a few organs are employable for this method of treatment; such as the eye, for example. The eye is a relatively isolated organ which is beneficial since it minimizes the risk of transgene infection on tissues away from the target site. Since the eye is small, transfection between target genes is a realistic possibility.

Ex vivo, meaning a patient's cells are manipulated outside of the individual and then reintroduced back, presents its own set of benefits and challenges. *Ex vivo* has a lower error rate, mostly since patients' entire body is not exposed to CRISPR-Cas9 directly, and scientists can better control and manipulate the cells of interest themselves. *Ex vivo* therapy has been proven sufficient for the treatment of difficult-to-treat diseases, such as hematological disorders and cancer immunotherapy. CRISPR-Cas is less effective in these contexts as DNA can only be transcribed within specific tissues with the corresponding promoters, however, tissues may be unresponsive causing *Ex vivo* to be a better alternative to CRISPR-Cas in cases like ASD.

Moving Forward and Conclusion

While the field has made improvements in many areas including addressing ethical concerns and experimenting with existing CRISPR-Cas technology to make it even more accurate, scientists are looking forward to new technologies. These new technologies include Prime editing, a variation of CRISPR, that is at the cutting edge of genomics.

Prime editing (PE) was developed in 2019 by scientist David Liu and is revolutionizing CRISPR-Cas technologies. [9] Unlike the original Cas9 enzyme applied in CRISPR technology, prime editing does not require double strand breaks. Instead, prime editing involves the introduction of a reverse transcriptase (RT) into the Cas9 enzyme. Within the PE-Cas9 protein there is also an edit-containing RNA as an extension of the prime editing guide RNA (pegRNA) as well as an RNA template; these RNA sequences replace the normal guide RNA found in

CRISPR-Cas9. Like Cas9, the PE-Cas9 nickase makes a cut 3 base pairs upstream of the PAM sequence, which allows the now separated strand of DNA to bind to the prime editing guide RNA template. The reverse transcriptase, not found in normal CRISPR-Cas9, will then transcribe the template of RNA into complementary DNA which provides the cell with a new hard copy of said gene fragment, corrected using the introduced RNA. This method was found to be superior to Cas9 alone as it has both high consistency and a low error rate.
In an experiment attempting more complicated editing,an adenine base-editor (ABE) and guide RNA combination were tested but caused severe bystander editing. Prime editing was consequently tried and corrected the mutation with no detectable bystander effect. Although this study ended in favor of prime editing, base editing (BE) potential with no cause for bystander effects would be better solved utilizing more tested approaches, such as base editing or homology directed repair.

Following the foundation and meticulous studies surrounding prime editing, there are multiple ventures to improve the precise technology. To avoid an increase in misedited DNA, an approach called PE3b includes prime-editing guide RNA designed to recognize the complementary strand of DNA only after the prime editing alteration has been made, and makes a single strand break which recruits DNA repair mechanisms confer a match to the newly edited sequence. In original prime editing strategies, the prime editing guide RNA only recognizes the existing complementary RNA. Technical improvements such as this are what have allowed for additional methods of treatment as well as prevention of a diverse range of conditions, mutations, and disorders.

Overall, CRISPR-Cas technologies have many improvements to be made in the future as well as bioethical concerns that continue to inhibit further exploration of its potential. While advancements such as Prime editing and PE3b are causing the reality of germline editing to shift, there are still issues including technological dangers and hereditary consequences. Preventing ASD using germline editing will not come easily, however, now that different delivery vectors, CRISPR-Cas variations, and research on related disorders arise, it is not extremely far off.

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Lumiere Research Scholar Paper By Kaiqin Zheng

Abstract

This paper examines strategies for low-income, nomadic groups in Inner Mongolia Autonomous Region (IMAR) to harness sustainable energy technology and entrepreneurship to move towards sustainable livelihoods local people's awareness of the renewable energy industry in IMAR. I used qualitative research methods to collect and analyze secondary data and primary (interview) data to identify challenges, opportunities, goals, and strategies, and government support schemes relevant to the renewable energy industry in IMAR. I use comparative case approaches to analyze secondary data to identify strategies used for establishing sustainable energy plants in another country (Mongolia), with the aim of identifying those that may be beneficial for IMAR. I use thematic analysis and grounded theory approaches to code primary data and identify significant trends and broader themes that have implications for theory, practice and policy. The findings of this paper provide strategy insights for the growth and development of not only the sustainable energy industry in the IMAR region, but also for improving the local economy through utilizing renewable energy industries related resources.

Introduction

In the past few years, the Chinese economy has expanded rapidly, with large amounts of energy being used for industrial activity. As a result, China has become the second largest energy consumer in the world (Calvin, 2009). Higher levels of energy consumption leads to the burning of large quantities of coal and fossil fuels, in the conventional methods of generating electricity. The Inner Mongolia Autonomous Region (IMAR) is the second largest supplier of conventional power in China, leading to high levels of fossil fuel consumption in this region (Calvin, 2009). According to local administration's data, IMAR utilized more than 1 billion tonnes of coal in 2021 (Fibre2Fashion, 2022). Burning fossil fuels like coal releases large amounts of carbon dioxide, nitrous oxide, and sulfur oxide into the air (Calvin, 2009), which, in addition to release of particulate matter, have a negative effect on human health (ADB, 2014).

In response to the need for greener and cleaner energy, China turned to renewable energy sources, like wind power. As the country has abundant wind energy resources - ranking third in the world in terms of wind power - it is predicted that the average annual growth of renewable

energy in China will reach 29%, which will lead to more attention and investment in related technologies in China's wind power industry. The trend of data identifies wind power as the third main source of large-scale energy in China (Zhang et al, 2012). China's demand for energy is growing, so the need for further development of the renewable energy industry is urgent. IMAR has the third largest land area in China over 450000 square miles, while the population is only 2% of the total population of China. In addition, IMAR has significant potential wind and solar energy resources, which are advantageous for the development of a robust renewable energy industry (Kwan, 2009). This in turn can help provide a robust livelihood to the members of the local community.

My research examines how the sustainable energy industry in IMAR can help the local community achieve sustainable livelihoods. Most of the existing research discusses IMAR as a region that stands to benefit by developing its sustainable energy industry. However, prior work shows that the industry has always been promoted by the government or by successful commercial companies for profits, while local nomadic populations are still forced to be reliant on livestock for their livelihood. In this paper, I attempt to identify strategies that can increase the participation of these native populations in this industry, and can help them make good use of local resources while further improving the economic development of local communities.

Methodology

The main research methods I will use are qualitative, specifically comparative case study methods. I plan to use two ways to collect data for the project: interviews and secondary data from news articles and archival sources. For data collected from interviews, I will carry out analysis using coding, discourse analysis, conversation analysis, and content analysis. For secondary data, I will draw from content and narrative analysis, first analyzing every interesting case, figuring out what kind of ideal type it is, and then comparing those case studies to propose observations and findings. More specifically, the first step should be to find many papers related to my research topic. I believe there are many interesting data or conclusions that can give me a lot of ideas. For example, what factors will I look for that lead to the low participation rate of local people in the renewable energy industry in Inner Mongolia? Why is the development of renewable energy in Inner Mongolia still invested in and developed by the government and foreign commercial companies? Such advantages and disadvantages? What source of electric

energy do the local people now use to maintain their lives? Fossil fuel, PV system, or wind energy?

Secondly, I will collect the development of renewable energy in different places through similar secondary media and compare the impact on the local economy, that is, comparative case studies. After collecting a certain amount of data, I will analyze them one by one to determine how to use them in my research. My two main research areas are Mongolia and Inner Mongolia. By constantly reading the secondary data of relevant renewable energy in these two regions, I used data coding to arrive at their results by classification through geographical environment, challenges, opportunities, solutions, goals, strategies and data. As for the source of interview data, I asked four nomads working in the IMAR area who depend on animal husbandry and one professional working in the IMAR local renewable energy industry. After transcribing the details of five different interviews, I also made an table by classifying on daily life, the impact of local policies on their lives, the impact of covid epidemic, the understanding of renewable energy, and the opinion about foreign countries helping IMAR renewable energy industry through excel coding way in their interviews. Based on the discovery analysis, conversation analysis, and content analysis, I will evaluate more in-depth insight on it.

Literature Review

Kwan (2009) explores the fit of the Inner Mongolia Autonomous Region (IMAR) as a place to build wind power and solar power industry based on its low population density and large flat lands. This paper identifies that IMAR is suitable for using renewable energy systems, and suggests some “green electricity strategies”, and suggests that renewable energy generation can be implemented using short term incentives by financing from third parties, and eliminating import duties for equipment for wind, solar, or clean coal related equipment.

Clark et al. (2007) in their paper find that cost effectiveness of hybrid energy is important to the development of new green energy, and that by learning from success and failure from the west, IMAR can harness proven and useful strategies to plan the development of its sustainable energy industry. Zhao et al (2012), in their SWOT analysis of the wind power industry in China, find that a major strength is the gradually increasing domestic capacity of China's wind power industry. The weakness they identify is heavy repayment and tax burden. The manufacturing

capacity of domestic fans lags behind that of the world's leading manufacturers. It takes a long time to develop a high-quality turbine. The opportunity is the development of offshore wind power generation can improve efficiency. The use of new energy, especially renewable energy, plays a key role in national strategies to address energy issues in China, which needs a lot of energy. The threat to the development of IMAR's sustainable energy industry is that it is hard to connect sustainable power units to the grid, there is high reliance on the government, that the industry still needs to be commercialized, and that there is poor coordination between the up and down streams of the supply chain (Zhao et al, 2012). From this SWOT analysis, we can learn that the current strategy used in China is an implementable plan, and that China should leverage IMAR's production capacity for growth of this sector.

Byrne et al. (1998) however, highlight that renewable energy development in rural China is affected negatively by insufficient funding, and that the high costs of renewable energy technologies are still big obstacles to rural populations building their own renewable energy systems that can provide electricity for them to form self-supporting rural communities. In order to spur market development of renewable technology in the countryside, it is necessary to evaluate the economic viability of different renewable energy systems like: PV, wind, and hybrid technology. Since pure PV and wind systems both meet two huge problems: unstable when the specific energy sources are not available and expensive. On the contrary, hybrid systems integrate the advantages of PV and wind power systems, which provide electricity stably and at lower cost. Hence, the government should support this system with various strategies. The government should begin to set goals and utilize smart systems to achieve those goals periodically; the government should promote more collaboration with local and other companies to spend more attention on developing renewable energy technologies; the government should offer subsidies; the government should publish more flexible loan rates and repayment plans in the market. Incentive policy is always an ideal strategy to spur the renewable energy market.

Zhao et al. (2019), in their paper, explain the development of wind power industry in China by swot analysis. The strength is China has a large number of wind energy resources with huge potential commercial value, and wind energy resources can help the environment reduce greenhouse gases. Moreover, the wind energy industry is developing rapidly in China, with a sufficiently mature scientific and technological level. The weakness is the cost of generating electricity from wind energy remains a huge obstacle to commercialization. As some advanced

technologies still use foreign resources, the situation of high costs will be difficult to change. Heavy taxes are also one of them. Offshore wind power resources are actually very rich in China, but China's technology in this area is still weak. Developing the wind energy industry could be a very good opportunity to promote economic development. At present, China is also gradually releasing relevant support policies to help develop the wind energy industry. The potential value of offshore wind power is huge. China can make good use of this resource for development. The threat is connecting the electricity generated by renewable energy to the grid is still a very big obstacle. The bidding of renewable energy exhibition industry is easy to generate an unreasonable low price. At present, the commercialization of wind energy industry is still insufficient, which will affect the scientific and technological development of wind energy industry.

Xia et al. (2009) illustrates that wind resources are relatively abundant in China due to its large landmass and long coastline. The development of wind energy can be improved in four ways: by importing technology from foreign companies, by offering subsidies, by offering more commercial opportunities, and by enforcing renewable energy laws. Yang et al. (2021) point out that the largest solar PV market in the world is in China. Now, China tries to avoid over-reliance on overseas PV market technology. In order to create a low-carbon economy, the central government in China plans to denote the solar PV industry, which they want to attract more investors. Importantly, a good solar incidence and large areas of available land, which are ideal for the installation of large-scale centralized PV power plants, make Inner Mongolia the best choice for national energy security concerns. Currently, IMAR uses a fit-and-conform pattern. Under the continuous comparative case study, they found that the renewable energy industry is more suitable to use the allocation work system to enhance work efficiency, which is also the strategy that some IMAR companies are adopting. They will study more internal work strategies of relevant companies to improve which institutional work IMAR companies should adopt.

Analysis And Findings

In the past, IMAR mainly generated electricity by burning a large amount of coal, resulting in serious environmental problems. Fortunately, IMAR realized this problem and decided to use renewable energy for energy supply to solve a series of problems caused by fossil fuels. The way I used it was qualitative analysis and comparative case study. Qualitative research

is mainly manifested in speech, conversation and interview. I decided to collect data from secondary sources and interviews as research data for qualitative research. As for the data collected from the auxiliary data, I summarized more useful information to help IMAR develop renewable energy by comparing it with IMAR in other countries that are developing renewable energy. For the data collected from the interview, I used coding, discourse analysis, conversation analysis and content analysis for analysis. Since the conversion of IMAR from burning coal to mainly using renewable energy has had an unavoidable impact on the lifestyle of local people, I interviewed local people about this phenomenon. In order to strengthen the connection between the interview and the renewable energy industry, I also chose to interview the local people who are working in the renewable energy industry.

In this section, based on my data analysis, I identify the strategies that nomadic communities in IMAR currently use to earn a livelihood, as well as strategies used by the sustainable energy industry to expand into rural areas in different parts of the world. Using the same, in the following section, I propose strategies that low-income, nomadic groups in Inner Mongolia Autonomous Region (IMAR) can use to harness sustainable energy technology and entrepreneurship to move towards sustainable livelihoods.

In the secondary data, the technology of Mongolia's wind energy industry is still immature, especially the turbine technology. Based on sources 11 and 18, the backwardness of Mongolia's turbine technology is mainly due to the bad weather environment and poor quality of roads. Their geographical environment makes their temperature 50 ℃ below zero in winter and 50 ℃ in summer. Based on source 14, Mongolia's energy market does not have mature auxiliary systems to provide efficient systems. In order to solve this series of problems, source 11, 14, and 19 put forward valuable solutions. The opportunity for Mongolia's energy sector is that there are projects that can provide technology and funding to help them connect electricity generated from renewable energy to the grid. EBRD is willing to provide Clean Energy LLC with approximately US $46 million to achieve this goal. The Asian Development Bank also said that it would provide funds to help Mongolia develop a better energy market and guiding advisory services. Mongolia also has clear goals in the energy sector. The country should rely more on renewable energy to reduce carbon dioxide emissions, which is expected to reduce about 164000 tons of carbon dioxide annually. In order to solve the problem of Mongolia's lack of energy market, Mongolia decided to adopt one of the strategies to increase the share of renewable energy in the

country, especially wind and solar energy, which will greatly help the development of renewable energy in Mongolia.

According to source 1, 6, 17, 18, IMAR's geographical environment has unique advantages. China's goal in 2030 is to adjust the energy industry structure of IMAR, and transform the coal energy mainly produced by IMAR into more environment-friendly renewable energy.

According to source 2, 16, 18, IMAR also encountered many problems. The heating infrastructure is very scarce, and the process of converting to renewable energy development is too fast, leading to the neglect of the impact on the local people. In the past, most nomadic people in IMAR relied on animal husbandry and had no fixed residence. When IMAR is developing renewable energy, wind power generation and other industries are forcing local people to reduce their nomadic life, which has greatly occupied and affected the living areas of local rural people. IMAR has also noticed this problem, and is providing many anti-poverty policies, providing free power resources, and allowing residents to gradually reduce air pollution.

According to sources 1, 3, 17 and 18, the current opportunity of IMAR is that the government emphasizes the flexibility of loans and investment in renewable energy technology development. For example, promoting the deployment of energy storage technologies will enable coal intensive areas to transition to renewable energy to reduce their carbon footprint. IMAR's main goal is to expand various local infrastructures to ensure the stability of renewable energy development. To be specific, fortunately, DHS subprojects include the installation of pre insulated pipes to repair or expand the heating network, the installation of SCADA systems and metering, water pumps, coal-fired boilers, ash handling equipment and heat exchange stations. Similarly, IMAR will also introduce hybrid systems to improve the stability of renewable energy and reduce costs. A US $150 million loan has been approved to introduce the first low-carbon and low emission heating system using natural gas and wind energy in Hohhot, the capital of the Inner Mongolia Autonomous Region (IMAR) of the People's Republic of China. This strategy can greatly solve the problem of environmental pollution caused by IMAR to coal. In addition, this loan also confirms the commitment of the local government to open more flexible loans as much as possible to accelerate the development of renewable energy.

Based on source 12, 13 , 16, 17, IMAR plans to adopt a mixed district heating system with low emission natural gas boilers and zero emission wind power boilers. This goal shows

that IMAR is aware of their neglect of clean natural gas and the problem of imperfect heating systems. This goal is to make the IMAR environment better. IMAR plans to put more than 10000 hydrogen powered vehicles on the road as far as possible under the continuous development of renewable energy in the future. This is also in line with other objectives of IMAR. The common theme is to reduce environmental pollution through the use of renewable energy. Moreover, As IMAR used to be a region mainly using coal to produce energy, the air pollution was very serious, and the local people often encountered haze weather. One of the strategies that the region intends to adopt is that the regional government will promote more wind, solar and other new energy equipment to improve the environment. After the National Energy Administration of Inner Mongolia ordered to stop all approvals and build new coal power plants for local use this year, the new goal of energy storage deployment is a step forward in expanding the market for renewable energy and low-carbon energy solutions in the region.

According to Int 1, 2, 4 and 5 nomads who depend on animal husbandry talked about the freedom of managing cattle and sheep on the grassland. When they talked about policies, they agreed that the poverty alleviation plan had indeed improved their lives. Specifically, the government will provide them with free and cheaper electricity. But they have different views on the epidemic. The three feel that the epidemic has indeed affected their daily lives, and the prices of cattle and sheep have also been negatively affected. The other thought he didn't go out much. There are few people on the grassland, and the epidemic is not very serious. As for their views on renewable energy, they all expressed their views on encouraging this emerging industry and believed that the country's choice was correct, but they still said that they would not want to join the renewable energy industry because they did not have much opportunity to really understand this industry. Animal husbandry is still their preferred way of life.

According to int 3, another worker who is really working in the renewable energy industry was also interviewed. He first clearly expressed why IMAR is a very ideal area for developing renewable energy: it is a vast area, sparsely populated and rich in energy resources. From his perspective, he believes that the local people are very active in the development of renewable energy, because it is a promising salary, which can increase a lot of income, and even the local people have established companies in this industry. He also explained that the primary goal of their industry is to reduce environmental pollution caused by non renewable energy.

To sum up, IMAR's current strategy for the development of renewable energy and the

goals set in the future are very clear, which shows that they not only focus on solving the environmental pollution caused by fossil fuel Tiele, but also express that they pay more attention to the lifestyle of local people to provide them with more help on the path of renewable energy transformation. At present, many poverty alleviation policies have been introduced to provide local people with cheaper or even free power resources. According to the interview, the employees of the local renewable energy company indicated that most of the people living in IMAR City have a lot of knowledge about the renewable energy industry and have many people working in this industry, while the nomadic people living in IMAR mostly rely on animal husbandry to survive. Today, the IMAR government is vigorously promoting educational resources for all people of IMAR, including nomads. However, nomads who have always lived on the grassland still love the free life brought by grazing, and are not interested in or even understand the current emerging renewable energy development. Perhaps it is because of the past to the present living habits and stereotypes, they still follow the past way of life, and do not want to break the current comfort zone. However, the development of renewable energy gradually allows them to change from nomadic life to settled life to manage their livestock. Most of them feel that this change makes their management more convenient and reasonable, and will not cause more conflicts with other herdsmen. Therefore, IMAR's renewable energy industry still relies on talents who have access to more educational resources in large cities. However, even though those herdsmen love to live on the grassland, they always send their children to school in big cities. It is believed that in the near future, IMAR will develop renewable energy more reasonably and effectively and drive the economic level of local people.

Tables

A. **Data Table 1: Comparison of Sustainable Energy Industry in Mongolia vs. that in IMAR**

Strategy	**Mongolia**	To decarbonize Mongolia’s energy sector, the government aims to increase the country’s share of renewable energy, especially wind and solar, which hold great potential for Mongolia.” (source 14)	The government focuses on renewable energy development

		Recognizing the challenges, the Government of Mongolia requested ADB to support the installation of a battery energy storage system (BESS) in the country. (source 14)	Introduce more investment and technology
	IMAR	"The region will also take measures to promote the development of the industrial chain for the manufacture of wind power, photovoltaic and other new-energy equipment", he was quoted as saying by official Chinese media outlets. (source 12)	The government focuses on renewable energy development
		following this year's order by the National Energy Administration for Inner Mongolia to halt all approvals and new construction of coal power plants for local use, the new target for energy storage deployment is a step forward for the region in expanding its renewable energy and low-carbon energy solutions markets. (source 16)	
		"The local government also has policies related to poverty alleviation projects (free and cheaper electricity, mainly hybrid technology) Free or cheap scenery complementary machinery for herdsmen" (INT 1)	
		With the support and leadership of national and local policies, the renewable energy industry is booming, and by the end of 2020, China's installed renewable energy power generation capacity reached 934 million kilowatts, accounting for 42.5% of the total installed power generation capacity, with wind power, photovoltaic power, hydropower and biomass	

		power generation capacity reaching 280, 250, 340 and 0.3 billion kilowatts respectively, ranking first in the world for For many years, it has been the first in the world. Inner Mongolia Autonomous Region, the 14th Five-Year Plan renewable energy installed capacity of 135 million kilowatts or more.(Int 3)	
		Support from national and local policies. (Int 3) 2) Huge revenue and business opportunities from the sustainable energy industry 3) Understanding the resource prospect of the local sustainable energy industry in Inner Mongolia	
		The state also gives some policy subsidies, solving many difficult problems. (Int 5)	
		Among them, wind power installed about 89 million kilowatts, photovoltaic power generation installed about 45 million kilowatts, solar thermal power generation installed about 60 million kilowatts, biomass power generation installed about 80 million kilowatts. Pumped storage energy started construction of 1.2 million kilowatts.(Int 3)	
		The continuous development of the renewable energy industry has led to the employment of a large number of local people and a continuous increase in income. (Int 3)	
		has approved a loan of $150 million to introduce	Introduce more

		a first-of-its-kind low carbon and low emissions heating system utilizing natural gas and wind power, in Hohhot, capital of the Inner Mongolia Autonomous Region (IMAR) of the People's Republic of China (PRC). (source 16)	investment and technology
Data	**Mongolia**	Mongolia's coal-dependent energy sector accounts for about two thirds of Mongolia's greenhouse gas emissions. (source 14)	Statistics of environmental factors
		The wind farm is expected to reduce CO2 emissions in the country by approximately 164,000 tonnes annually, enabling the company to sell carbon credits. (source 19)	
		According to the World Health Organization (WHO), annual mean particulate matter of less than 2.5 micrometers in diameter (PM2.5) in Ulaanbaatar is 6–10 times higher than the recommended safe levels of the WHO air quality guidelines. The pollution levels are worse during winter months, when the temperature can go below minus 40 degree Celsius. (source 14)	
		The energy sector is Mongolia's largest contributor to greenhouse gas (GHG) emissions, accounting for about two thirds of the country's GHG emissions. (source 14)	
		The delayed investment in new generation capacity combined with growing electricity demand have raised the utilization of aging CHP plants during peak energy demand hours in winter, exceeding 90%. (source 14)	

		The country's energy system is the most heavily dependent on coal among the developing member countries (DMCs) of the Asian Development Bank (ADB). In 2018, coal-fired combined heat and power (CHP) plants constituted 93% of total power generation in the country's Central Energy System (CES), which accommodated more than 80% of the domestic demand. (source 14)	
		The country's combined wind and solar power potential is estimated to be equivalent to 2,600 gigawatts (GW) of installed capacity or 5,457 terawatt-hours of clean electricity generation per year. The amount is enough to meet the country's energy demand (around 1.2GW as of 2018), and can meet northeast Asia's regional energy demand with a suitable transmission infrastructure. The government's target is a share of renewable energy in total installed capacity of 20% by 2023 and 30% by 2030 as announced in the State Policy on Energy, 2015–2030. (source 14)	Statistics of market and government
		The 50 MW Salkhit wind farm will be built about 70 km away from the capital Ulaanbaatar. (source 19)	Statistics of use of energy
		The EBRD is extending a loan of US$ 42.4 million to Clean Energy LLC. As part of the project financing, the EBRD will also take a further US$ 4.4 million equity stake in Clean Energy LLC. The company, created to build the wind farm, is currently 25 per cent owned by the EBRD and 75 per cent owned by Newcom LLC –	Statistics of fund

		a Mongolian incorporated company. Other participants in the project include the US-based General Electric which will supply thirty-one 1.6 MW wind turbines to the site. (source 19)	
	IMAR	The coal output in Inner Mongolia exceeded 1 billion tonnes. In terms of power transmission, it sent 246.7 billion kilowatt-hours of electricity out of the region in 2021, ranking first in China for 17 consecutive years. (source 12)	Statistics of use of energy
		With all wind energy companies based in Inner Mongolia, the region accounts for 40 percent of national wind energy output and, with over 1 terawatt (TW) of unharnessed wind power – enough to satisfy China's total energy demand - it is set to remain the centre of the country's wind energy revolution. (source 18)	
		The monthly coal output in Inner Mongolia during the last quarter of 2021 exceeded 100 million tonnes, a record high in the past three years, providing 53 million tonnes of coal for power generation in 18 provincial-level regions across the country. (source 12)	
		The region ranked first in China in terms of its coal delivery volume compared to other provincial-level regions last year. (source 12)	Statistics of market and goverment
		The PCR rated the project effective. It stated that outcome indicator targets from the RRP were revised after the changes in scope. Achievement dates were postponed from 2014 and 2015	

		to 2018. (source 16)	
		The total project cost is $403 million, of which the Shanghai Pudong Development Bank will cofinance $162.4 million and the Hohhot City Development, Investment, and Operation Company will provide $90.8 million through an equity contribution. (source 13)	Statistics of fund
		Established in 1966, it is owned by 67 members—48 from the region. In 2013, ADB assistance totaled $21.0 billion, including co-financing of $6.6 billion. (source 13)	
		District heating was identified as a potential sector to improve energy efficiency while reducing emissions as it obtained 95% of heating supply requirements from coal. Existing district heating infrastructure was old and inefficient. Small heating boilers were used and mostly reached the end of their design life. (source 16)	Statistics of environmental factors
		Of the disbursements, $4.62 million was for civil works, $126.60 million for equipment and materials, $1.13 million for project management, and $3.78 million for interest during construction and commitment charges. The last disbursement was in February 2019 for expenses incurred before the loan closing, and $13.87 million loan savings were canceled. (source 16)	
		outcome and outputs, as well as its limited	

		economic viability. The recalculated economic internal rate of return (EIRR) for the entire project was 15.7% with environmental benefits (compared to 27.6% at appraisal). Individual subprojects' EIRRs at completion ranged from 1.9% to 22.8% (source 16)	
		The PCR rated the project's development impact satisfactory, supported by the performance indicators in the DMF. By 2018, energy efficiency of the district-heating sector improved 32.5% (target of 15%) from 2010, and all IMAR cities and urban areas met improved air. (source 16)	
Outcomes	**Mongolia**	As a pioneering project on three fronts, Salkhit presented unique first of a kind challenges. The Mongolian environment is quite extreme, with winter temperatures dropping to -50°C and summer temperatures rising to 50°C, while there can also be large diurnal temperature variations. The environment created challenges with respect to turbine technology, constructability and operability of the project. (source 11)	Connection between technology and environment
		Turbines were built in China, and transport from the Chinese/Mongolian border to site was challenging due to the poor quality of roads in the south of Mongolia. The project was also the first renewable power project to connect to the Mongolian grid, representing a challenge to the grid operator, which was able to benefit from international capacity building efforts. (source 14)	

	IMAR	The series brought together people from a range of academic and non-academic backgrounds including the sciences, arts, humanities, and social sciences, and those working within policy, industry, activism, education, and media and continues as an occasional series hosted at the Mongolia & Inner Asia Studies Unit. (source 18)	Interdisciplinary impact

B. Data Table - Interview Data

Representative Quotes	**Topics**
my daily life is herding (Int 1)	**Local residents' lifestyle**
happiness is the most important (Int 2)	
I am currently working in a renewable energy equipment manufacturing company in Shanghai Shanghai Electric Wind Power Group (Int 3)	
The company produces a variety of offshore and onshore wind turbine products from 1.25MW-10MW, with more than 5,000 units installed worldwide and over 200 installed wind farms. The company has been the first in China for six consecutive years in terms of installed offshore market share, and in 2021 the company will have total assets of over 32 billion yuan, annual sales of over 20.6 billion yuan, a cumulative installed capacity of over 11 million kilowatts, and an offshore wind power market share of over 50%; onshore wind power is in the top 5 in China. (Int 3)	
Our daily life is to graze livestock, feed cattle and sheep, make fires and cook, a normal productive life. (Int 4)	
We still live in the past, we go back to our fixed home residence in winter, in summer to go to the summer pasture transitions, so as to facilitate pasture haying, forage storage for cattle and sheep in winter. There is	

nothing to like or dislike, it is such a way of life is used to..(Int 4)	
We have sheep and cows at home now, and herders basically live on these new cows and sheep, which are also our main source of livelihood. (Int 4)	
We have herdsmen raising cattle and sheep, and in recent years the Party and the country's policy is good, the price of cattle and sheep has gone up, and the life of herdsmen has also improved a lot. (Int 5)	
Now the grazing life is relatively fixed, in addition to the need for summer pasture herders, the other are more fixed life. There are very few nomadic herders anymore. I think herders still live on the grasslands, more free and spontaneous, living in their own family pastures. (Int 5)	
COVID-19 still has some influence, such as the price of livestock and forage (Int1)	
The COVID-19 has had some impact on our daily lives. For example, this year, our herdsmen could not sell livestock to collect cattle and sheep, which affected our economic sources. (Int2)	
There are some effects, such as we have to go into the city to buy household goods, need to do the nucleic acid, but still some trouble, but also can get the basic protection. (Int 4)	**Impact of pandemic**
The epidemic does not affect herders very much because if they don't go out and don't come into contact with people outside, it basically has no effect. If you go out, there may be an impact. We also have a lot of herders who have had vaccinations. (Int 5)	
"Not much is known about renewable energy, only solar energy and wind energy" (Int1)	**Opinion on renewable energy**

I think this industry is very good and I would like to join it. It is a great industry and can greatly improve the quality of life of our herdsmen (Int 1)	
It's about changing the quality of life, right? For example, having foreigners will allow herders to be able to learn more about (Int 1)	
Never thought about transformation! But we have started to use wind and solar energy! To protect our ecological environment is everyone's wish! (Int 2)	
I prefer the current grazing management! (Int 2)	
I think each industry has its own characteristics, regardless of whether it is good or bad! It is good for us to make the best of our industry. (Int 2)	
local people are particularly enthusiastic about their involvement in both equipment manufacturing and environmental energy, and some people have participated in advance and are now leading the way in some sustainable energy industries (e.g. Yili Resources Renewable Energy Company) (Int 3)	
renewable energy industry by domestic and international attention, at present, the global new round of energy revolution and science and technology revolution deep evolution, the flourishing, vigorous development of renewable energy has become a global energy transformation and climate change in a major strategic direction and consistent ambitious action (int 3)	
renewable energy industry like a variety of investment companies for profit, some of the early investment enterprises to earn pots and pans, also led to the rapid development of the industry upstream and downstream (Int 3)	
Bidding enterprises prepare bidding documents in accordance with local renewable energy conditions, set specification requirements, and entrust	

qualified bidding companies to publish bidding documents on the bidding network, and invite industry experts to review and evaluate bidding documents to achieve fairness and openness. (Int 3)	
Our current income is OK, we can have some savings in addition to meeting our daily life, and we are all satisfied with it. (Int 4)	
I don't know. Aren't Huaneng and Luneng owned by the state? (Int 4)	
"Nowadays, the quality of life of herders is improving rapidly, the price of cattle and sheep is better, and it is not difficult to sell them, so thanks to the preferential policies given by the Party and the government to herders, it is still not difficult to get rich as long as you work hard and are willing to work in the pastoral areas." (Int 5)	
No. All the ones I know are big state-owned enterprises doing it. (Int 5)	
Now the herders' life is better, besides animal husbandry there are also those who do live-streaming and family tourism, also to revitalize the economy, which is good. (Int 5)	
Many of our herders are directly pulling electricity through the power grid. There are very few herders with remote homes using solar electricity, it is also very convenient, with electricity some production and life can be used, the quality of life of herders is now much better. (Int 5)	
"It's about changing the quality of life, right? For example, having foreigners will allow herders to be able to learn more about" (Int 1)	**Opinion on foreign technology use in sustainable energy industry**
I really don't know. Can't we do it ourselves? (Int 2)	
The proportion of non-fossil energy in primary energy consumption reaches about 20%, the proportion of installed renewable energy exceeds 50%, and the proportion of total renewable energy power generation in total power generation exceeds 35%. The continuous development of the renewable energy industry has led to the employment of a large number of	

local people and a continuous increase in income. (Int 3)	
The participation rate of local or foreign scientists in the industry is very high (Int 3)	
Haven't thought about it (Int 4)	
I don't understand this one, maybe it's to seize the resources. (Int 4)	
The opening of the country has brought outside economy and information technology, as well as development and investment, but I still hope that Chinese people themselves can use their own technology to engage in energy production in this country. (Int 5)	

Discussion

Unlike Mongolia, Inner Mongolia has many advantages in developing renewable energy. Unlike the extreme weather in Mongolia, IMAR's weather is slightly more suitable for the development of renewable energy. All technologies in Mongolia are not mature enough. Although IMAR technology has developed relatively mature, it still quotes foreign technologies and is still immature for offshore wind power technology with potential good development opportunities. Although IMAR has made remarkable achievements in the wind industry, it is obvious that the government has not given enough consideration to the local people in the conversion from coal burning to renewable energy power generation, ignoring the negative impact on the animal husbandry that the local people have been living in. The goals of renewable energy development in Mongolia and Inner Mongolia are the same. The goal is to reduce environmental pollution and increase the local economy.

For Mongolia, the main strategy is financial support from other institutions and countries. The strategy for the development of renewable energy in Inner Mongolia is to increase the flexibility of loans, attract more investment from individuals and enterprises, reduce relevant taxes, and issue more relevant poverty alleviation policies. It is obvious that IMAR has more complete specific plans and strategies, and the stability of the energy market can support them to complete their plans step by step. More importantly, IMAR has not only made achievements in the development of the wind industry, but also did not neglect the development of solar power.

Therefore, they can have more choices than Mongolia. The local people of IMAR mainly use the hybrid system to generate electricity, because the cost of using these two technologies alone will be high and unstable. The hybrid system allows local people to use more and more.

The bad weather in Mongolia and the low quality of roads lead to the inability to import better turbines. IMAR should strengthen the infrastructure in the region to prevent the facilities and technologies in urgent need from being unable to be imported in the future. One of Mongolia's efforts in renewable energy development is to increase the country's share in the renewable energy sector, so as to devote more attention and support to renewable energy development. IMAR can follow this strategy and offer more support to the government in this regard to attract more talents and resources. After all, environmental issues are now the main trend in every country, and the government will vigorously support the development of renewable energy. Even if Mongolia has abundant renewable energy resources, its energy market and management system are not perfect: unstable prices, unstable supply, and inability to fully explore renewable energy all lead to the slow development of Mongolia's renewable energy. IMAR can learn to strengthen infrastructure just in case, and the government needs to introduce more regulations on the energy market to ensure the stable development and management of the market.

When I interviewed a local renewable energy worker, he gave me a very professional attitude and constantly provided me with specific data to show why IMAR has enough advantages to develop renewable energy and the advantages of government policies. What makes me puzzled is why this interviewer in renewable energy development said that many local IMAR people are happy to participate in this industry, while these interviewers in rural areas expressed no interest in this industry. I think that people in IMAR cities can not only access all kinds of information, but also really feel the stimulation of different lives. Compared with those herdsmen who have always lived on the rural grassland, it is hard to access rich sources of information. They have spent most of their lives on the grassland and living with animals, and have developed a sense of static curiosity and novelty about emerging things. Compared with previous studies, the current strategy of IMAR is indeed making progress and taking useful solutions. Source 3 mainly studies how IMAR collects useful information on past mistakes and successful cases in developing the renewable energy industry in western countries. First of all, source 3 shows that in the past, Western countries began to focus on the development of renewable energy to reduce

pollution caused by the use of fossil fuels, and provided IMAR with specific clean coal programs. IMAR's current goal in the renewable energy industry is also to reduce the pollution caused by IMAR's excessive burning of fossil fuels in the past. Secondly, source3 mentioned that western countries attach great importance to the development of renewable energy for transportation and daily activities in communities and campuses. To be specific, Western countries emphasize improving the renewability of infrastructure, such as improving the renewable energy system of buildings in communities, increasing renewable energy related education, and developing renewable hybrid system technology. Similarly, in many reports, IMAR has found problems with power transmission, heating and technology introduction due to the inconvenience of current infrastructure. IMAR has conceived solutions to these problems, such as introducing more investment in heating systems and local infrastructure to develop the renewable energy industry. More importantly, Western countries experienced a lot of capital shortage in the past, mainly because they did not commercialize the renewable energy industry more. Using this problem as a reference, IMAR is still a government dominated industry, so it still needs to increase more national shares in renewable energy development, to let more private companies join in this industry, to develop more advanced technologies to improve energy conversion rate, to strengthen the local economy of IMAR, and to reduce environmental problems caused by coal burning.

Conclusion

IMAR has a great prospect in renewable energy development. Environmental issues are of concern to everyone. The government's attention to this emerging industry has also reached an unprecedented level. However, although the renewable energy industry has indeed had a great impact on the local economy, for example, the interviewer working in the energy company said that the early investment in the wind energy industry can reap considerable returns in the later period, the local rural people have not been greatly affected except for the preferential policies for poverty alleviation, and they still rely on animal husbandry to survive as before. Maybe IMAR needs to let people in rural areas provide more resources on education and infrastructure, so that they can have more sources to receive various information to broaden their mind.

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Literary Techniques in *Great Expectations* And Connections With Pip's Personal Development by Yizhou Zhang

Abstract

Great Expectations was one of Charles Dickens's most successful works during his career, and it remains a masterpiece today. It is well-written, readable, and of enduring social relevance. In this Bildungsroman, the mature Pip recounts his development through a youth in which he attempted to fulfill ambitions of becoming a gentleman, before he ultimately learns to value others with less emphasis on social class and wealth. The themes of social class, personal ambition, and morality that mark Pip's life are just as relevant today. Consequently, this paper explores those themes and their connection with Pip's development by analyzing three main literary techniques that Dickens used in *Great Expectations*: point of view, mood, and personification.

Great Expectations was published serially from 1860 to 1861 in a weekly periodical called *All the Year Round* created by Charles Dickens himself ("Great Expectations"). His goals at the time were mostly financial, as he wrote the novel to revive his periodical from its failing state. Not only did this motivate his writing of the novel, but his childhood experiences during the First Industrial Revolution further compelled him to focus on themes of wealth, social class, and criminality. In this paper, I show how Dickens used point of view, mood, and personification to examine these themes in connection with Pip's development as a character.

First, though, it is important to briefly discuss the context of the First Industrial Revolution which heavily influenced the writing of this novel. During that time, the job opportunities created by factories, which were established in order to manufacture a large number of goods, attracted many to urban areas of England. However, instead of leading to widespread wealth, poverty increased due to the low pay of the working class (White). With the rise of poverty came an increase in debt, and although legal acts were created to imprison those in debt, that was insufficient for managing the spread of poverty. This was a personal matter for Dickens, as his father "was imprisoned for debt in Marshalsea and he himself (age 12) worked in a blacking warehouse" ("Dickens, Charles"). It is against this biographical background that themes of prison, wealth, and social class commonly appear in Dickens's novels. The plot of *Great Expectations*, in particular, centers around Pip migrating to London in pursuit of his own

ambitions to become a gentleman before gaining a more mature appreciation for the character qualities that exceed social class or wealth.

Within that context, Dickens wrote *Great Expectations* as a Bildungsroman that tells the story of Pip's development as he matures, while chasing after so-called "great expectations". Dickens used the first-person perspective to tell this story of a protagonist whose future self is also the narrator. According to Fred W. Boege, in "Point of View in Dickens", "[Pip's] own account of his changes of character is finer than anything Dickens ever achieved through the use of third person" (93). This magnificent story starts in a graveyard where Pip is persuaded to aid an escaped convict, Magwitch. We soon learn that at home Pip is constantly made fun of by everyone around him, except for Joe, who is his sister's husband. One day, he is invited to the home of a mysterious, wealthy woman, Miss Havisham. During that visit, he meets and falls in love with a girl named Estella, who also insults him repeatedly by calling him a "common labouring boy", which inspires Pip's great expectations (51). Eventually, he receives a mysterious fortune allocated for his refinement into a gentleman, which Pip eagerly accepts, assuming it to be from Miss Havisham. He travels to London to pursue his ambitions and spends money recklessly until the ex-convict Magwitch arrives and reveals that he is the source of Pip's fortune. Pip is disgusted that his money has come from a criminal, and this realization is pivotal to his personal development.

Having established the centrality of Pip's development to the novel, this paper will now examine one of the major literary techniques Dickens used: point of view, specifically the fluctuations between the points of view of the narrator Pip and the main-character Pip. This technique is neatly explained in an essay by Robert B. Partlow, where he compares the relationship between the "I-as-I-am-now" and the "I-as-I-was" in *Great Expectations* (124, 126). Partlow states that the narrator, "Unlike the Pip of all except the last two chapters, is a mature man, sober, industrious, saddened, aware of his own limitations, and possessed of a certain calm wisdom…" (123). I will show how Dickens highlights the differences between the perspective of the younger Pip and the older Pip (the narrator) by analyzing their perspectives separately in a scene where both are present.

For example, when the younger Pip is apprenticed at the forge after his regular visits to Miss Havisham have ended, Dickens provides a contrast between his values and those of the narrator. He does this by first describing the younger Pip's changing views of Joe and the forge.

Although Pip had originally thought of the forge as a highly-esteemed place, his visits to Miss Havisham have made him think of it as dusty and common. Here is how that change is conveyed: "Joe had sanctified [the forge], and I had believed in it… I had believed in the forge as the glowing road to manhood and independence. Within a single year, all this was changed. Now it was all coarse and common, and I would not have had Miss Havisham and Estella see it on any account" (86). This quote describes a change in Pip's values and ambitions, as he used to imagine that "manhood and independence" were gained through the forge, but now seeks to become less common by leaving the forge behind.

A tension emerges, however, as the narrator continues to hold Joe in high regard, giving him credit for a positive impact on the younger Pip. As the narrator states, "It is not possible to know how far the influence of any amiable honest-hearted duty-doing man flies out into the world; but … I know right well that any good that intermixed itself with my apprenticeship came of plain contented Joe, and not of restlessly aspiring discontented me" (87). The narrator's much higher view of Joe demonstrates what the scholar Partlow calls "psychological distance", where "the narrator does not feel identified with Pip" and instead judges him "from an adult position, with a sophistication impossible for a seven-year-old boy" (124). For, while both Pip at the time and the narrator describe Joe as "common" or "plain", the former sees this as a negative attribute while the narrator praises "plain contented" Joe in very high terms–as "amiable", "honest-hearted", and "duty-doing". As a result, this scene reflects the full-range of Pip's changing perspective on Joe, from first being a model of "manhood and independence" to then becoming an embarrassment to finally being an admirable person of good character and good influence.

The second main literary technique this paper examines is Dickens's manipulation of mood in relation to Pip's personal development through the foreshadowing of critical events and emphasis on the guilt that Pip feels. One of the main reasons that Pip finally turns his back on the fortune that was given to him is that he feels complicit with its criminal source. This sense of criminal complicity, however, has already been shown in Pip's reaction to the assault on Mrs. Joe through the mood. There is a remarkably gloomy mood before Pip and his relatives find out that someone has critically injured Mrs. Joe. The setting is described with the words, "It was very dark, very wet, very muddy, and so we splashed along. Now and then the signal cannon broke upon us again, and again rolled sulkily along the course of the river" (95). An ominous mood is

created by the use of words such as “dark”, “wet”, “muddy”, and “sulkily” and the signal cannons foreshadow the occurrence of an event that relates to escaped convicts, the attack on Mrs. Joe. As the leg iron used to injure Mrs. Joe is from the convict that Pip had saved years prior, he develops a strong sense of guilt. Indeed, Julian Moynahan’s analysis of the connection between Pip and Orlick states, “Orlick strikes the blow, but Pip feels, with some justification, that he supplied the assault weapon” (657).

Pip’s sense of guilt, of complicity, in association with this incident, is emphasized even further when Orlick accuses Pip of being the real murderer of Mrs. Joe. Moynahan highlights the dark mood of that scene too, saying: “The entire scene has a nightmare quality. This is at least partly due to the weird reversal of roles, by which the innocent figure is made the accused and the guilty one the accuser” (658). What gives this accusation its “nightmare quality” is the developing sense of complicity that Pip experiences. As mentioned above, he knows that he had supplied the blacksmith’s file to a convict several years prior, which is why a leg iron was left in the marshes, and that leg iron was the weapon used on Mrs. Joe. But more than that, Pip also wanted to be free of Mrs. Joe. There is a wider, albeit indirect, resonance with the complicity Pip finally feels in his transformational realization that the fortune he was given is from the same criminal he helped on the marshes: Magwitch.

Dickens portrays the dramatic change in Pip’s development not only through his use of first person perspective and mood, but also through personification, which is the final literary technique that I will examine. Personification, or what Dorothy Van Ghent calls the “pathetic fallacy (the projection of human impulses and feeling upon the nonhuman)”, is used to magnify Pip’s own emotions (651). For instance, when Pip goes to bring food and a blacksmith’s file to Magwitch in the marshes, he feels that “the gates and dykes and banks came bursting at me through the mist as if they cried as plainly as could be, ‘A boy with Somebody-else’s pork pie! Stop him!’” (19). In this example, the environment around Pip seems to magnify his feelings of guilt. Even positive feelings get magnified through personification. When Pip receives his fortune, Dickens again uses personification to express his feelings of pride. Pip’s pride is reflected even in “these grazing cattle” who “seemed, in their dull manner, to wear a more respectful air now, and to face round, in order that they might stare as long as possible at the possessor of such great expectations” (115). Notably, though, Dickens’s description here lightly lampoons Pip’s pride (how ridiculous to think that cows would gain a “more respectful air”

before this “possessor of such great expectations”), perhaps reflecting the narrator’s own more humble perspective, after becoming jaded by the source of his wealth.

Now there also is a potential counterpoint to my reading of Pip’s moral development, because his disdain for Magwitch may demonstrate a similarity with a characteristic that George Orwell described as Dickens’s “I’ve always kept myself respectable habit of mind” (642). Orwell claimed that Dickens had a form of moral snobbishness that limited his insights into his criminal characters. This description of Dickens bears some connection to the way that Pip is finally compelled to separate himself from Magwitch and his gift of wealth. So, I must admit that it is possible to read this not only as a tale of moral development but also as Pip’s attempt to forget his own criminal actions as a child and to keep away from the source of his later actions.

To conclude, by better understanding three main literary techniques that Dickens used – switching between points of view, changing and emphasizing the mood, and personification – we can see how he shows these themes in the novel and their connection with Pip’s character development. One way I demonstrated this was by showing how Dickens changes perspective between the narrator-Pip-from-the-future and the Pip-in-the-story to show the protagonist’s development through the changes in how he perceives Joe and the forge. Dickens’s literary accomplishments shine through these techniques, as they effectively connect the themes of the book, which are still seen in society today. Especially as the global income gap has grown significantly over the past several years, the theme of social class and money becomes increasingly relevant to our everyday lives.

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Assess the Relative Importance of the Enlightenment as a Cause of the French Revolution

By Zixuan Li

The Enlightenment was an intellectual movement initiated by philosophers during the late 17th and 18th centuries that challenged traditional ways of thinking and inspired revolutionary ideas. The Enlightenment consisted of three phases, the early Enlightenment, the high Enlightenment, and the late Enlightenment, with the early and high Enlightenment being the cultivation of the French Revolution. The first phase is led by prominent philosophes Issac Newton, John Locke, and Thomas Hobbes, creating famous publications such as "Principia of Mathematics" and "Essay concerning Human understanding," which are essential philosophical toolkits for primary advances of the Enlightenment. The high Enlightenment features the dialogues and publications of French philosophies such as Voltaire and Rousseau. It is best summarized by Voltaire's notion in his philosophical dictionary: "a chaos of ideas." Assessing the relative importance of the Enlightenment as a cause of the French Revolution, one will believe that the Enlightenment was among one of the most crucial driving causes for overthrowing the French monarchy because although the philosophes possess different perceptions regarding religion, it spiritually destroyed a monarch's legitimacy and inspired a desire for freedom and rights.

First, the Enlightenment spiritually challenges a monarchy's authority and legitimacy. The French monarch's power is based on the idea of divine will, announcing that the royal family is selected by the god and their will is god's will. Unfortunately, the Enlightenment stressed reason and progress over faith and tradition. For instance, during the period of high Enlightenment, Rousseau proposed the idea of the general will, the will of the citizens, as the most desirable society in opposition to the divine will. The third estate's members soon acknowledged these propositions and felt the status quo was oppressive and unfair. This outrage and unwillingness to be tormented were represented in a political cartoon drawn in the 1780s illustrating the first and second estates trampling on top of a third estate peasant. Furthermore, a regime's authority is based on physical and spiritual characteristics. However, in these two factors, losing a spiritual component is always a driving factor of a physical loss because the rebels need a reason to oppose the king in the first place. In this case, the spiritual revolution is the Enlightenment, as it emancipates the third estate from the idea of the divine will. Therefore, the Enlightenment serves

as the base for the latter advancement of the revolution, such as the storming of the Bastille, making it the most vital cause of the French Revolution.

Moreover, the Enlightenment introduced a desire for freedom and the right to the third estate. John Locke, arguably the leader of the early Enlightenment, proposed that humans have inalienable rights by virtue and that the relationship between the government and citizens is only mutual responsibility. He later published his famous piece "Two Treatises of Government" to defend a theory of political government based on the nature of individual rights and freedom and the consent of governed. In addition, Voltaire, the leader of the high Enlightenment, announced and idealized the English constitutional monarchy in his philosophical dictionary published in 1764, as stated in "The English Model," "The English constitution has, in fact, arrived at that point of excellence, in consequence of which all men are restored to those natural rights, which, in nearly all monarchies, they are deprived of" (Voltaire). For the third estate, which was constituted mainly of peasants, these insights for a more responsible government and social system created an extreme desire for change. Their motivation is clearly stated in the below quote, "Historians have estimated that in lean years 90 percent of the peasants lived at or below the subsistence level, earning only enough to feed their families" (Social Causes of the Revolution). In other words, over 90% of the farmers, 75% of the overall population of France, suffer below the poverty line. These inspirations and longings lasted until the beginning of the French Revolution, as proven by the tennis court oath and the 1789 "Declaration of the Rights of Man and of the Citizen" adopted by the National Assembly, stating that "Men are born and remain free and equal in rights, Social distinctions may be founded only upon the general good" and "The aim for all political association is the preservation of the natural and imprescriptible rights of man. These rights are liberty, property, security, and resistance to oppression" (France. National Constituent Assembly) Similar to philosophers' ideology, the National Assembly emphasized the revolution on the rights and freedom of men in these assertions, therefore demonstrating the long-lasting thirst for liberty and right in the third estate after being enlightened by the philosophes.

In conclusion, despite owning different perspectives on religion, the philosophers and their enlightenment ideas are a vital foundation of the French Revolution because they eradicated the spiritual dominion of the monarch and passed a thirst for liberty and rights.

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The Most Significant Cause of the French Revolution By Zixuan Li

The French Revolution was a period of radical political and societal turmoil in France that was initiated with the calling of the Estates General in 1789 and ended with Napoleon's repeal of the directory in 1799. Although it only lasted about a decade, the causes of the revolution began cultivating their seeds centuries before the actual commencement. The four major causes of the French Revolution are the Enlightenment, the financial crisis, the bread riot, and the status quo. Out of all, the status quo is the most detrimental aspect of Louis's regime because it sets the foundation for other causes.

First, the Enlightenment inspired ordinary third-estate members to fight for their freedom and rights despite tradition and religion. The Enlightenment was initiated and continued by 16th to 18th-century French philosophers who stressed reasoning and progress over superstition and faith. Unfortunately, this commonly spread ideology collided with the thesis of a monarch's legitimacy to rule, the idea of the divine will; thereby, the philosophes and those who enlightened viewed the monarchy of France as a burden to human rights and freedoms. Through the ideologies initiated through the Enlightenment, the philosophes planted a sensation of revolution inside the ordinary members of the third estate.

Second, France's financial crisis resulting from the status quo ignited the third estate's revolutionary thoughts and brought the revolution to a commencement. Similar to the Enlightenment, France's financial crisis has been brewing for an extended period. The origin of the crisis came from centuries of ambitious foreign policy efforts that only received mediocre responses. Near the decade of the French Revolution, Britain and France newly initiated the Seven Years War to compete for global supremacy, which resulted in a defeat in France by the Royal Navy. Fortunately, France's leading trade and economic support were not interrupted by this loss, as France continued to maintain their profitable Caribbean colonies. However, the effects of the Seven Years War on France were far more ambiguous and emotional than financial losses. Before 1763, the French armies had been the global standards many countries aspired to possess. Now, after the defeat, the army of Prussia succeeded France's reputation and became the international standard. Infuriated by this disgrace, the French Foreign Minister Charles Gravier began searching for opportunities to regain French prestige while damaging British global hegemony. He eventually settled his attention on the American Revolution. The only problem

that remained was, by 1764, military service consumed over 60% of the annual budget. To bolster the involvement in the American.

Revolution war, the members of the third estate, who are already at the edge of erupting, must take on new overwhelming taxes. To resolve this discontent, the king soon called the Estate General to hold a poll, and unfortunately, the sentiments burst due to unjustified treatment during it. Therefore, France's financial crisis single-handedly led to the calling of the Estate General and the establishment of the National assembly subsequently.

Moreover, the bread riot, another motivation for the French revolution, left citizens who suffered in poverty with no choice but to seek reform in the government. France suffered from a long last epidemic and food shortages from drought between 1600 to 1700. Reaching the 18th century, food prices had only worsened, as the economists appointed by the king believed that the improvement of the nation's wealth relied solely on highly-priced agricultural products. Later on, the food shortages became acute in the 1780's decade since the French population had already risen significantly without a correspondence in the increase of agricultural production. As we all know, the price of a product is directly proportional to its demand. This caused an intense elevation of food prices that directed to the horrifying fact that the average household in France spent about 60-80% of their annual income on food. This formidable expense and the famous quote from Maris Antoinette led to the growing popularity of revolutionary beliefs. Ultimately, the beginning of the French Revolution, the storming of the Bastille, commenced due to this outrage created by the bread riot, therefore placing the bread riot as a significant cause for the revolution.

Last but certainly not least is the status quo, which one could regard as the most significant cause of the French Revolution as it sets the foundation for generating other factors. The status quo refers to the estate system in France's monarchy. First, above all of the estates is the French monarch. He is absolute. His power came from the idea of the divine will, which means that god conferred his legitimacy and will. The first estate is the clergies, who constitute only one percent of the population. As an institution, the Catholic Church controls 1/10 of the land in France. These clergies also have the right to collect tax on agricultural products by individual or organization. The Second estate is approximately 300,000 to 400,000 Nobels. They enjoy many privileges, with the most outraging and famous one called taille, the exemption of tax. Below them is the third estate, constituted by up to 98% of the population in France,

including peasants, bankers, lawyers, bureaucrats, journalists and much more. They are subject to all taxes, such as property tax (capitation), military service tax (banalities), and much more.

One could justify this imbalance distribution of power and economics as the fundamental cause of the French Revolution because it is the foundation of many other factors. The status quo creates an undermining feature of the French regime - all of the capital and assets are owned and wasted luxuriously by the Nobels and clergies. At the same time, the government of France suffers from immense debt. In addition, the wealthy bourgeoisie has the opportunity to ennoble themselves, dodging taxation from the government. This is why a country as wealthy and elegant as France might receive unaffordable bills, directing to the financial crisis and the bread riots. Furthermore, the third estate had long endured this imbalance distribution of privileges and power, and this unwillingness to continue enduring had been represented by the brewing of enlightenment ideas and the calling of the Estate General, where the three estates' representatives gathered to discuss establishing new taxes. Using the vote ratio of 2: 1, the king successfully legislated this new tax. However, the two votes came from the estates that do not necessarily need to pay this tax. Infuriated by this lack of voice from the status quo, the third estate decided to initiate the National Assembly, which abolished the monarchy and began the French Revolution.

In conclusion, the Enlightenment, the financial crisis, the bread riot, and the status quo deserved the title as the four most prominent causes of the French Revolution because, as mentioned above, they each served as an essential aspect of the initiation process. As a result of this cooperation, the French Revolution has been inevitable since the establishment of the French monarchy because the status quo had already created a foundation for the brewing of three other destructive causes, therefore also positioning the status quo as the most crucial motivation for the French Revolution.

A Bloody Crescendo: The Usage of Chemical Weapons in Syria By Meghan Derby

In 2012, President Barack Obama stated that the usage of chemical weapons by the Syrian government would constitute a "red line" triggering international retaliation, a line which has since been drawn in blood (The White House). The development of the Syrian chemical weapon program emerged as a global security threat throughout the 1970s. As political tensions escalated amid the Cold War, Syria was motivated to enter the arms race and secure its position as a chemical threat. Despite international pressure to cease weapon production, the program has continued to advance, while Syria's diplomatic hostility has created regional insecurities and instability within the nation. In 2011, pro-democracy protests started to threaten the authoritarian regime of President Bashar al-Assad, who subsequently utilized excessive violence and political suppression to control civilian insurgencies. Internal opposition to the regime rose, and the political conflict had escalated into a full-scale civil war by 2012. Despite Syrian commitment to the Chemical Weapons Convention (CWC) in 2013, affirming that their chemical weapon stockpile would not be utilized, the government has recurrently weaponized its arsenal against insurgents and innocent civilians to devastating effect. The usage of chemical weapons has exacerbated socio-political instability in Syria because their indiscriminate and ineffectual use has prevented a logical resolution to the civil war.

Chemical weaponry has perpetuated the Syrian civil war because its usage has worsened regional tensions and incentivized military retaliation without eliminating the nation's internal or external threats. The Assad regime's primary security concerns are centered regionally, focusing on those they have had historical animosity with or that threaten their sovereignty. Syria has not developed nuclear capability; however, they have manufactured an extensive chemical weapon stockpile, including long-range missiles that pose the threat of striking foreign territory (Schneider 6). The production of this weaponry has frightened regional actors, as it indicates that Syria could be motivated to preemptively strike them. In the Syrian civil war, the Assad regime has utilized its chemical weapons against rebel forces to attempt to secure a military advantage, modeling Iraq and Saddam Hussein's example of aggressively using their chemical arsenal to remain in power ("Use of Chemical Weapons"). The weaponization of chemical agents against the rebels has not been effective, as these attacks are indiscriminate and damaging but not strategic. These resistance organizations have not been eliminated by chemical warfare, but

merely disoriented, which has just intensified their aggression directed at the government. Because chemical weapons have only exacerbated tensions, fierce resistance has continued, preventing negotiations. These chemical attacks have also drawn foreign attention to Syrian military operations. The proliferation of these weapons threatens other nations in the region such as Israel, who continue to resist Syrian encroachment into territories such as the Golan Heights. Israel and Syria have participated in peace negotiations; however, the Assad regime continues to utilize its chemical weapons arsenal to destabilize Israeli security and regional influence. This has motivated Israel to intervene in the transfer of Syrian chemical weapons through strategic airstrikes (Steinberg 96). Despite prior productive relations such as their negotiation of the common usage of the Euphrates River, Turkey also currently recognizes Syria as a regional security concern. The threat of Syrian chemical force in the region has motivated Turkey to back anti-government resistance movements throughout the Syrian war (Diab 107). Both of these nations have provided military aid to the insurgents, increasing the strength of resistance against the regime. This has provoked the government to retaliate with even greater force. Even regional allies to Syria such as Iran have condemned the use of chemical weapons; demonstrating intent to take retributive action against the regime. Iran has backed the Assad government throughout the civil war. However, millions of Iranians were exposed to chemical agents in the Iran-Iraq conflict, causing mass destruction and killing thousands, which created a national revulsion against chemical weaponry. Chemical weapon usage has created political tensions with Iran, which has indicated its intent to cease military support to the Assad regime. Iranian officials have encouraged the international community not to hesitate in the elimination of chemical weapons in Syria (Adams 5). Iran shifting its position on the regime would influence Syrian military operations, as they would lose the Iranian military support they currently receive to defend against anti-government resistance. In an interview, former Iranian representative to the United Nations Mohammad Javad Zarif asserted Iran's opposition to Syrian chemical weapon usage:

> We won't stay quiet, but the United States cannot say that they have a red line. We have rejected the use of chemical weapons, regardless of the victims or culprits, regardless of the victims or perpetrators. We have said that there has to be an international on-site investigation, who used the chemical weapons, how they were used, whether they were used, and there has to be an international reaction. (Zarif 1:10-35)

This demonstrates that the weaponization of chemical agents in Syria has directly triggered responses by regional entities, forcing their entrance into the conflict. Foreign military intervention has taken the conflict to a greater scale. The introduction of foreign combatants and artillery has perpetuated the war because it has reinforced resistance movements, obligating the Syrian regime to reciprocate. Without Iranian assistance and threatened by the operations of other nations, the Assad regime has become more vulnerable, causing them to increase their use of force as a defense mechanism to maintain their authority. With conflict escalating, the civil war has approached no resolution, demonstrating that the usage of chemical weapons has been counterproductive to mitigate regional tensions.

The use of chemical weapons has also worsened the current state of social instability because it has intensified the humanitarian crisis, aggravating resistance against the government which has prevented conflict resolution. Chemical weapons, a key facet of the Syrian military arsenal, have been utilized by the regime throughout the civil war to retaliate against resistance forces. However, in comparison to the strategic use of rifles or artillery, chemical agents are entirely indiscriminate, therefore, attacks have devastated civilian communities on a large scale to affect rebel militants only minimally. Studies have identified 336 incidents of chemical weapon usage in Syria from December 2012 to April 2018 (Lütkefend and Schneider 3). Estimates suggest that 1,742 victims have been killed and 9,989 have been critically injured in documented chemical weapons attacks against innocent civilians. 98% of these incidents were perpetrated by the Syrian government or associated parties (Koblentz 4). These attacks are physically and psychologically devastating, decimating communities throughout Syria. Moaed Dumane, an opponent of the regime that survived a 2018 chemical attack in Douma, a suburb of Damascus, retold his account:

> On Saturday, heavy shelling and airstrikes started in Douma, targeting everything that was moving. I was with my family and the neighbors in the shelters. The Assad regime was attacking us. Several barrel bombs fell from a helicopter, and then there was a strong, strange smell. We, my friends and I, who document atrocities, couldn't move closer to the area because of continued shelling. After the bombardment subsided, we went to check out where the barrel bombs fell, then we saw a lot of families in their homes who couldn't escape. (qtd. in Nawa)

This attack demonstrates the mass destruction caused by chemical weapons, the regime using indiscriminate violence to force rebel militants out of these locations while brutalizing civilians in the process. These short-term strategic victories have had long-term impacts on the Syrian population. The health consequences of chemical weapons that have been witnessed in Syria are devastating, causing mass suffering throughout affected communities. Nerve agents such as venomous agent X(VX) or sarin impact the nervous system, causing muscle paralysis, salivation, seizures, or neurological issues (Brooks, J., Erickson, T.B., Kayden, S. *et al.*). Chlorine, another chemical agent used by the Syrian government, affects the respiratory system, causing chronic lung conditions, nausea, abdominal and chest pain, corneal burns, or respiratory failure (Elsafti Elsaeidy, Abdallah M et al.). These indiscriminate attacks have exacerbated the humanitarian crisis in Syria, causing prolonged destruction to the civilian population without substantially reducing insurgence against the regime. After chemical strikes, rebels can reposition themselves, while communities affected by the attack are left devastated, their livelihoods reduced to rubble. This has created a refugee crisis, as citizens must relocate to other regions of the country. The less affected parts of Syria have become overpopulated, causing resource scarcity, disease transmission, and social instability (Lütkefend and Schneider 30). The crisis of chemical weapon usage has prevented a resolution to the conflict because it has worsened internal tensions between the government and the citizens. The indiscriminate nature of chemical weapons is what causes them to be so brutal and inhumane, however, it is also what causes them to be such an ineffectual method of warfare. Their usage is not strategic as it brutalizes innocent civilians without effectively eliminating insurgents. This has created a humanitarian catastrophe, worsening the current socio-political situation and mobilizing further resistance against the hostile regime. Chemical weaponry has therefore exacerbated social instability in Syria, intensifying insurgence against the government and prohibiting de-escalation of the civil war.

Chemical weapons have perpetuated economic strife in Syria because they have imposed significant infrastructural costs and mandated debilitating intervention from international entities; intensifying the tensions that have inhibited peace negotiations. The Syrian government has utilized chemical agents to target locations critical to the nation's economic infrastructure with the objective of forcing enemy combatants to abandon them. They have attacked fuel storage sites, transport centers, sewage systems, water, and power systems with chemical

missiles not to annihilate militants, but to obstruct their logistical operations (Diab 110). These attacks, while strategically effective, have caused significant economic impacts, damaging the operations of these necessary infrastructure systems. These strikes have exacerbated the current water, fuel, transportation, and electricity crises, continuing to destabilize the Syrian economy without eliminating the threat posed by insurgents. These indiscriminate chemical attacks are recognized as violations of the CWC and therefore have forced the international community to pay attention. In February 2017, Russia and China vetoed a draft resolution sponsored by France, Britain, and the United States to institute UN-enforced sanctions on Syrian government operations. The rationale for their opposition was that they determined this measure could negatively affect the upcoming peace negotiations between Syrian political parties. This action, as the representatives from Russia and China assert, would aggravate the current situation but not effectively pressure the Syrian government (Chauhan). The hesitancy of Russia and China to impose sanctions, despite evident violations of international law in Syria, indicates the direct consequences these measures could cause to negotiations. Sanctions intentionally destabilize a nation economically, and this method of coercion can create more animosity between opposed factions without substantially threatening the aggressor. Despite this, state actors such as the United States have instituted measures themselves. The U.S. Caesar sanctions, instituted in 2020, penalized 39 separate Syrian entities. These measures can be renewed after 5 years or lifted if the Syrian government ceases targeting civilians with chemical or conventional weapons, prosecutes war criminals, liberates political prisoners, and undertakes other initiatives to resolve the humanitarian crisis (Yacoubian). These sanctions theoretically pressure those in control of military operations and chemical weapon distribution in Syria to protect the civilian population, however, they can have the opposite effect. U.S. and E.U. sanctions imposed to penalize the Syrian government and political elite have continued to have adverse consequences on civilians. The intended targets of these economic measures have been unaffected or even profited off wealth scarcity, however, these sanctions have damaged the Syrian economy and therefore the civilians, as now more than 80% of the population lives in poverty (“U.S. Sanctions”). Sanctions reduce commercial trade and increase inflation, causing a declining national income that has negatively affected civilians. However, these penalties have neither destabilized the Syrian enough to be overthrown nor pressured them to end their brutal and illegitimate operations. Therefore, insurgents have maintained their resistance. The government continues to retaliate

against the citizenry, which has prevented the Syrian war from approaching a resolution. Sanctions instituted on the government, as well as critical industries such as aviation, construction, energy, and the military have harmed reconstruction efforts and disincentivized Gulf or European companies from engaging in infrastructure development (Yacoubian). Punitive economic measures have contributed to the blockage of rehabilitative and infrastructural development services. Measures such as the Caesar Act have regulated technological resources and negatively impacted the operations of international NGOs providing economic aid (Alalwani and Shaar). Deficits to key sectors of the Syrian economy have minimally affected the hostile regime but devastated the civilian population that is dependent on profits from these industries to survive. Restriction of external support has perpetuated economic strife throughout the nation, as the war has decimated communities and infrastructure systems, but no aid has come to rebuild. Syria has been damaged economically by the direct infrastructural damage of chemical attacks, and the crisis has only intensified as the international community penalizes their industries with punitive sanctions. The crisis has caused anti-government resistance to surge and the regime to retaliate, escalating the tensions that currently inhibit negotiations. Therefore, the usage of chemical weaponry has contributed to a worsening economic situation, preventing the resolution of conflict in Syria.

The conflict in Syria has become a prolonged, devastating civil war, exacerbated by the indiscriminate usage of chemical weapons. The weaponization of these chemical agents has intensified political tensions and escalated resistance against the regime. Chemical attacks orchestrated by the government have also worsened the current humanitarian crisis and economic strife in Syria, creating instability that has prohibited conflict resolution. Chemical weapons have been neither the only nor the principal vector of mass destruction in the Syrian war. However, their weaponization against both combatants and civilians has been strategically ineffectual, independently exacerbating the already severe socio-political situation. The conflict is on the precipice, and the elimination of chemical weapons in Syria could be a critical first step toward disarmament in the region. Chemical weapon proliferation poses a grave threat to global security. However, this situation also provides a promising opportunity: an opportunity from which the international community can set a precedent to eliminate chemical weapons on a greater scale, prioritizing cooperation in the interest of a more safe and secure future.

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The Evolution Of Reinforcement Learning in Board Games By John Hu

Abstract

Board games such as chess and Go test players' intelligence, reasoning ability, long term planning, and risk estimation ability. For this reason, they also serve as an ideal testing ground for artificial intelligence. While the last few years have seen tremendous growth in the scope and capabilities of reinforcement learning (RL) applications in board games, there are still many possible areas to improve the performance of RL agents in non-ideal environments, such as when acting with imperfect information. Herein, we review early developments in RL, highlight current progress in complex collaborative games, and discuss potential areas of research and benchmarks. A focus on these topics will potentially lead to insightful technical strategies and improved understanding of collaborative decision-making processes in society.

Introduction

In recent decades, artificial intelligence and specifically deep learning has been able to play board games of greater complexity. Board games are interesting testing grounds for studying artificial intelligence for three main reasons: they provide a strong heuristic for human expert intelligence; interpretable rules, and a discrete action space. Firstly, games provide useful heuristics to judge machine intelligence since many complex games cannot be solved with classical programming techniques such as a brute force search or game-specific heuristics. Variation between board games can affect other fields such as natural language understanding, vision, and more. Secondly, their relatively interpretable logic allows for direct comparison with existing strategies and board configurations to determine if the AI approaches the game with novel intuition. Finally, common turn-based board games such as chess, Go, and Shogi take place in discrete action spaces, thus avoiding complexity of continuous action spaces. Agents do not need to evaluate a distribution over a continuous action space when playing board games, rather the agent selects from a finite, discretized set of actions. In chess, for instance, a bishop can only move to unoccupied diagonal positions whereas a robotic arm can move to a continuous 3-D position. Hence, model training and evaluation is potentially less computationally expensive and more conceptually tractable than other domains such as robotics. In this review, we examine the progression of reinforcement learning in board games and propose potential environments.

Discussion

Board games share a common characteristic as they can be modelled as a sequence of decisions. A Markov Decision Process (MDP) is a framework used to model decision making; an MDP includes a set of states (state space), a set of actions (action space), transition probabilities, and a reward function. The transition probability refers to the probability of moving from one state to another given an action. MDPs are typically described as an "agent-environment" loop, where an agent chooses an action, and this action causes the state of the environment to change and emit a reward signal. The most common paradigm in machine learning is supervised learning, which uses regression or classification to predict outputs given exemplar pairs of inputs and outputs. However, supervised learning (SL) is less suited to solving board games; most supervised learning approaches do not account for the sequential nature when describing a task using an MDP; there is not a clear set of inputs and outputs to match together. Reinforcement learning (RL) uses a different approach: the goal of RL is to find some policy for selecting actions that maximize the future sum of expected reward. This quantity is called value, and it can be defined per-state. Value can be thought of as describing, for a given pattern of choosing actions, how much reward an agent will receive in the future as it visits more states in the MDP. If the true values are known, then a policy that chooses actions that leads to the highest value will be the optimal policy, i.e., the one that leads to the most reward. Indeed, if the state space is small and fully available to the experimenter, values can be found through exhaustive search or dynamic programming. Optimal values are also, under some conditions, guaranteed to be found through sampling-based methods such as Monte-Carlo methods or temporal difference (TD) Learning.

RL approaches are guaranteed to learn the true value for every state in a tabular state space. However, in large state spaces, it becomes costly to store all possible state value in a table. Deep Reinforcement learning (DRL) computes the policy or value using a neural network function approximator, and then learns by minimizing the error between its predictions and the actual reward obtained in each environment. This allows observations with high dimensionality—such as the pixels in the frames of an Atari game— to be compressed into an approximate value without needing to store the states or values themselves. A neural network with more than two layers and an activation function can approximately represent any given function, which means that deep learning has strong theoretical guarantees (Hornik 359).

Early Deep Reinforcement Learning

An early successful application of neural network-based function approximation to RL was in the game of Backgammon, a two-player dice game. Each player attempts to remove all their checkers from the board while strategically delaying the opponent's movement. Although the game involves a low-dimensional state space, it has a high branching ratio with several hundred possible states reachable per move. The conventional expert systems were unable to strongly play the game. TD Gammon (Tesuaro 58), an agent that plays Backgammon obtained superior results compared to earlier programs that relied on hand-crafted features such as Neurogammon (Tesuaro 386). It learned values through TD Learning, calculated the discounted reward added to the error between subsequent evaluations over time, multiplied by a learning rate factor at each time step. However, it obtained suboptimal results for board games with higher complexity such as Go and Chess. The game of Go is more complex than Chess in various aspects. Like chess. Go involves two players, one white, one black. At the beginning of a round of Go, the black player starts by placing a stone along the intersection lines of the grid. The white player places their stone in an unoccupied lattice point. The aim of each player is to occupy the most territory or encircle the most stones since a point is awarded for any of the above. When the stones in a group are encircled by the opposing color and if there are no more remaining adjacencies, the stones are removed from the game. Players take turns until the board is full, at which point, the player with the greatest number of points is the winner. Although the movement mechanism in Go is simpler than Chess, there are multiple reasons it is less tractable: the size of the state space, the branching coefficient, and the larger depth. A standard game of Go occupies a 19×19 board compared to the 8×8 board in chess. This leads to a combinatorial state space, the number of unique configurations, of 10174 which is many orders of magnitude greater than Chess's state space of 1044. Most importantly, the game expands from its initial state across the entire board in multiple directions, and the branching complexity of Go is 250 vs 35 for chess. The major expert systems for Go used effective search strategies to sample moves and they relied heavily on hand-crafted features to evaluate the value of each state. This is because the game is not possible to simulate given is high depth and number of possible moves. Early RL programs such as NeuroGo (Enzenberger 7) used TD learning to compute the action-value at each state, but it was highly inefficient and unable to surpass expert systems.

RL In Go

In the past decade, RL has been used to play Go at an expert level. AlphaGo, a RL model, was able to achieve state-of-the-art performance at the game of Go. AlphaGo simulates multiple games to find optimal moves; it was able to improve upon earlier models by applying deep neural networks and model-free reinforcement learning(Silver 486). AlphaGo trains separate value networks to evaluate the value for a given board configuration and policy networks to find the optimal policy. The value network approximates and evaluates the unknown value function while the policy network returns the final move probabilities. Compared with earlier models, AlphaGo used a modified version of Monte-Carlo-Tree-Search (MCTS), an efficient algorithm to sample actions. MCTS was crucial for the game of Go as it proved to be highly effective at policy evaluation and policy improvement. Principally, MCTS repeats these actions: Selection, Expansion, Simulation, and Backpropagation. At each time step, MCTS traverses the tree of possible moves and conducts a full rollout of the policy, stochastically selecting moves until the game is decided (win/loss/tie) and then propagates its estimation back up to the parent tree. After multiple rollouts of the policy, the network learns to prioritize nodes with higher value to learn an optimal policy. AlphaGo also considers the dilemma of exploration vs exploitation in RL, which can result in suboptimal policies. This is critical to board games where it is improbable that the agent can explore all possible states. Instead, it must balance the tradeoff between exploiting existing knowledge about rewards and finding unknown nodes which have greater reward. To avoid capitalizing on rewards in the short term while neglecting sparse rewards in the long term, AlphaGo uses Upper Confidence Bounds. This technique assigns lower scores to nodes which have been frequently reached, thus penalizing repeated exploitation, and rewarding exploration.

AlphaGo was initially trained using data from the games of expert Go players. When playing, it would determine the optimal policy by passing the features of the game strategy through its neural networks. AlphaGo reached 9 dan rank by defeating Lee Sedol 4-1 in a series of 5 rounds, which established the effectiveness of RL at Go. While AlphaGo was highly capable, it exclusively relied on expert knowledge. Its successor AlphaGo Zero removed expert knowledge and trained entirely from a process called self-play, where it generates random board samples and completes games with its network playing both black and white stones (Silver 354). Alpha Zero(Silver 362) relied on the visual configuration of black and white pieces on the board

and simulated different board configurations. It was able to reach superhuman performance on Go as well as chess, and Shogi. In a fraction of the training time for AlphaGo, it was able to reach a 4650 ELO rating, surpassing AlphaGo's rating of 3168 and well-known chess bots such as Stockfish's rating of 3371. Later, the next iteration of this MCTS-based agent, AlphaZero was more sample efficient, requiring less training time to reach superhuman performance in less time despite eliminating its dependency on state space symmetry.

Analyzing Go as a Benchmark

Go revolves around different strategies in the early, middle, and end game. During AlphaGo's match against Lee Sedol, it demonstrated a fundamental understanding of joseki- established opening moves - which require careful counters. Crucially, it excelled during the middle game due to its strong lookahead capabilities. The middle game is a strong marker of expertise during which players must judge whether certain regions of stones on the board are figuratively already "dead", still "alive", or merely "unsettled" (Bozulich 2). To maximize their long-term success, a player must factor the risk vs reward of preserving such regions.

Long term planning is another attribute that indicates human expertise. In this regard, AlphaGo frequently prioritized its long-term influence on the board over short-term territory gains. It repeatedly chooses to place stones on the second most outer line, despite an expert consensus to avoid this area. When stones are far from the center, they have a greater range of options to influence, link with other stones, invade and enclose territory. This shows that AlphaGo's intuition can differ from accepted consensus. During the opening moves of the second round, AlphaGo played Move 37, which placed a stone on position P10. Since the stone did not seem to offer any material advantage, commentators believed this was a novice mistake. However, as the game progressed, the position of this piece was critical to the AI's victory because it linked together two groups of AlphaGo's stones. Despite the success of AlphaGo, it is necessary to exercise caution when discussing its performance. While the MCTS architecture behind AlphaGo samples many decisions, it can still miss nodes if the parameters of Upper Confidence Bound favor exploitation. During the fourth round of the game, Sedol played a move referred to as Move 78 which was unexpected for AlphaGo as it later resigned. This instance qualitatively shows that the AI is still unable to fully solve the game of Go despite extensive training through self-play.

Lack of Perfect Information

Chess and Go are both board games where both players always have access to perfect information; all the knowledge is openly available to all participants in the game. Players do not directly gain an advantage from the information they possess and can perform perfect planning each turn. However, there are also games such as Poker where the current state is unknown, and the states are not completely observable. In this scenario, a game can be modelled with a Partially Observable Markov Decision Process (POMDP) in which an agent receives a set of observations and is required to formulate a "belief state". Furthermore, since actions occur sequentially, the dominant strategy for each player will change as the game progresses. When compared to games modelled by traditional MDPs, the optimal policy is more intractable. Work has been made in this direction through a game called Stratego, which has imperfect information, and greater game complexity, which cannot be solved by traditional rollout-based methods with MCTS or belief-state methods using POMDPs (Perolat et al. 3). Their model applied Regularized Nash Dynamics is able to converge to a Nash Equilbrium and achieve a win rate above 97%.

Cooperative Games

While many board games are purely competitive and zero-sum, there are also popular board games which involve cooperation or a mix of cooperation and competition. Examples of such games include Risk and Chinese Checkers. This poses a critical problem for classical RL which maximizes individual reward but struggles to interact in multiagent environments, known as Multiagent RL(MARL). For example, the optimal strategy for Chinese checkers is strongly solvable for two players but becomes unknown for more than three players because of the possibility for cooperation(Sturvetant 10). Furthermore, the conventional method of training through self-play may not reach the most efficient equilibrium which poses a problem for existing models (Hu 2). So, an accurate benchmark for AI intelligence should also test for the agent's ability in fully or semi-cooperative environments. The game Hanabi is an ideal choice which combines both incomplete information and collaboration. Hanabi, also known as fireworks, is a multiplayer, team-based card game where each player cannot see their own cards and must rely on their teammates to provide clues on their card color and number. The final objective of the game is to arrange 5 stacks of cards in ascending order from 1 to 5, with the

same color. Each turn, a player gives a clue to their teammate or make a guess if they believe a stack is in the correct order, to a maximum of 3 guesses. The unique communication protocol affects the way that information is passed since each player must deduce their deck based on the meaning of clues. A paper on two-player Hanabi first demonstrated that the use of model-free reinforcement learning and specifically Actor-Critic Methods was able to outperform rules-based agents but could not achieve superhuman performance (Bard et al. 14). Work on semi-cooperative games has also developed in conjunction with natural language understanding. One such game is Diplomacy, a turn-based negotiation game that requires players to send messages to potentially form alliances with each other. They showed thatthat model-free RL in conjunction with a large language model can strategically reason and optimize a policy that defeats the top 10% of human players online (Bakhtin et al. 1069).

Generalizability

It can be argued that machine intelligence should have some ability to draw on prior experience to generalize to a wider variety of situations to mirror human ability. Most RL methods for board games focus on achieving expert performance in a specific game without gaining the ability to generalize their learned knowledge towards other games with high intergame similarity. AlphaGo Zero played 29 million games just for Go and AlphaZero was able to achieve strong performance at chess, Go, and Shogi in a shorter period; however, it was trained for each game individually with over 4.9 million games, which add up to multiple lifetimes of game play. There is theoretical support that board games, mathematically modelled as MDPs, can generalize under the "Weak Proximity" condition which requires similar state-action spaces and reward functions (Malik 5). Notwithstanding generalization between games, current RL techniques struggle to effectively generalize within the same board game with modular rule variations. For example, when AlphaZero played modified versions of chess ranging from minor changes such as no castling or sideways pawn movement to major changes such as randomized piece positions in Fischer's Random Chess (McGrath et al. 3). The model was unable to generalize, requiring training for greater than 1 million training steps despite high intragame similarity. This highlights a fundamental avenue of research into the capability of RL agents which can learn implicit patterns and strategies which generalize to multiple games, while using fewer samples than present.

Conclusion

Board games have served as reliable metrics for assessing complex strategies, reasoning, and risk taking for human intelligence. The application of Reinforcement Learning to board games has seen tremendous growth recently, with the application of deep neural networks to capture policy or value functions allowing traditionally unsolvable games like chess and Go to be played at a high level. Different varieties of board games that feature imperfect information and cooperation such as Hanabi remain useful benchmarks to investigate further. By doing so, these novel insights can not only inform existing strategies but also shed light on human intelligence in the process.

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Julius Caesar and The True Roman By Sidharth Vij

Julius Caesar's *Commentarii De Bello Gallico* (*BG*) is one of the only primary sources regarding the Gallic Wars. The commentary is divided into multiple books and explains the progression of the war in terms of tactics, trade, movements, and motivations for war. Many historians disagree on the intended purpose and accuracy of Caesar's work—some claim the *BG* is a piece of literature with a propagandic intention, while others believe it to be a true recitation of events from the war.

The war began in 58 BC due to the migration of the Helvetii tribe. According to Caesar, the Helvetii could outdo any of the Gauls in courage as "they fight almost daily battles with Germans."[1] One of the leaders of the Helvetii, Orgetorix, persuaded the tribe to pack up all worldly possessions and conquer the rest of Gaul. As the tribe advanced, they came across the region of the Allobroges which had recently become a Roman territory (*BG* 1.2). The Helvetii's intrusion onto this land provided the *casus belli* ("cause of war") for Caesar.

There were numerous losses on both the Romans' and the Gauls' side. War was engaged on land, cavalry, and the sea as each side attempted to maintain the upper hand. Despite the many disadvantages the Gauls faced, they completely stalled Caesar's advance during the Battle of Gergovia in 52 BC; but, later that year, Caesar conquered Gaul in the Battle of Alesia (*BG* 7). However, there are many debates regarding the accuracy and intentions behind the depiction of the battles in the *BG*.

The purpose and accuracy of the *BG* has caused many debates among historians. Some historians believe that the *BG* is a piece of literature created by Caesar in order to disseminate propagandic material that supports him. Other historians believe that the commentaries are historically accurate and represent a truthful rendition of the events that took place during the Gallic Wars. There are a variety of rationales used for each argument; however, overall I will consider the *Commentarii De Bello Gallico* a literary piece serving as promotional material for Caesar.[2] The use of a third-person, omniscient narration style in the *BG* both gives the readers a holistic view of the war and furthers Caesar's self-portrayal. For the sake of brevity, I will be limiting my conversation of these techniques to Book 1 of the *Commentarii De Bello Gallico*.

[1] O'Donnell (2019).
[2] Riggsby (2006).The narration style and point-of-view are the primary arguments that demonstrate *Commentarii De Bello Gallico* being viewed as a piece of literature.

This promotional material benefited Caesar in many ways. The foremost one was by increasing his own standing in Roman society. By showcasing his outstanding victories, as well as advanced knowledge of military strategy, he proved himself to be an effective leader to the Roman populace. Additionally, he proliferated the idea that he exemplified the ideal qualities of a "true Roman," specifically that of *dignitas* ("dignity").

The idea of a "true Roman" is one that was institutionalized and reinforced by Roman society in order to maintain social order. These qualities came in many shapes and forms but primarily dictated a Roman's actions. Caesar embodied these qualities through the actions he took; for example, while communicating with Ariovistus, leader of the Haedui, regarding Rome and her allies, Caesar states:

> *Populi Romani hanc esse consuetudinem, ut socios atque amicos non mudo sui nihil deperdere, sed gratia,* ***dignitate****, honore auctiores velit esse.*
>
> The people of Rome customarily wanted their allies and friends to suffer no losses, but to enlarge in influence, **dignity**, and honor. (1.43)[3]

Here, Caesar pushes the idea of loyalty to one's allies, something that many Romans would look favorably upon. *Dignitas* is the pride and dignity one would have as a Roman. To be a proud Roman, one defends their nation as well as any who are considered their allies to the best of their abilities. By specifically mentioning this trait Caesar has showcased how he is a "true Roman" and provided an example of the quality in action.

In addition to *dignitas*, one of the most prominent traits of a Roman was *pietas* ("piety"). Specifically, filial piety was the respect and reverence one holds towards their parents and ancestors, as well as towards the ancient gods and goddesses. This trait was emphasized later in Book 1 when the Helvetians were crossing the path to conquer Gaul. The Helvetians were going to cross into Roman territory, and Caesar saw this as an opportunity:

> *Quā in rē Caesar nōn sōlum pūblicās sed etiam prīvātās īniūriās ultus est, quod eius socerī L. Pīsōnis avum, L. Pīsōnem lēgātum, Tigurīnī eōdem proeliō quō Cassium interfēcerant.*
>
> Caesar avenged not only public but even private losses, because the Tigurini had killed, in the same battle as Cassius, the legate Lucius Piso, grandfather of his own father-in-law Lucius Piso. (1.12)

[3] All Latin text is taken from Steadman's Edition and all translations are from O'Donnell (2019).

The filial piety Caesar shows his ancestors served as a *casus belli* for the Gallic Wars. By choosing to attack, not for material gain, but instead to avenge his family and the stains on Roman history, Caesar proved himself to be a "true Roman." Through this, Caesar pushed the idea of filial piety and showcased his own commitment to this ideal. Not only did Caesar propagate this idea, but he also earned the trust of many of his Roman readers who understand *pietas* to be a deep part of their identity.

Section 1: Omniscient Narrator

Throughout the *Commentarii De Bello Gallico*, Caesar utilizes an omniscient narrator in order to recount the Gallic Wars and to emphasize the *dignitas* he holds as a "true Roman." An omniscient narrator is an all-knowing third-person narrator through which all details are revealed. The omniscient narrator has all information regarding any situation at any given time. An omniscient narrator has complete control over the direction of the story as they control who is talking, what is said, the details that are revealed, and any other aspects of the plot.

The use of an omniscient narrator by Caesar holds great significance toward the interpretation of the text. Agreeing with Grillo and Krebs that Caesar wrote the *BG*, I will also consider him the omniscient narrator of the story. As such, all information that was written in the text was what he chose to reveal to the general populace of Rome. We see this taking place as he describes the Helvetians, who were later enemies to the Romans:

> *Quod ferē cotīdiānīs proeliīs cum Germānīs contendunt, cum aut suīs finibus eōs prohibent aut ipsī in eōrum finibus bellum gerunt.*
> They fight almost daily battles with Germans, either keeping them out of their own land or taking the war right to them. (1.1)

Caesar makes statements such as this regarding people, cultures, and situations that a Roman audience may not have the knowledge of. The use of an omniscient narrator creates trust between the audience and the narrator. This trust is formed due to the implication of an omniscient narrator knowing all details and, therefore, revealing the whole truth. As a result, readers do not question whether the information provided by Caesar is true, and from where he obtains the information. The use of an omniscient narrator in order to manipulate information continues when Caesar states that the reason the Helvetians attacked in the first place:

Prō multitūdine autem hominum et prō glōriā bellī atque fortitūdinis angustōs sē fīnēs habēre arbitrābantur.
They thought their land too small for so many people so brave and so good at warmaking. (1.2)

Once again, a statement is made regarding a group of people; however, the source of this information is not explained. Due to the use of the omniscient narrator revealing all facts, the audience trusts the information that is provided. The *Commentarii De Bello Gallico* is the Roman peoples only glimpse into the war and they believe it to be an accurate representation of the battles that took place. By revealing information in this way, Caesar has established a basis for a cause of war and, in doing so, a justification. Justification was an important part of the Roman way and was a part of the *dignitas* of a "true Roman." The use of the omniscient narrator was an effective way for Caesar to obtain the Roman citizens' trust as well as propagate the "true Roman" ideal of justification and *dignitas*.

The use of an omniscient narrator was necessary for Caesar to propagate the idea of what it means to be a "true Roman" in other facets besides justification. When in negotiations with Ariovistus, the chief of Suebi and a military leader of the Germans, regarding the ownership of Gaul, the narrator describes some of the thoughts of Ariovistus. Ariovistus believed that Caesar could be an enemy, as he possessed a standing army in Gaul that could attack them at any moment. Despite that being the case, Caesar demonstrated his commitment to *dignitas*, one of the Roman ideals:

Multa ab Caesare in eam sententiam dicta sunt quare negotio desistere 1 non posset: neque suam neque populi Romani consuetudinem pati uti optime merentēs socios desereret, neque se iudicare Galliam potius esse Ariovisti quam populi Romani.
He could not abandon the matter, for neither he nor the Roman people were used to abandoning allies of great merit, nor did he think Gaul belonged more to Ariovistus than to the Roman people. (1.45)

By utilizing an omniscient narrator in order to highlight thoughts that Ariovistus may have had, Caesar showcased his own *dignitas*. If an omniscient narrator were not employed, he would be unable to accurately state what Ariovistus had thought and, therefore, all statements made would be openly based on assumptions. By utilizing an omniscient narrator, Caesar

establishes Ariovistus' thoughts as fact and, therefore, the Roman readers are led to believe that the actions Caesar took were prideful ones of a "true Roman."

Section 2: Third-Person Point of View

In addition to narration, the point of view of a work heavily impacts the reader's interpretation of the book.[4] In the *Commentarii De Bello Gallico,* Caesar employs third-person point of view. Third-Person point of view is a narrator who utilizes third-person pronouns ("He/She/It/They"). They observe all events and illustrate the actions and thoughts of the characters within the story. This stands in contrast with first-person point of view in which a narrator uses first-person pronouns ("I/We"). First-Person point of view allows the reader an indepth look into the thoughts, actions, and perspectives of the narrator. In first-person point of view, the thoughts of other characters remain hidden.

The use of third-person point of view within the *BG* is an effective method for Caesar to create a sense of identity and camaraderie between himself and other Romans. By constantly switching between how he refers to his troops as a whole ("we," "our") as opposed to himself ("he," "Caesar"), Caesar makes an important distinction in the motivations for actions as well as who is in charge. This is especially visible when discussing battle narratives:

> *Caesar singulis legionibus singulos legatos et quaestorem praefecit, uti eos testēs suae quisque virtutis haberet; ipse a dextro cornu, quod eam partem minime firmam hostium esse animadverterat, proelium commisit. Ita nostri acriter in hostis signo dato impetum fecerunt, itaque hostes repente celeriterque procurrerunt…*
>
> Caesar put legates (and in one case a quaestor) in charge of each legion so every soldier's bravery would have a witness. He began the fight on the right flank, noticing the enemy was weaker there. Our men answered the signal eagerly and ran at the enemy suddenly and swiftly… (1.52)

From this excerpt the use of third-person point of view clearly creates a shift in the focus of the paragraph. It starts off with Caesar ordering legates to look over each legion and serve as witnesses to the soldier's bravery. Caesar highlights who put the legates there in order to showcase his camaraderie and value of the Roman soldiers, something that his Roman readers

[4] Grillo and Krebs (2018). The difference within narration was discussed in Chapter 11 *Literary Approaches To Caesar: Three Case Studies*.

would appreciate. After starting off with Caesar and his orders, the narration then switches to the effects of Caesar's actions on his fellow soldiers. The use of third-person point of view is key in highlighting the *dignitas* that Caesar displays. He takes pride in the actions his men have as they immediately follow his instructions and display the true might of the Roman soldiers. However, the main point here is the fact that Caesar is emphasized as the one who notices the enemies weakness.

After emphasizing his own accomplishments, Caesar then switches to first-person point of view. He begins to refer to the Roman soldiers as "our men" who "answered the signal," rather than keeping with third-person and referring to them as "the men." The use of third-person point of view was necessary for Caesar to propagate the *dignitas* of his actions and keeping it in contrast with first-person emphasized Caesar as the main character who is the very ideal of a "true Roman."

Caesar utilizes third-person narration in order to build himself up as well as his deeds; however, that was not the only way it was employed. By highlighting the actions of other individuals, including his own army, and contrasting them with his actions the readers are able to see certain personality traits of Caesar positively without him actually stating it. This is demonstrated right before Caesar and his troops were engaged in battle and his men had overheard rumors of their enemies ferocity:

> *Tantus subito timor omnem exercitum occupavit ut non mediocriter omnium mentēs animosque perturbaret. Hic primum ortus est a tribunis militum, praefectis, reliquisque qui ex urbe* ***amicitiae causā*** *Caesarem secuti non magnum in re militari usum habebant; quorum alius aliā causā inlātā quam sibi ad proficiscendum necessariam esse diceret, petebat ut eius voluntate discedere liceret.*
>
> Great fear suddenly seized our whole army and upset their minds greatly. It started from the military tribunes, the prefects, and the others who followed Caesar **out of friendship** from Rome without much military experience. One and another suggested reasons why they had to leave and asked his permission to go. (1.39)

Many of Caesar's men and soldiers were upset and fearful after hearing tales of the German warriors from the Gauls and wandering merchants. Caesar clearly states how many soldiers felt great fear due to the rumors. Not only that, but Caesar continutes to state how there were people who followed him to this war *amicitiae causā* ("out of friendship") and not some

other reason. Yet, all of this culminates to showcase that Caesar was someone who was not afraid of the Germans, no matter what rumors his men had heard. By utilizing third-person point of view, the audience is separated from the fact that Caesar is basically bolstering himself as someone who is brave and courageous. Caesar exhibits the "true Roman" *dignitas* for not backing down in the face of adversary and continuing to lead his soldiers.

Conclusion

The use of an omniscient narrator combined with a third-person point of view allows Caesar to display his *dignitas* to the Roman citizens who read his commentaries. Through the use of omniscient narration, Caesar controls the information that was presented to the audience and the general assumptions that Roman readers could make. This distinction between Caesar as the author and narrator of the story and Caesar as the main character created a trust between the audience and the author as an unbiased party narrating the war. Caesar utilizes the naivety of Roman citizens regarding Gallic traditions and cultures in order to achieve this effect. In addition, Caesar also primarily employs a third-person narration of the story, centering himself as the protagonist. However, at times the narration switches between third-person and first-person. Caesar purposefully switches between third and first-person in order to emphasize certain ideas, traits, or actions that he himself has taken versus others. Caesar's use of both of these techniques ultimately built trust with his Roman reader as he demonstrated his own *dignitas* as a "true Roman."

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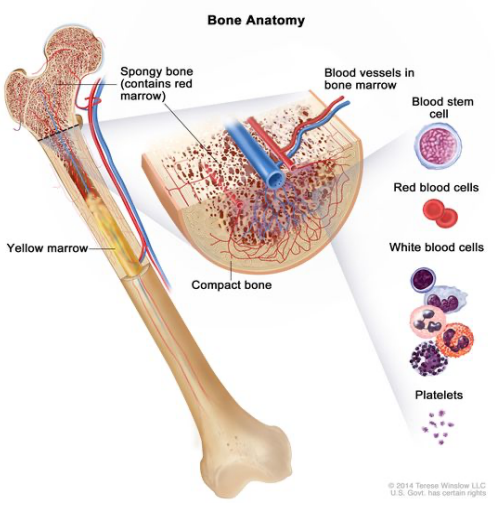
Immunotherapies: The Next Wave of Treatments for Acute Lymphoblastic Leukemia

What is Acute Lymphoblastic Leukemia (ALL)? By Claire Loftus

Acute Lymphoblastic Leukemia, known as ALL, is an acute blood cancer that arises from the bone marrow (**Figure 1)**. The cancer itself is the overproduction of anomalous, immature lymphocytes, which are within the sub-category of lymphoblasts (early form of lymphocytes). These immature lymphocytes are unable to fulfill their role, thus, weakening the immune system and its ability to fight antigens (foreign substances). Like many cancers, ALL begins as a miniscule error in the DNA called a genetic mutation (change). When protein synthesis is performed based on the genetic code, these defective proteins are produced and they may no longer function, function abnormally, or are simply different (19). When the signals to restrict a cell from replicating are unable to function properly, the cell will begin to multiply uncontrollably and is then considered malignant. Once a cell is cancerous, it will continue to proliferate rapidly and potentially metastasize to other parts of the body. Unlike other cancers where groups of these cancerous cells form solid masses called tumors, the ALL-affected cells spread to other regions of bone marrow and body by utilizing the bloodstream. Given that ALL cells have the capability of migrating into the bloodstream, metastasis is made notably easier for ALL cells moving throughout the body because the bone marrow is highly vascularized. Thus, it is easier for ALL cells to affect key organs and tissue around the body (11).

Figure 1

Bone marrow diagram

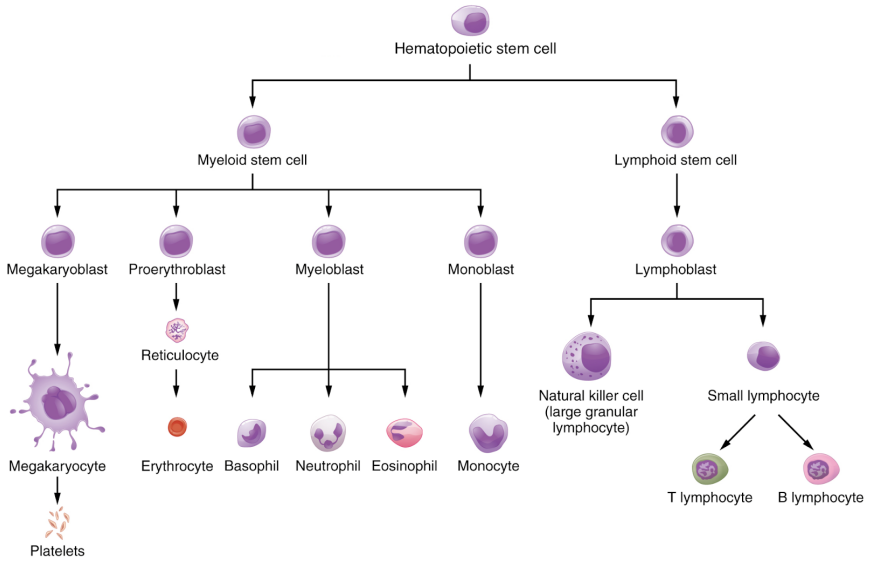


What Role Does the Immune System Play?

The multi-faceted immune system is a complex network of cells, tissues, and organs, that hold the responsibility of protecting and defending your body against foreign agents that can cause diseases. Some of the most pertinent organs of the vast immune system include the lymphatic system, the spleen, the thymus, and the bone marrow. All of these parts collectively work together to protect the body against infection and recognize harmful germs (23). The bone marrow is an influential part of the immune system in the regard that it produces white blood cells. Bone marrow is a spongy tissue that is an environment located at the core of a bone (11). In the bone marrow, there are hematopoietic (bone marrow specific) stem cells that hold the power of developing into three types of blood cells including erythrocytes (red blood cells), leukocytes (white blood cells), and platelets (33). These hematopoietic stem cells first begin by differentiating into common myeloid progenitor (CMP) cells or common lymphoid progenitor (CLP) cells. Within the group of CLP cells, there are white blood cells that specialize even further into B, T, and NK (natural killer) lymphocytes (**Figure 2)**. In a functioning body, the stem cells will regenerate where needed to compensate for deficits. In the case of patients with ALL, there is an overproduction of immature lymphocytes which consequently causes a deficiency in other blood cell types. This low proportion of other blood cell types due to an excess of white blood cells may result in anemia (red blood cell deficit), thrombocytopenia (platelet deficit), or becoming immunocompromised (2). In the instance of ALL, the immune system is further suppressed by the fact that the blood is lacking healthy, white blood cells. The immune system typically plays a critical role in identifying foreign antigens including cancer cells. However, as cancer evolves, it gains the ability of staying undetectable, thus making it harder to treat.

Figure 2

Hematopoietic stem cell differentiation



What is The Epidemiology of ALL?

The prevalence of ALL is rare, accounting for not even half of 1% of all cancers in the U.S. and the average person's chance of developing ALL being only 0.10%. However, it is still one of the most common types of leukemia. Not only is ALL the most common type of leukemia amongst children, it is also the most common childhood cancer in general. ALL accounts for 75-80% of children with leukemia and 60% of all ALL cases are children. Despite ALL being more common amongst children, the survival rate for children is much higher than it is for adults because children with ALL are often healthier and have fewer medical complications than adults, so their bodies are capable of handling the strenuous treatments. According to the American Cancer Society (ACS), it has also been shown that ALL is slightly more common in males than females. Out of a total of 6,660 new ALL cases in the U.S. in 2022, women accounted for 43% of cases while men accounted for closer to 56% (5). In terms of racial demographics, data shows that those who are of White and Latino background are at an increased risk for developing ALL compared to those who are Black or Asian. When combining cases of all age groups and genders from the year 2000 to 2016 in the U.S., out of 23,829 patients with ALL, 34.8% were Hispanic and 49.2% were White. The connection between ALL affecting specific ethnicities is still relatively unknown (37).

What are the Risks for Acquiring ALL?

The three known ways of contracting ALL are either by environment, by inheriting it genetically, or the random chance of acquiring an oncogenic mutation. Exposure to toxins, radiation, chemicals, or carcinogens are all examples of environmental risk factors. The clearest distinction between them is that environmental factors are slightly more controllable while genetics are established before birth and are determined by the genetic makeup of the parents. Many of the risks for acquiring ALL have been discovered, yet there are still a few to be uncovered (8). At the moment, there is no known way to prevent developing ALL.

How is ALL Diagnosed?

Patients may be prompted to see a doctor when they present with symptoms such as fatigue, pale skin and weakness due to anemia, frequent infections due to low white blood cells, bleeding from the gums or nosebleeds due to low platelets, or swollen lymph nodes. From there, the doctor will assess if it is necessary to pursue a complete blood count (CBC) to analyze the blood cell numbers for any imbalances that could be a sign of active ALL. Diagnosing ALL consists of conducting a bone marrow biopsy which involves extracting a sample of tissue to be further examined. The first step of this procedure is having the patient go through imaging to identify the general area of the cancer (e.g. CT, MRI, or PET scan). Physicians use imaging techniques to identify the general location of the ALL. Once the location of the cancer is identified, a hole is created by drilling through the external layers of the bone then inserting a small needle into the bone marrow to extract the tissue (**Figure 3)**. After the bone marrow sample is collected, it will be examined by a hematologist-oncologist or pathologist who will determine if it is malignant (cancerous). In some cases, supplementary specialized blood tests may also need to be performed with the purpose of confirming the diagnosis as well as determining the subtype of ALL (1).

What are the Traditional Chemotherapy Regimens Being Used to Treat ALL?

For decades, cancer has been traditionally treated using chemotherapy, radiation, or surgery. Like many treatments, chemotherapy comes with its advantages and disadvantages. Despite this, it is continuing to be used because of its high efficacy and unmatched success rates. Many people tend to focus on the detrimental side effects, when in reality, chemotherapy has

saved innumerable lives and prolonged the life of many, giving them a chance at a better future. Thus, chemotherapy is a go-to choice when it comes to treating ALL. The most consequential part of chemotherapy is that it affects cells that are highly mitotic (actively replicating), hence this is why many patients going through chemotherapy experience hair loss or skin and nail irritation. Other common side effects include fatigue and becoming immunocompromised (9). The remission rate when treating ALL with chemotherapy, the proportion of patients who experience a decrease or disappearance of symptoms, is 80-90%. The chance of relapsing when treating ALL with chemotherapy, the return of signs of the disease after a period of reduction or improvement, is 50%. Given that half of these patients relapse, the overall cure rate is around 40% (10). Chemotherapy has established itself as a fundamental treatment in the oncological world, so for now, it remains the primary treatment for patients with ALL.

Imatinib is a renowned drug that falls into the category of oral-chemotherapy and is used to treat individuals with the BCR-ABL1 mutation. This mutation has been traced back to the source of multiple types of leukemia including CML, ALL, myeloid leukemia, and occasionally T-lymphoblastic leukemia. BCR-ABL1 is a classic example of an insertion mutation and occurs when the BCR and ABL1 proteins come together to form a faulty protein. This drug's function is to block the signal from the abnormal proteins telling the cells to divide (38). The success rate for imatinib is about 83.3% after 10 years making it one of the most extensively used drugs for patients with ALL (21).

What is Radiation Therapy and how Does it Pertain to ALL?

Radiation has proven itself in the cancer field with a general success rate of around 90% or higher. Although it shows promising success, radiation is not commonly used to treat ALL because it is a localized treatment, and the side effects are typically worse. Radiation is a treatment that functions by using high energy rays or particles to destroy leukemic cells. Similarly to chemotherapy it also causes damage to the surrounding cells and tissue. The most frequent side effects are damaged skin and hair loss in the areas treated, fatigue, and becoming immunocompromised due to low blood cell counts (7). Prior to immunotherapies, unsuccessful attempts with chemotherapy and radiation would leave the patient with no other options.

What are Immunotherapies and How are They Applied to Treating ALL?

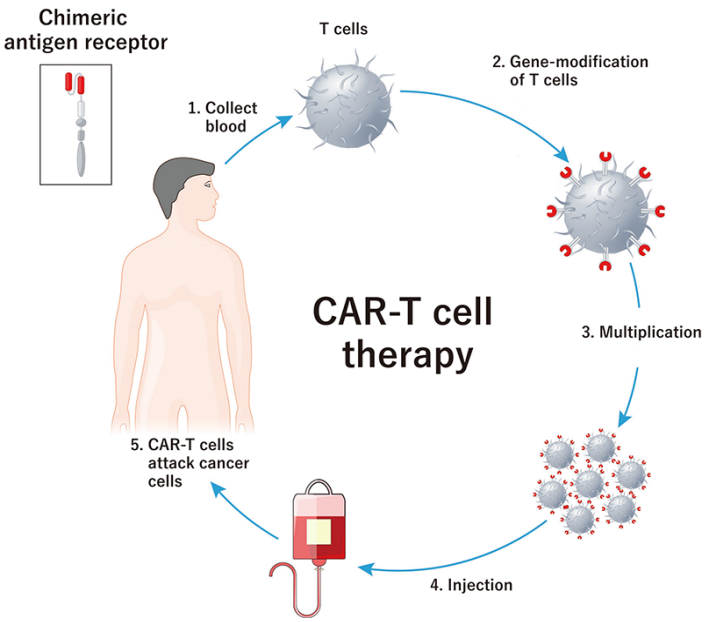
Immunotherapy is the use of the body's immune system to attack cancer cells. The idea of using immunotherapies to treat cancer was originally proposed in the late 19th century, however, it was not widely accepted until the mid 1900's. The earliest immunotherapies were interferon-alpha 2 (IFN-a2) and interleukin-2 (Il-2), both of which were categorized as antitumor cytokine drugs (20). Cytokines are particles released by immune cells that help signal, regulate, and stimulate the body's immune response. Immunotherapies are a significant advancement in the medical field because they target specific, atypical cells and utilize the body's own immune system. Although the concept of immunotherapies has been around for a while, none have been as efficient and effective as some of the newest findings. Some of these newer immunotherapies come in forms such as CAR-T therapy, monoclonal antibodies, stem cell transplantation, and checkpoint inhibitor drugs. The remission rate for immunotherapies in general used to treat ALL sits at a staggering 93% (25).

What is Chimeric Antigen Receptor T Cell (CAR-T) Therapy?

T-lymphocytes are a type of immune cell that originates in the bone marrow and are produced when the blood stem cells mature further. Their main function is to activate the immune system when necessary, and roam the body looking for target antigens and irregular cells to be attacked (31, 15). CAR-T uses the body's own CD8 T cells to attack and kill cancerous cells. This is done by genetically altering the DNA in T cells so that they can recognize and bind to specific proteins on the surface of leukemic cells such as CD19 or BCMA (16). Following this, the T cells will kill the target cell by releasing cytotoxic mediators that provoke the target cell to undergo apoptosis which leads the cell to its death (36). The first step of this treatment involves removing some of the patient's T cells through a process called leukapheresis (26). Blood is removed from a vein, and with the use of an apheresis machine, T cells are separated from the rest of the blood (18). After isolation, they are sent to the lab where they are modified to express chimeric antigen receptors (4). The altered T cells are then reintroduced to the body, now trained to recognize and attack the proteins on the surface of the cancerous cells (12, 17)(**Figure 4)**. With a lasting remission rate of 30-40% with no additional treatment, CAR-T therapy is on its way to becoming a top choice for ALL patients (12).

Figure 4

Steps of CAR-T cell therapy

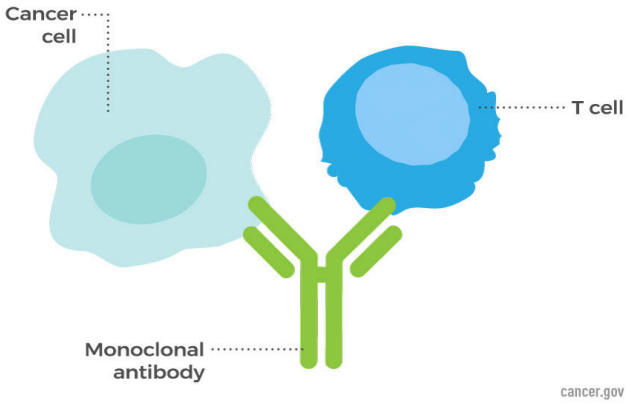


What are Monoclonal Antibodies(MABs)?

Antibodies, also known as immunoglobulin, are produced by plasma cells as an immune response to antigens or an infection (27). Their function is a critical element in an immune response because they identify, bind to, and flag pathogens. Monoclonal antibodies are fabricated (man-made) antibodies that can target proteins on the surface of both B cells and T cells. They are synthetically produced in a lab by B cells that are designed to secrete these antibodies. Once they have been produced in the lab, they are then infused back into the body through an intravenous infusion (IV). These bispecific antibodies are capable of attacking and binding to two proteins at once (4). With this capability, the antibodies will bind to both the proteins on the surface of T cells and the target cells, forcing them together (6)(**Figure 5)**. Prior to this, the cancerous cells may go undetected by the T cells, but with these antibodies in place, the T cells are now able to successfully attack the harmful cells. The remission rate of 80-90% is remarkably high and the overall cure rate of 40-50% is also very promising (24).

Figure 5

Bispecific "Y" shaped monoclonal antibody binding to T cell and cancer cell



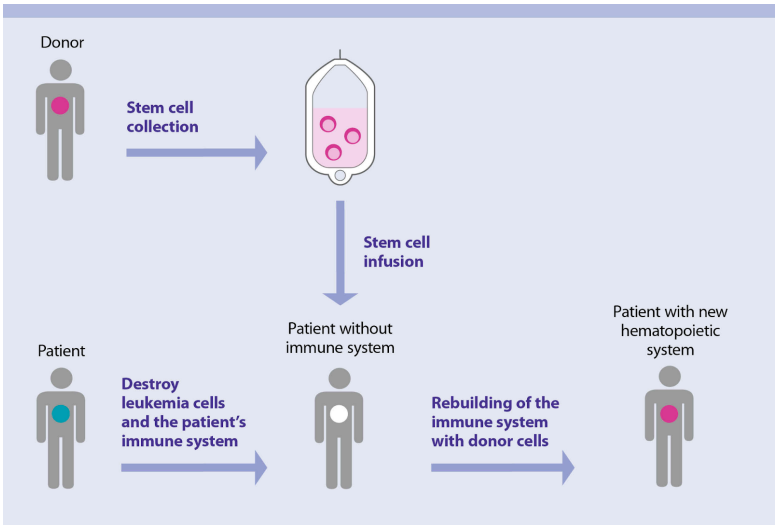
What is Allogeneic Hematopoietic Stem Cell Transplantation?

Allogeneic transplantation is the process in which the leukemic cells and some of the surrounding cells are destroyed, then replaced by healthy stem cells that compensate for the loss. Stem cells are the origin of all cells and because they are undifferentiated, they hold the potential of developing into various types of cells (28). This method of treatment was not specifically designed for ALL, but rather many types of cancer. The first step involves finding and receiving a stem cell match. A stem cell match is determined by DNA markers (HLA) which are molecules found in all cells (35). Without a stem cell match, the patient risks rejection, also known as graft versus host disease (GVHD) which occurs when the immune system attacks the donor stem cells. The two primary types of stem cell transplantations are autologous and allogeneic. Allogeneic transplantations involve a donation of stem cells from a close relative or an unrelated donor, while autologous transplantations use the patient's own stem cells. In the case of ALL, the transplantation is typically done using the allogeneic method because the risk for relapse is lower. This low relapse rate can be credited to an immune mediated response known as graft versus leukemia(GvL) which refers to the ability of the donor cells to eradicate the leukemic cells (**Figure 6)**. Instead of injecting these new stem cells on top of the leukemic cells, the patient first receives a heavy dose of chemotherapy (occasionally alongside radiation) (34). Therefore, resulting in the destruction of leukemic cells along with a deficit in normal bone marrow cells. This is when the stem cells are infused back into the patient's blood so they can repopulate the amount of healthy bone marrow cells (28). Compared to other immunotherapies, stem cell

transplantation has a significantly higher success rate with 69.9% at 5 years then an increase to 80% if there is no recurrence after 2 years.

Figure 6

Immune system reconstruction using donor stem cells



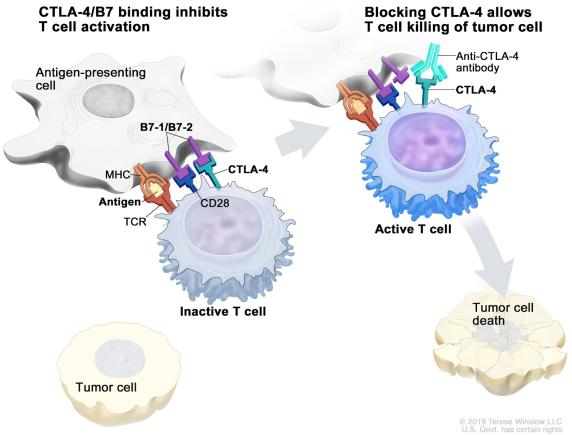
What are Checkpoint Inhibitor Drugs (CID)?

One of the most influential parts of the immune system is its ability to control the amount of T cells being utilized throughout the body. Generally this is controlled by the checkpoints. However, the cancer cells are capable of manipulating the T cells by telling them to send signals to turn the production of effector T cells off. This is problematic because in reality, the T cells are still desperately needed. When this happens, this allows the cancer to progress further while staying undetected. A key to overcoming this problem is by using a checkpoint inhibitor drug. Checkpoint inhibitor drugs work by finding T cells that are functional, then activating them to proliferate and attack the cancer cells (29, 14)(**Figure 7)**. One of the notable drugs known for having a higher success rate than its competitors is the drug PD-1. This drug has been extensively studied and clinically proven to have promising results. Some of the drugs that function similarly to PD-1 include PD-L1 and CTLA-4 (13). Not only are these drugs used for ALL, but also for numerous types of cancers and patients. Depending on the type of drug used, the success rates will fluctuate, but in general the cure rate is 43% after one year (39).

Figure 7

Images show the interactions without(left) and with(right) CID.

Figure 7A **Figure 7B**



What Scenarios are Each of the Immunotherapies Used In?

A common, valid question that one might ask is what scenario each immunotherapy is used in. The therapy itself is only effective if it is used to treat the right patients. For CAR-T therapy, this is often for patients with fairly advanced ALL that have been resistant to prior treatments (17). Monoclonal antibodies are commonly used when an attackable antigen is present (6). Allogeneic transplantation is frequently applied when the bone marrow is damaged and no longer producing healthy blood cells, whether this be caused by the cancer or the result of an intense treatment such as chemotherapy (32). Furthermore, because allogeneic transplantation is a high-risk procedure, this method may only be pursued when the patient has failed to respond with other treatments and if an appropriate donor is readily available (35). Finally, checkpoint inhibitor drugs are usually prescribed when handling an advanced case or severe stage of ALL and depending on the checkpoint protein being targeted, the type of drug being used will vary (14).

What are the Typical Side Effects of Immunotherapies?

In general, some of the most prevalent side effects associated with immunotherapies include fatigue, becoming immunocompromised, and flu-like symptoms. However, the possible side effects extend far beyond just these. In addition, it is worth noting that depending on how the immune system responds to the treatment, the duration and extremity of the side effects may

fluctuate (35, 30, 3). Scientists are continuing to discover new side effects that are correlated with ALL, while still maintaining a primary focus on ways to minimize and potentially eliminate them altogether.

Key Takeaways

For numerous years now, ALL has been one of the most prevalent leukemias that doctors and scientists have been tackling. With immunotherapies heading in a positive trajectory, they may also be leading scientists to an answer for the question 'Can we cure every patient with ALL?'. Treatments for ALL are now being redefined with the application of the immune system. Especially with the growth of personalized medicine, immunotherapies are well on their way to becoming a complementary line of treatment to chemotherapy and a new standard treatment for some applicable cancers. Immunotherapies have already gained a respectable reputation in the medical field because of their unparalleled levels of potential. Ultimately, families are getting to spend more time with their loved ones and countless lives have been saved. By bringing the future to life, they are also bringing new hope for patients that was once lost. CAR-T therapy, monoclonal antibodies, allogeneic transplantation, and checkpoint inhibitor drugs are the birth of a new wave of treatments that promises a great future ahead and for more to come in following years.

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The Neglected Mental Health Crisis: How the COVID-19 Pandemic Impacted Minority Groups and Youth in the United States By Valeria Ramirez

Abstract

The COVID-19 pandemic has caused various challenges throughout our society and health care system: the most overlooked being how our youth, especially marginalized youth and minority communities have been affected. The COVID-19 pandemic has resulted in mental health deterioration across the general United States population but has seemed to impact the youth/minority populations strongly. Unfortunately, little research has been done to investigate the pandemic's effects on these groups who are particularly vulnerable to mental health challenges. Pre-pandemic, research has shown that minority groups and youth are more susceptible to higher quantities of mental health issues, more commonly, depression and anxiety, as a result of systemic inequalities. This article discusses the harmful effects the pandemic has had on youth/minority groups and raises potential solutions that may alleviate stress and suggestions to improve our healthcare/ mental health services and education system.

Introduction

Public health crises and other disasters can leave adverse mental health effects on socially disadvantaged groups and youth: which have the potential to have long-lasting effects (Purtle). Historically, socially advantageous groups with access to more resources have enabled them to cope better during public health emergencies/disasters (Purtle). Systemic implementations of power place low socioeconomic minority groups at a disadvantage compared to their privileged counterparts. In emergencies like the COVID-19 pandemic, financial difficulty before and during the event, unemployment, lack of access to education, transportation, protection, and housing segregation makes merely living extremely difficult. Youth, in particular, are vulnerable during public emergencies because they may also lack resources and an understanding of the current situation. This is especially harmful towards young children, who lack the coping strategies to escape the psychological dangers of public health emergencies. This may leave adverse mental effects as their daily routines and lives are altered in various ways. The COVID-19 pandemic is not an exception to these “rules” of past public health emergencies/ disasters. It has created and exacerbated societal, economic, and medical disadvantages, leaving minority groups suffering

high rates of psychiatric morbidity. In this paper, I will discuss the societal, economic, and medical effects of the COVID-19 pandemic and how they've affected minority groups in the United States, as well as present potential solutions in order to alleviate its effects.

The Effects of the Covid-19 Pandemic

The COVID-19 pandemic has caused drastic societal changes in the United States, resulting in a decline in mental health among the general United States population. However, racial/ethnic minorities, youth, and those with intersectional identities face various challenges generated by the pandemic and higher rates of psychiatric morbidity. Lockdown measures have drastically altered our lives and how we commit to school, work, and interact with others. These changes, however, may be harmful to adolescents, those with pre-diagnosed mental disorders, and intersectional youth due to the absence of in-person interactions they require during this vulnerable stage of development. Lockdown has also limited the resources available to those needing them. This is especially harmful to members of minority communities who already face systemic inequalities and potential unemployment, making access to such resources even more difficult.

The substantial economic downturn created and exacerbated financial issues for many, predominantly minority individuals, including unemployment, fear of unemployment, and insufficient income to meet needs. Additionally, the pandemic has forced families to spend more time together. However, some families may face problems that spark conflict in the home. On the other hand, minority individuals that managed to keep their jobs face a higher probability of contracting COVID-19 which may cause further financial stress due to possible hospitalization and part-time occupational leave.

The stresses of the pandemic create different challenges for parents, whose moods and emotional states can directly impact their children. Unfortunately, parental stress is possibly correlated to the increased rates of domestic abuse among youth and intersectional youth. Furthermore, LGBTQ+ youth may be presented with different conflicts within home environments, as they may be confined in unsupportive homes during the pandemic- sparking further conflict and mental health conditions. These economic and social inequalities and consequences of the pandemic exacerbate the mental health outcomes among the most vulnerable groups in our society.

Why Have We Seen Worsening Mental Health Since the Start of the Pandemic?

Strict Lockdown Measures. At the beginning of the COVID-19 pandemic, strict lockdown regulations were put into place, such as school closures, which limited social interactions due to rapidly increasing infection rates. Almost everywhere, you could find advertisements plastered reminding the public to stay six feet apart and commercials warning about the severity of COVID-19. As we began to distance ourselves from each other, the general population began to suffer mentally because social interaction is a big part of human nature, and lack of it can take a significant toll on humans, even more so on adolescents(de Figueiredo et al.). During this stage of development, adolescents begin to rely more on interactions with their peers because adolescence is a time of psychological transition between childhood and adulthood and a period of heightened sensitivity to social contexts (de Figueiredo et al.). Throughout this developmental stage, multiple crucial aspects of social cognition continue developing, such as the comprehension of other people's emotions, intentions, and beliefs leaving adolescents more vulnerable to social contexts (de Figueiredo et al.). School is one of the most critical social environments and one where peers drastically affect each other's self-concept, behavior, and well-being (de Figueiredo et al.). Unfortunately, school closures have restricted adolescents from engaging with their peers in their everyday face-to-face interactions- disrupting their social networks. Previous studies have demonstrated that regular school patterns can potentially act as an essential coping mechanism, especially for adolescents with pre-existing mental health conditions. School routines are like an anchor in life, and sudden closure could lead youth with mental health disorders symptoms' to relapse (Lee). Long periods without regular school routines are correlated with less physical activity, increased screen time, irregular sleep patterns, and unhealthy diets among youth, all of which pose high risks for worsening mental health (de Figueiredo et al.).

Further implications for youth under lockdown regulations are the development of long-term psychiatric disorders (de Figueiredo et al.). Studies have found correlations between social isolation and loneliness, lower life satisfaction, and increased self-harm and suicidal ideations (Imran et al.). As quarantine and social interaction policies continued to fluctuate with the waves of the pandemic, adolescents continued to miss meaningful milestones and significant face-to-face interactions. Additionally, these constraints continue to impact family and financial

responsibilities, further pilling up the stress youth experience and possibly resulting in long-term mental impacts. The mental health disorders adolescents develop now in such a vulnerable stage will follow them into adulthood.

As we now know, lockdown restricted social opportunities for youth. However, the stresses of lockdown are even more grave for minority youth who are more likely to experience societal and economic disadvantages, as the lack of socialization and access to supportive resources hinder them even further (Purtle). For example, school closures restricted LGBTQ+ students from accessing necessary counseling, identity-based resources, and physical and mental health programs offered. The mixture of an unsupportive environment and lack of supportive resources conjures a high risk of decreasing mental health among LGBTQ+ youth during and after the pandemic.

The Latinx community, especially youth, are another group vulnerable to the effects of COVID-19 and its government regulations. Approximately 6.1 million Latinx children live in poverty in the United States: more than any other group of children (Rothe et al.). As lockdown measures were implemented, unemployment rates skyrocketed, subjecting more families to the negative financial effects of lockdown. This poses a threat for Latinx immigrants, especially undocumented ones, and those in poverty: who often have little support and aren't eligible for government benefits which result in an increased probability of stress-related mental illnesses and substance use. The United States Centers for Disease Control and Prevention (CDC) conducted a study highlighting that 21.9% of Latinx adult respondents began using substances as a coping mechanism for pandemic-related stress, 18.6% had considered suicide within the last 30 days, and 52.1% had more than one mental health symptom (Czeisler et al.). Without governmental support, low socioeconomic Latinx are more susceptible to COVID-19 exposure, financial issues, and adverse mental health effects.

The Latinx community faces high rates of COVID-19-related deaths and hospitalization, unemployment, financial strain, and childcare responsibility which pose threats to the healthy development of adolescents. Latinx youth, especially girls, are susceptible to the negative effects of COVID-19. Latinx youth under the age of 17 represent 52.4% of COVID-19 cases: making them the highest percentage of child cases among all ethnic groups (Rothe et al.). As schools closed down due to COVID-19 regulations and parents really began feeling the stresses of the pandemic; Latinx adolescents were increasingly given the burden of having to take care of

younger sibling(s) due to the limited childcare options, causing a flare-up in mental health symptomatology and declining school performance. However, it's important to note that even though schools have opened nationwide, Latinx adolescents may still be dealing with childcare burdens due to tight familial financial situations created by the pandemic. This may still be affecting students' school performances and symptomatology. For example, Latinx girls are especially susceptible to the effects of social isolation, which resulted from school closures, and increased symptoms of depression and anxiety along with problems concentrating on schoolwork. However, Latinx adolescent girls underwent increases in internalizing symptoms and GPA declines from prior to during the COVID-19 pandemic and faced additional childcare responsibility which was associated with adolescent girls', and boys', rising internalization and externalization symptoms (Roche et al.). Internalization symptoms may include anxiety, sadness, fear, and social withdrawal; externalization symptoms can be categorized as aggression, poor impulse control, and non-compliance. As a result of the hardships of lockdown, Latinx adolescents are deprived of essential social interactions with their peers, burdened with additional childcare responsibilities, face financial strain, and worry about contracting the virus; which induces additional stress and therefore risk increasing mental health symptomatology and declining school performances.

As discussed, lockdown regulations posed a serious mental health risk for multiple groups and proved especially challenging for those managing eating disorders (ED). Lockdown measures were one of the main challenges for mental health and EDs: as it increased the risk of experiencing loneliness and isolation. Both are risk factors for developing mental health conditions and developing and maintaining eating disorders (Cooper et al.). Individuals struggling with eating disorders may have faced additional challenges managing their ED in isolation due to the lack of social support, which is a vital part of recovery. The impact of social distancing regulations may have been even more severe for members of minority communities with EDs. For example, LQBTQ+ individuals require social support because it is a vital factor of positive psychological functioning. Those confined in unsupportive homes without social support are at a greater risk of developing ED symptoms (Cooper et al.).

Stresses Surrounding Homelife. Due to the implementation of stay-at-home orders due to rising COVID-19 cases, families began spending more time at home together. Lockdown forced families to spend more time together, creating closer bonds between family members, but it

could also have sparked conflict between family members. Unfortunately, lockdown measures caused a flare-up in new and previous financial woes, parental stress, domestic abuse, and lack of familial support which can leave long-lasting effects on youth mental health- especially marginalized youth (Purtle). Minority families have felt the greater extent of COVID-19 created complications within the home due to pre-pandemic social inequalities which have worsened over time (Purtle).

Minority groups in America face social, economic, and educational injustices which restrict many individuals to low-paying jobs, and were forced to take the pandemic's heaviest blows (Purtle). According to data reported in April 2019 and April 2020 by the United States Bureau of Labor Statistics, the United States unemployment rate increased from 3.6 to 14.7, but increased from 11.5 to 31.2 among Black Americans and from 3.7 to 16.7 for Latinx Americans (Purtle). Black and Latinx Americans make up a large portion of the essential workforce which are often physically intensive jobs that are very difficult to transition onto online networks, resulting in many workers losing their jobs and fearing being laid off. The stresses of not having a reliable income affect those who are responsible for taking care of a family and that may create conflicts among family members at home, which, in turn, impact mental health. More than 50% of parents reported that financial struggles due to social isolation were affecting their parenting skills (Imran et al.). Additionally, essential workers faced greater COVID-19 exposure and infection rates, placing many minority families under further financial strain. Infection could cost individuals their jobs and other financial woes if hospitalization was required. The financial ramifications of the pandemic directly affect home life and the mental health of family members as they deal with these stresses.

Many minority families are placed at risk due to the hardships they face during the pandemic. The stresses of financial insecurity, COVID-19 infection, lockdown measures, and the needs of their children place many parents in difficult situations and at an emotional breaking point. A parent's emotions (especially fear) directly impact their children as they are susceptible to the emotional states of the adults around them, and rely on them as a source of security and well-being both emotionally and physically (Imran et al.). Children with parents who suffer from poorer current mental health, declining mental health from the pandemic's hardships, and fear of infection exhibited negative COVID-19-related mental health effects such as anxiety and emotional negativity (Imran et al.). Assessing a child's safety at home during the pandemic has

presented itself as a significant obstacle mental health professionals must overcome. Educating parents and guardians on how to safely communicate the events of the pandemic to their children, access social support, and reestablish a sense of security via daily routines would greatly help overcome this issue.

The pandemic lockdown has caused many home conflicts and trapped multiple youth in abusive settings. From April 2019 to April 2020 the contact volume of the National Domestic Violence Hotline increased by 15% (Drotning et al.). Abuse rates are more likely to inflame after public disasters due to the economic and social instability, fear, boredom, and frustration they may have caused. Children of parents who were terminated from their jobs were found to be five times more likely to be psychologically mistreated in the forms of verbal threatening, ridiculing, and belittling (Listernick and Badawy). Parents experiencing the harsh effects of the pandemic are placed under an immense amount of stress, and may, unfortunately, take out their frustration on their children, placing them in danger of developing harmful mental health effects: including increased aggression, hyperactivity, anxiety, depression, and disordered eating behaviors. Children who experience domestic violence, also known as an Adverse Childhood Event (ACE), are adversely altered by its future physical and mental health ramifications.

LGBTQ+ youth also experienced conflicts at home between unsupportive family members during the pandemic. Although experiences vary, the pandemic lockdown forced LGBTQ+ individuals to spend more time with family members that cause them harm, rely on them financially, make them feel unsafe about expressing their true selves, were cut off from their supportive peers, and were unable to access useful services only increasing their risk for domestic abuse (Drotning et al.). These individuals may still be facing these restrictions placed by their harmful family members. The possible limitation of LGBTQ+ individuals in abusive and traumatic settings makes it vital to put more effort into surveillance, reporting, and intervention of child and domestic abuse during and long after the pandemic has ended. Experiences such as parental rejection and victimization may cause internalized homophobia and transphobia and LGBTQ+ identity rejection, which are linked to substance abuse, psychiatric symptoms (depression, anxiety, and PTSD), and suicidal ideation (Salerno, Devadas, et al.). Studies have shown that LGBTQ+ youth are eight times more likely to commit suicide and six times more likely to be depressed if they've experienced parental rejection (Salerno, Williams, et al.). Additionally, about ⅓ of LGBTQ+ youth experience parental rejection, and ⅓ won't come out

until adulthood. Transgender and non-binary youth face even more of a risk. LGBTQ+ youth will only suffer in these toxic settings without access to some support.

COVID-19 Related Fear. COVID-19 is a deadly virus and is responsible for 1,037,953 in the United States alone (Centers for Disease Control and Prevention, 2022). The virus is perilous for minority groups such as the Black American and Latinx communities (Purtle). These communities experience societal, medical, and economic inequalities, making them vulnerable to the pandemic's effects due to the lack of available resources. Because of these inequalities, Black and Latinx Americans have the highest rates of COVID-19 infections and deaths among all ethnic groups in the United States. Naturally, such a threat will instill fear in the hearts of many, especially children who may have a more challenging time comprehending the situation. Many members of minority groups are more likely to lack knowledge about how COVID-19 is spread, how to prevent infection and its severity. Fear of the virus due to lack of knowledge and its increasing death rate may lead to increased mental health symptomatology among vulnerable groups.

The Latinx community constitutes approximately 18% of the United States population, but Latinx individuals make up ⅓ of the total COVID-19 cases: almost double the percentage of other ethnic groups (Rothe et al.). The large number of Latinx individuals working in essential labor forces contributes to the high number of COVID-19 cases the community faces (Rothe et al.). Because so many Latinx individuals are working out of the home, they risk contact with multiple people, thus increasing the likelihood of contracting the virus. Additionally, not all members of the Latinx community (especially low socioeconomic or Latinx immigrants) have access to protective equipment such as masks, leaving them susceptible to COVID-19 exposure and contributing to a high COVID-19 infection rate.

Black Americans are the most vulnerable ethnic group in the United States socially, economically, and healthwise, especially in COVID-19 (Ibrahimi et al.). Black Americans comprise 12% of the United States population but have disproportionately higher COVID-19 death and infection rates (Kirksey et al.). Years of racial discrimination have segregated Black Americans, making them more likely to live in densely-populated areas and take up essential jobs. According to research from 2018, of 152.7 million workers in the United States, 33% of Black workers represented the essential labor force (University of Illinois Chicago, 2021). These jobs require in-person interactions, placing workers at a higher risk of catching COVID-19.

Workers contracting the virus can then spread it, contributing to the high rates of COVID-19 infection and death among Black Americans and creating further psychiatric morbidity. Furthermore, fear of racial discrimination in treatment sites, frequent grief and loss, and re-traumatization of once traumatized communities continue to discourage Black Americans from seeking medical provider care and mental health resources (Bhogal et al.).

COVID-19-related fear due to a lack of knowledge about how the virus spreads and how it's affecting our society affects young children and adolescents. This lack of knowledge about how to protect oneself from the virus is a result of a lack of access to credible tools and resources as well as limited access to education. For example, more than ten conspiracy theories have been trending in the media since the pandemic's beginning (Ibrahimi et al.). However, children are not spared from the negative psychological consequences of the pandemic. These factors leave children highly psychologically susceptible to public health disasters due to their limited understanding of the situation. Previous studies have found that children twelve years old and younger are more likely to experience persistent and excessive worry due to their little comprehension of COVID-19 (Bhogal et al.). The pandemic threatens children because their limited coping mechanisms restrict them from physically and mentally escaping its dangers. This especially affects young children due to their high risk of experiencing long-term consequences as a result of negative experiences as this developmental stage is particularly malleable (Imran et al.). However, because there is limited research on minority children, there is a possibility that COVID-19 may impact their mental health in different ways. These would need to be assessed with culturally appropriate assessments to investigate further. Due to different socioeconomic and cultural aspects among minority groups, research is minimal because we may not have conducted proper culturally appropriate analysis of these different groups, and the mental health impacts of COVID-19 (Bhogal et al.).

Lack of Access to Resources. Heteronormitive and cisnormative policies created by governments and international organizations in response to public health disasters continue to fail LGBTQ+ populations as they do not meet the needs of these communities. In general, LGBTQ+ individuals and youth face a higher probability of experiencing food insecurity, homelessness, foster care, other unstable housing, poverty, and managing pre-existing mental health conditions (Salerno, Devadas, et al.). These social inequalities, combined with the pandemic lockdown worsen the stakes for LGBTQ+ populations and make it especially

challenging to seek help compared to their cis and hetero counterparts. Furthermore, trans individuals and youth, especially those who may have been displaced during the pandemic, undoubtedly face obstacles blocking them from receiving gender-affirming mental and general healthcare. This may result in experiencing gender dysphoria, anxiety, depression, and suicidal temptations during the COVID-19 pandemic (Salerno, Devadas, et al.). On another note, it's important to consider those with intersectional identities. For example, an individual may be a member of both the LGBTQ+ and Black American community as well as have a mental disorder. Individuals with intersectional identities face a multitude of societal challenges affecting their co-existing identities because of their membership in various communities. This can make accessing any form of support even more difficult due to the inequalities limiting them.

With COVID-19 infection rates increasing, schools began switching to online learning and employers began laying off many of their employees. Both sites provide access to healthcare and mental health services for LGBTQ+ individuals. 40% of LGBTQ+ individuals in the United States work essential jobs in the service industry compared to 22% of non-LGBTQ+ individuals; thus, making LGBTQ+ individuals, especially those of color, more susceptible to financial and health insurance issues during the pandemic (Salerno, Williams, et al.).

Black youth are even more vulnerable and struggle with many barriers blocking mental health services including: different understandings of mental health challenges between medical providers and parents/guardians of black adolescents, distrusting mental health service providers, lack of perceived necessity for mental health services, fear of COVID-19 exposure, lack of belief in the efficiency of treatment, privacy concerns, transportation and scheduling difficulties, childcare issues, and high mental health stigma (Banks). Black adolescents are less likely to pursue help from formal mental health services, and COVID-19 has only worsened existing challenges for Black American adolescents (Banks). Additionally, poverty is a prime contributor to low mental health service usage among all ethnicities and ages (Banks). Many low socioeconomic Black American adolescents are restricted from accessing helpful services simply because of expenses. Healthcare and mental health service providers need to assess the accessibility issues reported by providing affordable treatment options and placing clinics in close proximity for black adolescents to access.

People managing eating disorders (ED) are at risk of experiencing worsening symptomatology in the midst of the pandemic partly because of restricted access to important

services. In 2019, about two billion people experienced moderate or severe food insecurity worldwide, and early estimates from developed countries report that these results have continued to rise exponentially during the first couple weeks of the pandemic (Cooper et al.). In the US alone, 13.8 million households were food insecure at some point in 2020 (U.S. Department of Agriculture, 2022). Food insecurity poses a large risk for ED psychopathy as it could cause binge eating, fasting, and compensatory behaviors, and individuals experiencing lofty amounts of food insecurity are more probable to develop binge-eating disorder or bulimia nervosa (Cooper et al.). Those experiencing food insecurity may have to rely more on food banks and possibly would not receive sufficient nutrients. However, lack of access to food banks, and other services, are limited during the pandemic. Access to healthcare is also restricted during the pandemic which places individuals with EDs in an even more difficult situation. Lack of access to healthcare is especially dangerous for those with EDs who are medically compromised and require frequent medical visits. In-person checkups often require physiological assessments such as monitoring weight change, vital signs, and laboratory tests which can't be done without access to services that provide them (Cooper et al.).

Effects of Media Consumption. The pandemic had isolated people prompting greater consumption of electronic devices and networks as a source of information, communication, work, and entertainment. However, as one spends more time surfing online media networks, one is placed at a higher risk of developing negative mental health impacts. Social media outlets often advertise misinformation, stressful and traumatic world events, unhealthy diet and body image ideals, and hateful comments (Cooper et al.). This was already the case before the pandemic, and now that more people are finding themselves using media platforms more often, there could be a potential surge in mental health symptomatology. These threats are harmful to youth especially girls and individuals with eating disorders as they are significantly more vulnerable, and experience increased anxiety, depression, and disordered eating habits.

Restricted in-person interactions resulting from lockdown measures may result in increasing media consumption and social media usage, which studies have associated with increased ED symptomatology. Exposure to stressful media coverage of public disasters increases psychological distress, such as disordered eating (Cooper et al.). During the pandemic, several news stories are related to the exacerbating number of COVID-19-related infections and fatalities, global health and safety concerns, and the economic and social impact of COVID-19

which is associated with increased risk for ED behavior. Additionally, the spread of misinformation may be deliberately causing individuals further distress. Furthermore, social media sites promote unrealistically thin/athletic ideals that stem from diet culture, food, strict exercise, and fatphobic messages all of which contribute to heightened ED risk. Advertisements seen throughout media would often promote messages of wellness and staying healthy during the first year of the pandemic, but would still harmfully imply weight loss just as years prior. It is very common for photos to be edited on social media; according to one study conducted in Nepal ¼ of participants edited their photos on social media (Agrawal and Agrawal). These techniques spread unrealistic body images and may further harm those with EDs. Social media is known for glorifying ED behaviors which further increases the likelihood of developing such dangerous habits and ruining one's body image (Hamilton et al.).

Similarly, children and adolescents are exhibiting increased screen time. For all ages, children's screen time has doubled, averaging about 3 hours before the pandemic, to nearly 6 hours during the pandemic (Wiederhold). Spending time with their peers is important for adolescents, and social media networks serve as a substitute for in-person interactions (Hamilton et al.). However, social media has many risks which can alter adolescents' mental health. Social media is prone to spreading misinformation which may cause a struggle for adolescents to differentiate between what is "fake news" and what is accurate information (Hamilton et al.). For example, posts or memes demeaning the severity of COVID-19 may encourage adolescents to not follow proper regulations, thus placing themselves, their families, and the public at risk (Hamilton et al.). Content related to COVID-19 may be scary, overwhelming, and sad, while adolescents spend more time online they will come in contact with such information, resulting in exacerbating anxiety, frustration, helplessness, and negative moods. An unregulated amount of time online will lead to more exposure to "fake news" and stressful content.

Adolescents are especially vulnerable to how others perceive them and how they present themselves. Self-presentational theories express how individuals participate in impression management tactics in order to present themselves as best as possible (Hamilton et al.). Social media encourages teens to present themselves in the most favorable ways and carefully curate how they present themselves via photos, videos, and text. Teens are especially attentive to physical appearance, and attractiveness is a central part of many adolescents' self-worth, especially girls who are pressured by social media's unrealistic standards (Hamilton et al.).

Social media sites are overrun with edited photos glorifying unrealistic beauty standards which may cause adolescents to negatively compare themselves to these standards. Multiple studies have found correlations between social media use (specifically photo-focused behaviors) and body image dissatisfaction and increased eating disorder symptomatology among adolescents (Hamilton et al.). As teens spend more time scrolling through photos of their peers, they may compare themselves to the lifestyles and material possessions of others. This may cause teens to want to obtain social approval, status, and satisfaction through likes and views. Adolescents may experience the Fear of Missing Out (FoMO), which is caused by social media and may cause depression, anxiety, and loneliness (Hamilton et al.). FoMO causes adolescents to worry that their peers are interacting without them, resulting in increased pressure to spend more time on social media in order to not miss anything (Hamilton et al.). These impacts of social media may worsen for teens previously experiencing low self-esteem, a tendency towards impulsive decisions, mental illness, and stressful life events. Previous research demonstrates that adolescents diagnosed with depression may use social media in a way that exacerbates their symptoms, and those with a high tendency toward social comparison are likely to engage in negative body image views (Hamilton et al.).

A Deeper Look At Systematic Racism During the Pandemic

The United States has a deep-rooted history of systemic racism which has created multiple societal obstacles for racial minorities. These obstacles are exacerbated during public health disasters causing racial/ethnic minorities, especially those on the low socioeconomic scale, more psychiatric morbidity compared to socially advantageous groups.
Socially-advantaged groups have a history of power and privilege that enable them to cope with stressors caused by disaster due to the abundant availability of resources. In the midst of the COVID-19 pandemic Black, Asian, and Latinx Americans faced exacerbating amounts of racial, social, and economic inequalities, which can leave harmful impacts on such vulnerable communities.

Systemic racism has curated the types of occupational opportunities Black Americans can perform and generated housing and school segregation policies that place them in high-risk environments for COVID-19 exposure. For example, Black Americans comprise a large part of

the service workforce, 30% bus drivers, and 20% food industry workers (Ibrahimi et al.). These jobs have been declared essential during lockdown, thus increasing the probability of contracting COVID-19, which contributes to the high rates of COVID-19 infection and death among Black Americans, and creates further psychiatric morbidity. As previously stated, the pandemic has left many minority individuals unemployed, thus increasing the already significant income inequality gap in the United States. The increased unemployment rates exhibited by the pandemic are predicted to result in 9,750 additional suicides per year worldwide (Purtle). Black Americans also faced further stress from the police killings of unarmed and innocent Black Americans during the pandemic and from years prior which has left negative mental health impacts on the once traumatized community. This exacerbated wave of racism increased anxiety and depressive symptoms among Black Americans, especially those who experienced first-hand racist encounters (Purtle).

Pre-pandemic, Asian Americans reported significantly lower instances of harassment, insults, and threats as well as fewer mental health conditions than White Americans. However, since the pandemic's start, there has been an increasing level of mental health conditions among Asian Americans. Asian Americans have been targets of COVID-19-motivated discrimination and were blamed for starting the pandemic. According to the STOP APPI HATE project, there have been over 2,500 events of COVID-19-related hate attacks on Asian Americans since March 2020 (Wu et al.). As previously discussed, racism and the systemic inequalities it creates can adversely affect the mental health of ethnic and racial minorities, as they must face more stressful societal obstacles. The minority stress theory states that stigma, prejudice, and discrimination curate hostile and stressful environments, resulting in a higher prevalence of mental conditions among minority communities (Wu et al.). Post-Traumatic Stress Disorder (PTSD) and Acute Stress Disorder (ASD) often result from events related to perceived or personal accounts of racial discrimination, such as threats, humiliating events, and witnessing harm to other minorities (Wu et al.). Personal experiences with racial discrimination can also threaten an individual’s identity, resulting in hopelessness and the internalization of harmful stereotypes (Wu et al.). However, I have found that data relating to the negative effects the COVID-19 pandemic has had on Asian Americans is minimal.

Conclusion and Solutions

It is clear that minority groups and youth are the most vulnerable groups in the United States, and it is imperative to provide these individuals access to the same resources as the most advantaged in order to grow and advance as a society, as evidenced by the systemic inequalities limiting their capabilities. Systemic racism, overcrowded and segregated housing, occupational segregation, financial instability, lack of transportation, and lack of social/familial support often block racial/ethnic minorities, youth, and disadvantaged/ intersectional individuals from accessing resources such as food banks, healthcare, mental health services, and more. Everyone is unique and has different needs that must be met. In my opinion, school advisers, health care providers, and government officials should work with minority groups and youth to provide easy access to supportive and affordable resources. It is also imperative to continue to conduct further research that is beneficial to all. We must ask ourselves how we can improve access and quality of resources, offer financial aid, and improve family environments to alleviate the negative mental health outcomes during the pandemic and long after.

Across the country, minority communities, youth, those with pre-existing mental conditions/disabilities, and individuals with intersectional identities have faced increasing mental health symptomatology and exposure to COVID-19 due to the inadequate availability and affordability of resources. We have repeatedly seen healthcare, mental health services, school resources, and more fail those in need of their services throughout the pandemic: exacerbating the harmful mental health impacts on members of minority communities and youth. Furthermore, lockdown measures, financial instability, and systemic inequalities accessing these resources has become more of a challenge, especially during a global pandemic. Healthcare providers need to create more affordable and accessible options for minority communities, who often lack the finances and transportation to access them. Healthcare practitioners need training on how to treat individuals from specific minority communities, what obstacles these communities face during the pandemic, and the mental health implications of such obstacles. Health care practitioners and providers must be prepared to provide treatment and access to those with pre-existing mental health conditions/disabilities with culturally responsive treatment, trans and LGBTQ+ affirming care, telehealth outlets, self-help resources, and online support groups/messaging with clinicians. While making sure to not use non-stigmatizing language and eliminate discriminatory policies. However, it’s important to keep in mind that many low socioeconomic individuals might lack

access to digital devices that allow them to utilize digital health services, so there must be clinics within close proximity to residential areas.

Schools often provide resources such as support groups, counselors, and mental health services, however, shutdowns prevent access to these services. It's essential for schools to still offer their students access to these resources if they're still on online learning (via online platforms) and provide students without access to the internet with the proper tools. Minority youth may not have the resources at home to access these tools anywhere else other than at school. Therefore, it should be the schools' job to give equal opportunity to all of their students. Schools also must educate students on how to maintain good mental health, how to identify when help is needed, and where/how to reach out for help.

It's important to make sure families, especially low socioeconomic and racial/ethnic minorities have access to proper resources. Many families would greatly benefit from affordable housing, healthcare, education, financial aid, food banks, accessible forms of transportation, and job opportunities. Currently, these families lack these services, which became vastly essential during the pandemic and more difficult to come by. Unfortunately, these stressors and negative emotions have caused an increase in domestic and child abuse. Therefore, it is crucial to place more effort into surveillance, reporting, providing support for victims, and properly intervening in abusive homes during and after the pandemic. In the context of child abuse, we must educate parents on how their emotions can affect their children and how to properly manage their own stress in order to keep their children safe.

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The Humbert Humbert of Lexicography By Addison Moss

In David Foster Wallace's "Tense Present," the author proudly declares that he is a "SNOOT," self described in a footnote as "*Sprachgefuhl* Necessitates Our Ongoing Tendence" and/or "Syntax Nudniks of Our Time." (40) Of course the meaning of this acronym is coupled with the connotations of snobbishness which Wallace readily embraces despite some feigned protestations along the way. In the essay, the author's praise of Bryan Garner's "A Dictionary of Modern American Usage," acts as a kinder, gentler vehicle to communicate his own convictions regarding American lexicography. He laments, mocks, and recoils as the English language is manhandled even by those who are highly educated and charged to protect it. Identifying as an "elitist nerd," (41) Wallace ascribes a moral value to ways of speaking and writing. He is resolute that there exists a proper way to use the language, discouraging patois and slang while avoiding the modification and co-opting of words (despite his own dalliances with these practices throughout the essay.) However, Wallace acknowledges that some rebuff his linguistic dogma, and even argue that semantic correctness is a mere social construct. This approach, Descriptivism, neither judges nor specifies the "right" usage but rather observes and reports. Its central pursuit is to uncover the "real" nature of language. Here, meaning and value are not tied to grammatical correctness. As there is palpable tension between these two schemas, Wallace often feels under attack and tries to undermine his ideological counterpoint. While his arguments are convincing especially regarding Garner's work, at times Wallace's motivations seem questionable; is his campaign against Descriptivism truly in service of discouraging less clear and effective forms of language, or are other ambitions at play? If, per the Descriptivists, objective right and wrong were to become irrelevant, the value in being a "SNOOT" would likewise diminish, and the aim of Wallace's project (and by extension his identity) would become fraught, muddied, and compromised. Perhaps for Wallace, the ultimate role of language is not only to convey meaning but to signal expertise, authority, sense of self, and social class.

Although Wallace's agenda might be complex, even specious at times, he nonetheless makes persuasive points regarding the limitations of Descriptivism. As an allegedly evidence-based method, Descriptivism asserts the primacy of spoken language and its correctness as originating in usage. Rather than corresponding to a framework of linguistic rules that better serve society's purposes, the "right way" is consistent with how real people practice

verbal expression everyday. But the difficulty here, as Wallace points out, is that all usage is relative, thereby calling into question whose dialect should be the metric, or if primacy can/should even exist. The stated mission of "these permissive, sham populists" is to "find and objectively describe meanings that were right there." (46) In other words, they are trying to elucidate the alternate true form of language while rejecting the conventional standards, known to them (at least according to Wallace) as "custom and superstition and ovine docility." (43) As the Descriptivists embrace all styles of speech as proper in their own right, they preclude the notion of objective right and wrong, a collectively held set of norms and rules that frame and evaluate grammar and vocabulary per community interests such as clarity and accuracy. Just as the post-structuralists, such as Jane Tompkins, reject ultimate truth, the Descriptivists challenge ultimate correctness. For both, validity or fact only exists as it is embedded in one's vernacular or perspective. This universal endorsement gives rise, once again, to the dilemma of slippery sameness wherein hierarchy and discernment are frowned upon. But here, the resulting crisis of authority is insightfully addressed by the author (through lauding Garner) as he quotes,"I don't shy away from making judgements…rhetoric and usage… aren't scientific endeavors. You don't want dispassionate descriptions; you want sound guidance." (43) Through this rhetorical and ethical appeal, Garner/Wallace eschews the Descriptivists' inherent trivialization of his and other conservative linguists' work while reasserting the value of "SNOOT" skills, and therefore himself. Most importantly, Wallace illustrates that without these tangible standards, critical and interpretive acts and explorations of the English language become impossible.

In further undermining the Descriptivists, Wallace insightfully reveals inconsistencies of logic that characterize their approach. The fallacy of neutrality is one of the most egregious examples. Descriptivists presume that as a scientific practice, their observations are "neutral, careful, and unbiased." (46) Yet, Wallace points out this fundamental misunderstanding regarding the nature of their process: they fail to recognize that "an act of observation is itself part of the phenomenon observed and is analytically inseparable from it." (46) While aims of objectivity may be noble, they are unattainable. Wallace insists that meaning can never be divorced from interpretation, which is always biased and informed by the agent's *a priori* set of beliefs. Descriptivism as a scientific lexicography, therefore, is necessarily subjective. Whether conscious or not, one's personal philosophy will always shape his/her assessment; to expect otherwise is flawed thinking. The crux of Descriptivism relies on an impartial methodology, and

as Wallace successfully challenges it, he compromises the approach wholly. But, in asserting the impossibility of neutrality, the author (unwittingly) implicates himself. Wallace writes; "Objectivity in language study is now the stuff of jokes and shudders." (46) Here, and in numerous moments throughout the essay, the author makes his point utilizing mockery and condescension. Consequently, what was a judgment about Descriptivism, also becomes a metacriticism of his own approach, exposing the bias of the work. If observation is indeed influenced by experience and beliefs, what has Wallace revealed of his own? Well, he is a proud "SNOOT, " raised by a nuclear family of "SNOOTS" that proofread William Safire on Sundays, educated in and employed by fine institutions promulgating SWE, and a "Privileged WASP Male in a position of power." (56) While these would not by definition lead to the undeniable elitism that permeates the essay, the author curiously provides no counters to these identifiers. Instead, he offers them up and seems to take pride in the status that they signify. These aspects of his identity inform and imbue Wallace's project. The author is often (offensively) defensive of the erudition he holds so dear, tirelessly and unrelentingly working to prove his smarts and superiority. At times it appears that his selfhood is inextricably tied to his nimble ability to manipulate language and narrative in the service of championing his standing and that of Modern American Usage.

Ultimately it is this call to elitism which dominates, and therefore frustrates, much of the essay. Even as he potentially crafts robust critiques of Descriptivism, he sabotages the arguments with disdain: "It isn't scientific phenomena they're tabulating but rather a set of human behaviors, and a lot of human behaviors are- to be blunt- moronic." (47) Here, the author makes a salient point out about linguistic laxness and errors that have become commonplace, leading to the overall lesser and substandard version of language. The *ad hominem* attack, however, is ineffective in displacing Descriptivist authority. In relegating human behavior to dim carelessness, he positions his "SNOOT-itude" as extraordinary, distinguishing himself as the brilliant exception amidst an inarticulate lot. This exclusive sensibility (also reflected in his use of the imperious third rather than first person) is furthered as the writing often feels like a test; who is intelligent enough to recognize the abstruse references, earning acceptance and admission into Wallace's special club? Despite his condemnation of Academic English wherein "a scholar's vanity/insecurity leads him to write primarily to communicate and reinforce his own status as an Intellectual," (56) the author's *modus operandi* of academic name-dropping is very similar.

Within one paragraph, DFW invokes Heraclitus' flux, Plato's "Phaedrus," and Derrida's Deconstruction. The author continues to conflate erudition and status in one of his primary arguments, positing SWE as providing access to higher echelons of society and influence: "SWE is perceived as the dialect of education and intelligence and power and prestige, and anybody… who wants to succeed in American culture has got to be able to use SWE." (54) Here, the Wallace's cynicism and exploitation are laid bare, no apology, no shame. He advocates for a means-ends, Machiavellian approach of using proper language to gain advantage and game the system rather than question it. There is no pretense of social equality, nor any promotion of progressive ideals, reform, or justice. Self preservation and aggrandizement, within the construct, are the primary goals. And indeed, Wallace has benefitted from and thrived within this apparatus that strengthens the status quo and extant power structures. Cloaking himself in faux transparency and even patting himself on the back for "bullshit-free" candor, the author fails to perceive the insidiousness of his premise. Even in the face of cringe-worthy classroom speeches such as "…you're going to learn to use it [SWE], too, because I'm going to make you" (54, 56) that appropriately resulted in disciplinary action, Wallace ascribes his blunder to mere naïveté, mistakes of rhetoric, rather than a fundamental classism.

Indeed, Wallace writes a compelling essay in "Tense Present," but the duality of the argument and the nature of the persuasion ultimately undermine his case. His thesis is two pronged; he critiques Descriptivism citing the value of collectively held linguistic standards that benefit the community at large while he also advances a causal relationship between proper language and status. The former successfully imparts the need to promote and protect correct usage through cogent reasoning and elucidating perspectives. He eloquently identifies society's desire to "want their language to be graceful at times and powerful at times." (58) The latter campaign, however, appeals to baser tendencies, and the persuasive quality of his discourse begins to feel coercive. Wallace seems more preoccupied with his own authority, simultaneously presenting as a witty hipster and an established prig. His *arriere-pensee* distracts, and at times negates, the important project better represented by Garner (who's humility he tries to co-opt.) It is no coincidence that the essay is replete with superfluous sexual allusions: cum, ass, pussyfoot, seamy, sniff genitals, corsets, naked, aerated and unchafed, f**, boners, and that doesn't even cover the innuendos. Wallace is a skilled and deft writer, and his prose verges on pressuring, seducing rather than convincing in order to get what he desires: linguistic and personal power.

Utilizing his disarming charm, he becomes the Humbert Humbert of lexicography. Consequently, his pleas to "trust me," using Garner as his earnest proxy, are that much more disconcerting. Both preening and predation permeate the work and the persona, a fitting parallel to Nabokov's observation that "you can always count on a murderer for a fancy prose style."

Fabrication of Subjects: Blade Runner & Panopticism By Addison Moss

Although disconnected in space and time, there exist uncanny similarities between the society depicted in Michel Foucault's *Discipline & Punish: The Birth of the Prison* and that portrayed in Ridley Scott's *Blade Runner, The Final Cut.* Both describe an abstract world simultaneously recognizable and fundamentally transformed; Foucault presents a conceptual community regulated by external and internal systems of surveillance while Scott illustrates a futuristic dystopia in Los Angeles wherein patrol and auditing are similarly dominant. Hierarchical structures and pyramidal systems of power characterize both cultures. They reflect the ascension of capitalism and technology, the emphasis on discipline and the role of the individual within that framework, the expansion of multiplicities and scale, and the primary function of vision. The works diverge, however, in that the panoptic schema is perpetually promised in the film, but never wholly delivered. While *Blade Runner's* social and political landscapes resemble Foucault and Bentham's, the construct depicted never quite achieves "advanced panopticism." Similar to Marxist justifications of interim violence during the transition of ideology, throwback measures and penal thuggery seem necessary in Scott's rendering. The very need for blade runners (death squads that terminate rogue replicants) contradicts Foucault's self-checking and self-subjugating conclusions. While these inconsistencies may indicate that the project is incomplete and evolving, perhaps they reveal an alternate truth: the panoptic model itself is materially flawed, not unfinished but rather unrealizable.

The ambitions of Eldon Tyrell, the founder and head of the Tyrell Corporation in *Blade Runner*, reflect tenets espoused and conditions specified in *Panopticism*. The latter contends that panopticism both reinforces and is reliant on capitalism and technology. The panoptic apparatus is defined by triple objectives: exercising authority efficiently and inexpensively, extending its reach intensely and broadly, and coupling this control with increased output. Indeed, all three are realized by the Tyrell Corporation, largely through its technological invention of replicants. Tyrell's purview extends beyond the outer planets while it controls the means of production through cheap, competent, abundant, and easily replaceable android slave labor. There is no confusion as Tyrell's assistant Rachel affirms, "Commerce is our goal here at Tyrell." The primacy of capitalism is undeniable as the corporation supersedes traditional government. The

company is the sole authoritative body: crafting policy, ruling, supervising, and enforcing. There is no mention of presidents, parliamentarians, or judges; power is held in the literal and symbolic pyramid of Tyrell headquarters. The police, including Gaff and Deckard, report to Tyrell rather than a public judiciary. In this society, corporate and governmental institutions are conflated. As administrative norms are thwarted, imbalances of power assume their stead, effecting the "underside of the law," wherein "growth of a capitalist economy gave rise to the specific modality of disciplinary power…the technique, universally widespread, of coercion." (17) Here, the dominance of private enterprise cultivates control through an expansive matrix which operates at both immense and minute scales.

These tactics of power advanced by capitalism and technology are made possible by certain disciplinary mechanisms. Again, the approaches in the essay and film dovetail; as Foucault writes about "hierarchical surveillance, continuous registration, perpetual assessment and classification… though the ensemble of technical inventions," (16) he precisely foretells the methods in *Blade Runner*. In the film, the police continually use the Voight Kampff test, examining one's retina, in an effort to detect if the subject is human or replicant. The "technical invention" of interrogation is the only tool capable of this determination and is utilized broadly and frequently, with coerced consent, in the service of categorizing, monitoring, and ranking. Visible yet unverifiable (administered without warning or sharing conclusions) the Voight Kampff is a looming mode of scrutiny and discernment, a panoptic model of indefinite observation and threat of "correction." Here, the gaze of the blade runners parallels that described by Foucault: a "normalizing gaze" that surveils and makes possible cataloging and punishment. The gaze is also turned inwards as this perpetual evaluation is internalized by those in the film, thereby furthering the panoptic agenda and establishing yet another layer (in the widespread web) of discipline. As characters in the film are often uncertain of their android status, the consequent anxiety and fear create a climate of endless self-checking, "the file that is never closed." (20) Rachel, Leon, and Deckard all compulsively scrutinize their photographs and memories; are they authentic or planted false evidence of humanity? The unknowing is a means of control that paralyzes and fixes these individuals in place; their disequilibrium fosters a compact model of self-questioning and therefore self-observation. In this way, the potential replicants police themselves. As Foucault describes, "he simultaneously plays both roles; he

becomes the principle in his own subjugation." (5) Deckard is not just the means of discipline but the subject of it; within *Blade Runner's* panoptic structure, the inmates become the bearers.

As manufactured beings, these androids also straightforwardly fulfill Foucault's forecast of the fabrication of subjects. As the panoptic schema depends on a multiplicity of individuals, the replicants serve as a means for swift, economical, customized, and responsive population growth. The panoptic system not only anticipates this increased scale, but the role of the subjects within as well. Operating in a climate of surveillance and ultimately the centralization of knowledge, people are not necessarily subjugated nor altered by the machine, but rather invested, even subconsciously complicit. As Foucault writes: "…the individual is carefully fabricated… we are part of its mechanism," (p.14) Rachel reflects this tenet as she asserts, "I'm not in the business. I am the business." Here, subjects are contrived as part of the construct. Further, if one reads the "fabrication of subjects" as a metaphor as well, it acts as a double entendre. Namely, the premise of the film relies on the distinction and hierarchy of humans and replicants and the consequent need for the blade runner bounty hunters. As the narrative evolves, this classification becomes specious. Since the rogue replicants have a built in expiration date (Roy dies "naturally" before Deckard can kill him,) the need for these professional hitmen becomes entirely superfluous. More importantly, a fundamental erasure of difference between humans and androids ensues. If anything, the latter seem superior in intelligence, strength, beauty, and even emotional development. Indeed, they embody the Tyrell Corporation slogan: "More Human, than Human." Hence, the alleged project of the blade runners is a subterfuge, a fabrication of a subject. This distraction enables the quotidian work of the panoptic machine to remain unbothered, unquestioned; it also serves to promulgate the ever-present threat of enforcement, which is perhaps the real value of the blade runners.

This schema of control and the specter of punishment rely on vision. The panopticon, etymologically Greek "all of/for sight," must communicate the potential to watch and account for everything, which is the precise aspiration of power structures in *Blade Runner*. The film is replete with visual motifs. The opening scene flashes from an aerial city view to a close up of an eye that reflects futuristic Los Angeles, the Voight Kampff requires an examination of the pupil, Roy and Leon take a memorable visit to Hannibal Chew's Eyeworks laboratory, and the android "skin job" Zhora is the constant object of the male gaze (a meta-panopticism) as she endures the leering eyes of men in the strip club and Deckard's warning that there are peep holes in her

dressing room. Meanwhile, the policeman Gaff has eyes that shift from blue to brown, conveying a nimbleness of his vision; the narrative intimates that only Gaff can observe Deckard's true nature (i.e. a replicant,) as he creates an origami unicorn referencing a scene that must have been implanted in Deckard's memory. Lastly, It is no coincidence that Leon attempts to kill Deckard by gouging out his eyes while Roy successfully murders Eldon by pressing "the eye of the genius" (14) into his own brain. Here, imagery and allusions to optics serve as consistent reminders that movements are monitored, but they also hint at a distinction between the mechanisms of eyesight and actually "seeing."

Eyes as iconography are constant reminders of surveillance while they also suggest (in)capacity for insight. This is epitomized by Eldon Tyrell who dons coke bottle glasses. Severely nearsighted, he is unable to view the broader picture. Despite being an inventor with an imaginative and innovative view of the future, he literally and symbolically lacks perception. In the film, at times real vision, especially Tyrell's, is limited compared to that of the androids. This is poignantly introduced as Roy says to Hannibal, "If only you could see what I've seen with your eyes." Even more tender and moving is Roy's death scene wherein he describes the wonders and pain of existentialism through the power of vision: "I've seen things you people wouldn't believe... All those moments will be lost in time, like tears in rain... Time to die." Roy continually eschews the conception of an individual as machine cog, as a body in the apparatus of production. When he drives a stake through his hand just to feel pain and to know he's alive, the replicant becomes unrecognizable and irreconcilable as a Foucauldian fabricated subject. Although *Blade Runner* embodies the theme of vision, as well as other panoptic archetypes, the film simultaneously elucidates their failure. The irony is that panopticism is a theory constructed on the ability to see, but its architects, whether they be Foucault or Tyrell, are blind to the fundamental beauty, resilience, and indomitable spirit of humanity.

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The Modern Techniques and Consequences of Genetic Manipulation By Amanda Tapia Garbellotto

Abstract

All the characteristics of living beings are defined or influenced by specific genetic sequences, the genes, present along the DNA strand of each organism. Recently, investment in biotechnology has made possible the development of methods that aim to alter the natural codes of species and manipulate them to obtain scientific advantage. This procedure, the basis of genetic engineering, requires not only a high level of knowledge of the biological structures of living beings, but also safe and precise technological resources. Besides the various alternatives of procedures to promote the alteration of genetic material, there are varied applications of the method, which maintain specific objectives and targets. One of the most researched opportunities today is gene therapy, whereby genes responsible for pathologies could be inactivated or replaced. Although there are already theoretical and experimental tests about its application in living organisms, the subject is still extremely modern and, due to the rapid speed of technological advances, divides opinions about its future consequences. Therefore, the impact that this technique has on nature engages the scientific community in a broad discussion about its harms and benefits to society, especially in the medical field.

Introduction

The human genome project (HGP), launched in 1990, concluded, in 2003, the goal of mapping all the genetic sequences present in the human genome. The proposal was presented by the United States, but, in the end, it gained the international collaboration of eighteen countries, among them Brazil, which led teams of researchers in renowned educational institutions. Accumulating a total investment of 53 billion dollars, concomitant with the rapid technological innovations of the time, the project could be completed two years earlier than initially planned.

From the data collected it was possible to identify all the genes and nitrogenous base pairs that constitute human characteristics. Genes are stretches of DNA which contain specific codes, recognized by the sequence of combinations of nitrogenous bases of each nucleotide, which transmit information for the production of a certain protein. These, in turn, are responsible for defining the characteristics of individuals, which are acquired hereditarily. The genetic makeup of human beings is called genotype, but it is not the only regulator of the traits observed

in people, since the environment also influences their apparent and behavioral characteristics, which are called phenotype; both denominations were founded by Wilhelm Johannsen, in 1909.

Because it was carried out by several global research institutions, the genome project centralized all the collected results in a digital base and was organized by a specific inaugurated body, HUGO (Human Genome Organization). Currently, the main objective of the association is to ensure the application of the knowledge generated through the study of the human genome for the improvement of the health of individuals. In this way, in-depth research into the specific functions of genes aids in the diagnosis of diseases and the discovery of new technologies, including drugs and techniques for their treatment.

The technological evolution of scientific equipment plays a key role in the development of processes related to the use of categorized genetic information. One of its main examples is the advance of genetic engineering, which provides the manipulation of the genetic material of an organism, from the implantation or substitution of specific genes. Therefore, with the use of this resource, it is possible to modify characteristics present in living beings, adapting them to human pretensions regarding the creation of transgenic foods, animal cloning, or disease treatment, topics that demonstrate some of its impacts on nature.

Being inserted in a very modern area of science, several practical applications of genetic engineering are still frequently questioned, giving rise to a critical debate regarding the consequences of its future implementation within society. On the other hand, the improvement of technological means offers the opportunity to expand research with respect to the innovation of different existing methodologies, which will be analyzed in detail, and have, above all, the purpose of altering the biological structures responsible for chronic diseases.

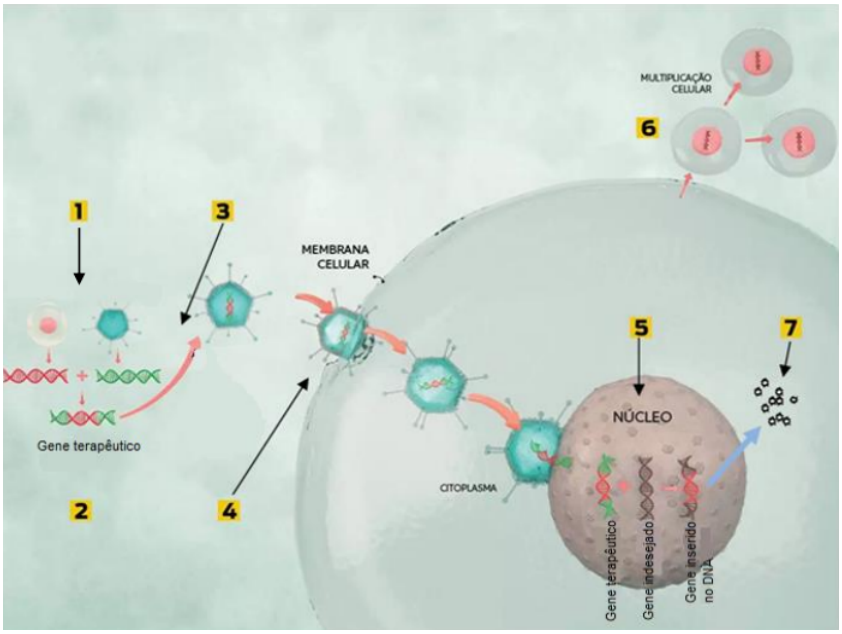
In order to broaden the understanding of how current methods are developed within this area and the influences they receive from the conclusions drawn from research, this paper will additionally evaluate the social impacts involved. It will investigate its most notable techniques of practical application and singularities of each, along with the analysis of actual results already released, and explanation of the resources still intensively researched by the scientific community, whose conclusions gain great recognition for offering relevant data enabling the future advancement of these methodologies.

Gene Therapy

Gene therapy is, in modern times, one of the areas which concentrates more effort within the sphere of genetic engineering applications. Although its initial projects sought to develop treatments focused on hereditary diseases, which are usually associated with defects in specific genes, its objectives were re-evaluated so that they could reach acquired diseases such as AIDS and several cancers, since their incidence in the population is more frequent. Thus, nowadays, more than half of the investments for the exploration of new techniques for the application of gene therapy are directed to the study of fighting cancers.

Another aspect that differs from the original principles of this field of research is the methodology used. The idealization of genetic engineering consisted in the removal of the stretches of DNA responsible for commanding the production of defective proteins, generating diverse pathologies; and their substitution by genes which contained adequate information for the synthesis of correct chains. However, because it requires a complex procedure, and mostly dispensable, nowadays, it is preferred to perform only the introduction of a regular gene in the organism.

There are numerous ways of inserting specific genetic codes into a cell, a process known as gene transfer; the most widely used ones, however, fall into three fundamental categories: physical, chemical, and biological. In the first, the transgene is mechanically injected into cells, which can be done using an electronic device, the micromanipulator, whose function is to add DNA fragments directly into the nuclei of target cells. Nevertheless, besides the need for specialized equipment and professionals, this method reaches an extremely limited part of the organisms' tissues. In contrast, chemical procedures facilitate, by means of chemical substances, the entry of the genes of interest into the cells.



Still, the main practical way of carrying out the implantation of transgenes is the biological one, which is carried out with the aid of living organisms that are naturally capable of transferring genetic material into cells, such as certain bacteria, and especially viruses (Fig.1). To ensure that the vectors will not present health risks to the organism, related to its natural life cycle, both the genes in charge of ensuring its proliferation and the pathological ones are removed from the microorganisms and then replaced by the material with therapeutic intent studied. There are four families of viruses that, through this structure, have obtained the most satisfactory results, these being retroviruses, adenoviruses, adeno-associated viruses and herpesviruses. Fig.1: Selection of therapeutic gene and vector; 2, Replacement of virus genes with therapeutic genes; 3, Introduction of genome into virus; 4,transfection; 5, Replacement of defective gene with therapeutic gene; 6, Correct gene is passed to daughter cells; 7, Correct proteins start to be produced. (PAIVA, JULIO CESAR CASTRO DE, 2017)

Additionally, gene transfer is also performed in two ways with respect to the contact of the implanted vectors with the organism's tissues. The in vivo mode consists in applying the vectors directly into the individual or restricted to the cells that are to undergo transformation, thus ensuring more reliably that they reach their target. On the other hand, it is also possible to implant the vectors in a particular group of cells, which are previously taken from people, usually from their bone marrow, and cultivated in vitro (Fig.2). After they have received the

intended genes, they are implanted back into the body, already containing the specific modifications; this technique is called ex vivo.

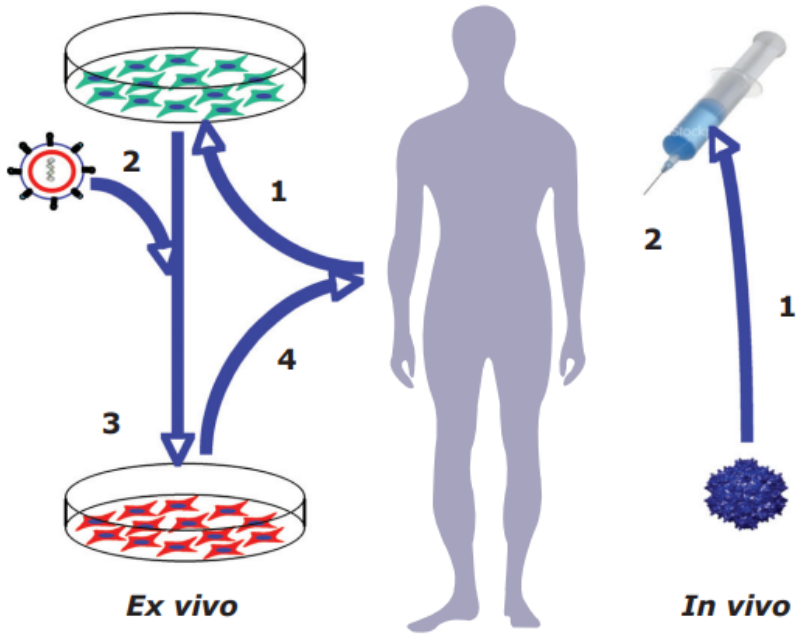


Fig.2: Ex vivo: 1. collection and in vitro culture of the patient's cells; 2. transduction with a vector carrying the therapeutic gene; 3. selection and expansion of the cells with therapeutic genes; 4. reintroduction of the modified cells into the patient. In vivo: 1. appropriate formulation of the vector carrying the therapeutic gene; 2. direct injection of the vector into the patient's target tissue. (Source : usp magazine)

Stem cells, not only from embryos, but also from adults and children, are often the targets of research involving the insertion of genes, especially for therapeutic purposes, because of their ability to differentiate into different types of cells. In this way, the aim is to increase the effectiveness of this method for the treatment of diseases in specific tissues. Furthermore, the execution of induced pluripotent cells is being intensively studied, that is, cells at first normal would obtain a potential for differentiation into different groups, which can be selected from the codes induced by scientists to them, according to people's needs.

"An example of this combination of gene therapy and stem cells would be the generation of gene transfer vectors for the creation of induced pluripotent stem (iPS) cells, in order to generate the differentiation of iPS and provide an additional phenotype from this differentiated

derived cell. Patients with chronic liver disease with hepatitis virus infection (e.g. hepatitis B virus and hepatitis C virus), who require liver transplantation, may be amenable to liver transplantation of mature hepatocytes or iPS-derived hepatocytes. Not only may gene transfer be necessary to convert stem cells into hepatocytes; since transplanted cells are susceptible to being reinfected by the hepatitis virus, transfer of a vector encoding a short hairpin RNA directed against the virus would constitute the transplanted cells with resistance or 'immunity' to reinfection. Resistant cells can repopulate the liver over time and restore normal liver function." (Gonçalves, Giulliana Augusta Rangel and Paiva, Raquel de Melo Alves, 2017)

In addition, the examples mentioned above mainly highlighted the application of genetic engineering in various cells of the body, not linked to reproduction, exclusively modifying the stretch that causes the pathology. For this reason, this technique can be compared to a transplant, replacing defective cells with healthy ones, and is called somatic. However, the same technologies mentioned above are also used in embryos or germ cells, female or male gametes. This technique gives rise to wide debate and controversy about its objectives if implanted in human beings.

First of all, the germ alteration generates the multiplication of this induced change to all the following cells of the individual, consequently ensuring that the characteristics are transmitted to their descendants. For this reason, although it has already been tested in laboratories on mouse species since the 1980s, in many countries genetic manipulation in embryos was prohibited, even before this application was developed for humans. However, the study of methods of inserting genes into both germ cells and the embryo are increasingly being encouraged as they present a possible solution to a large number of diseases.

Mice, which serve as objects of research within the field, have conquered an important role, since through the addition of specific stretches of DNA, they begin to present specific diseases that can be more deeply analyzed, and that belong mostly to fields associated with oncology, immunology, and neurobiology. Therefore, even if it does not mean the direct use of genetic engineering in human health, the experiments performed in other living organisms have the objective of helping the understanding of genetic information related to a certain disease and how they can be treated.

Practical Applications of Genetic Engineering

In the early 1970s, the experimental application of genetic engineering techniques in living organisms began. Led by Paul Berg, a team of researchers completed the first cloning of genetic material, using recombinant DNA technology, and winning, in 1980, a Nobel prize. For the success of the research, restriction enzymes were necessary, in charge of cutting specific stretches of the DNA strand which would be implanted in other cells. The first step is to cut the nucleic acid molecule and then insert the DNA fragment into the nucleic acid of a compatible host cell. When the latter divides, it duplicates the molecule of the inserted DNA fragment. (CANDEIAS, 1991). Recombinant DNA technology produces artificial combinations of DNA molecules, usually from two different sources, most often from different species. (KLUG et al., 2010, p. 323).

From this procedure, the possibility of using the manipulation of the genome of living organisms, with the most diverse objectives, came closer to the reality of various scientific fields, which visualized innovative opportunities for their area. At this point, the main applications of this technology related to medicine will be presented, not limiting its influence on the development of gene therapy, but highlighting other, perhaps less talked about, ways in which it offers alternatives for the treatment of diseases through antibiotics, vaccines, and even hormones.

"Vaccines, for example, can be classified into three groups or generations by the manufacture or preparation of the active ingredient, the vaccine antigens. First generation vaccines employ in their formation the pathogens, inactivating or attenuating the micro-organisms. In the second generation the induction of antibodies directed at a single target, such as a toxin, responsible for the disease symptoms, can be obtained (LINDEN, 2010) and finally, the most advanced generation of vaccines, called gene vaccines or DNA vaccines. The genes for the antigen of interest are located and cloned, where the DNA is injected directly into the muscle of the individual or animal, after the vaccination of the antigen of interest the muscle cells start to express it, triggering the desired immune response (REIS, 2009). In the recombinant vaccine the individual receives the gene that encodes a typical protein of the aggressor agent, where, his body will start to produce the exogenous protein, stimulating his immune system (LINDEN, 2010)." (OLIVEIRA and SILVA, 2010)

Because of the variation in utilities of the recombinant DNA method, specific bacteria have also become fundamental for the production of insulin, hormone responsible for the reduction of glycemia (rate of glucose in the blood) by promoting the ingress of glucose in the

cells (LINS, BARBOSA and OLIVEIRA), which is essential for people with different types of diabetes. From the isolation of the messenger RNA of the gene responsible for insulin production, the complementary DNA is obtained and inserted into a plasmid, which in turn will be injected into an Escherichia coli. (BAESHEN et al., 2014).

Even today, any application of gene therapy in people is contradictory and raises both positive and negative criticism, simultaneously from the scientific community, and from society itself. However, there is already the disclosure of experiments carried out, which were based on the use of this technology in human organisms. In these cases, the patients are submitted to a long-term follow-up in order to document the body's future responses, especially when the modifications are made in embryonic and germ cells, since besides the immediate safety risks during the alteration of the individual's genome, the impacts that may influence the body's functions in the future, present as a consequence of the procedure, are not fully known.

One of the biggest outrages related to the premature application of these resources was the conviction of the Chinese scientist responsible for using CRISPR technology to modify the genome of two twin children. The main alleged purpose of the procedure was to make them resistant to the HIV virus, considering that their father was HIV-positive. However, when announcing its realization, through less credible means within science, the team was harshly reprimanded, as it was claimed that the technique was not yet completely safe, and could impact the other functions of the bodies of the individuals who would develop from the manipulated embryos. Therefore, two years after the case was exposed in the media, the doctor who coordinated the experiment was sentenced to prison and fined. Additionally, the country was widely accused of not having sufficiently strict regulations on the genetic modification of embryos considering its possible biological and social effects.

"More recently, in August 2017, a similar experiment was published by the journal Nature. Conducted at Oregon Health and Science University by scientist Hong Ma's team, the study sought to correct mutation in the MYBPC3 gene in human embryos. This variation is known to cause hypertrophic cardiomyopathy, a disorder characterized by thickening of the heart muscles." (FURTADO, RAFAEL NOGUEIRA, 2019). The results were considered positive by the scientific community, because of 54 embryos fertilized with sperm containing the mutation, 36 had this characteristic changed, while 13 had only part of the embryonic cells corrected. If compared to the percentages of the pathology appearing naturally, the data are extremely

motivating. Moreover, considering that the tests were worked on embryos created specifically for the purpose of scientific study, not presenting any intention to be developed, as recommended, for example, by the Academy of Science, Engineering and Medicine of the United States, the research was better accepted and internationally recognized.

Another therapy already applied in medicine was worked on by the San Raffaele Scientific Institute in Milan, Italy, and involved three children from families with a history of metachromatic leukodystrophy. Before the manifestations of degenerative impacts to their brain functions, stem cells were taken from the patients, which were cultivated in vitro and had the correct genes implanted by a modified viral vector. The most notable consequences for the three were generally positive, since all were able to have a regular development, when compared to people affected by the pathology. On the other hand, it is described that they had side reactions that required further long-term follow-up, although, according to scientists, these effects do not prove the ineffectiveness or unreliability of the method. In the article. Published by Science magazine there was also the report of one of the researchers involved in the project, Alessandra Biffi, assuring the encouragement whose patients' responses brought to the group responsible for its execution, and stating, that aware of previous imperfections, the scientific community seeks to increasingly perfect the ways of applying genetic engineering to improve the quality of life of individuals with some disability. "Gene therapy can be improved. We may be living in a new era, where we may be able to do more than we have done in the past."

Crispr-CAS9 Technology

As already mentioned, genetic engineering integrates a field of science which is committed to the constant advancement of information and technologies that influence the research methods and applications worked on. In this context, one of the most significant discoveries for the area, which refers to a technique that intends to facilitate and improve practical gene therapy, is CRISPR Cas9.

At first, it is relevant to distinguish the origin of this tool in order to understand how it can be used in the treatment of diseases in humans. From its translation in English "clustered regularly interspaced short palindromic repeats", CRISPR refers to genetic information present in bacteria, which is interspersed with stretches of viral DNA, taken from species of the microorganism that have already invaded the bacteria or their ancestors. In this way, part of the

genetic code of the antigens is integrated into the bacterial organism, helping to send an immune response to a new attack from the same individuals. Then, the invader is combated by means of an enzyme capable of cutting the double strand of viral DNA compatible with fragments of its nucleic acid already recognized by the body; this released protein, in turn, is called Cas.

"Cas nucleases become pathogen-specific by a unique property of the enzyme, which is the requirement for a gRNA (guide RNA) sequence that activates the enzyme and selectively directs the nuclease to complementary DNA sequences. This property of Cas proteins has led to their application as a high-fidelity nuclease to produce DNA breaks or cuts at virtually any desired location in genomic DNA in vivo (Fig.3). Among the Cas nucleases, Cas9 has become the most widely studied and widely used." (CONG et al., 2013; MALI et al., 2013; FRIEDLAND, 2013; DICKINSON, 2013; CAI et al., 2016)

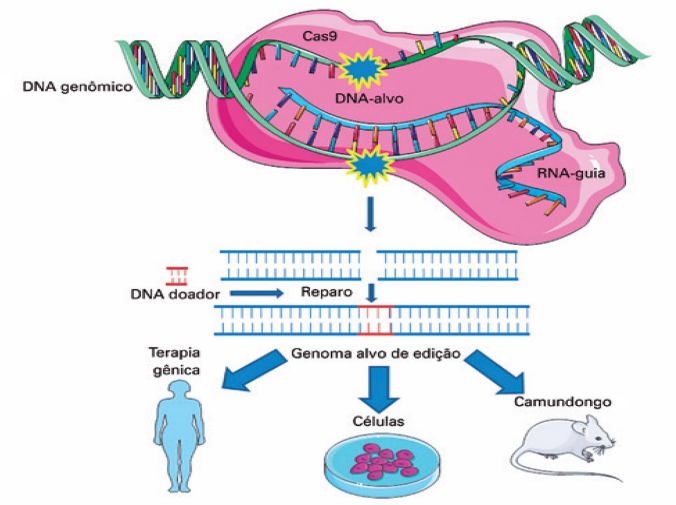


Fig.3: CRISPR Cas9 system. The technique basically involves three molecules: a nuclease (usually wild-type Cas9 from Streptococcus pyogenes), a guide RNA (known as single guide RNA), and the target (often DNA).(GONÇALVES, and PAIVA, 2017)

In addition to the CRISPR method, it was found that within the cells themselves, there are mechanisms to repair sections of the broken DNA strand. Therefore, it was concluded that modifications in the original codes present could be made from the fragmentation of specific parts, being them, in the case of gene therapy, those that have irregular combinations, causing pathologies.

Based on these properties, it is possible to use the CRISPR Cas9 technique to disable genes responsible for diseases, if the sequence of bases that encode the production of irregular proteins is known. Once this is decoded, scientists are able to create a guide RNA complementary to it in order to precisely orient the Cas9 nuclease to the fragment that is to be cut. Due to the simplification offered by this technology, the enzyme's function is constantly being compared to that of a pair of scissors. The cells will then start the process of reconstructing their DNA double strand in the area of the gene that has undergone the intervention. In this process the bases are correctly combined with their pairs already present in an orderly fashion.

One can, however, have the mechanical induction of the gene that will be formed, substituting the disabled one. This procedure is executed starting from the insertion of a specific stretch of DNA selected, which will connect the two ends that have been cut off. Therefore, a process of manipulation of biological characteristics is built not only in human beings, but also in animals and food. Furthermore, the study of this technology, applied mainly in embryonic or germ cells, exposes the opportunity to introduce certain qualities in future living organisms, one of the main visualizations of this project being the treatment of heart, respiratory, viral, genetic, and cancer diseases, since they currently present a higher degree of complexity.

In recognition of the various advances allowed from the gene editing method proposed by the CRISPR Cas9 technology, the two scientists responsible for its development were awarded the Nobel Prize in Chemistry in the year 2020. Dr. Jennifer Doudna and Dr. Emmanuelle Charpentier were the first pair of women to receive the prize, which was awarded based on the publication of the technique in the scientific journal Science in the year 2012.

"Jennifer Doudna, Emmanuelle Charpentier and team decided to do an experiment to prove the hypothesis raised regarding CRISPR-Cas9. They decided to use genes from a jellyfish for the experiment. Researcher Martin Jinek did the process manually of the performance of CRISPR and Cas9. He chose five different gene sequences and "chemically" prepared five RNA molecules to combine them. Then he incubated the RNA with Cas9 and the jellyfish DNA and waited for the result. He then verified that the jellyfish DNA was cut off. The RNA molecules had acted in the exact place where the researcher had selected for the "cut", which occurred through Cas9. A new technology capable of editing any genome in any organism was validated and built!" (DOUDNA; STERNBERG, 2017, p. 82-83)

Biologist and president of the Carioca Association for Assistance to Mucoviscidosis (ACAM-RJ), Cristiano Silveira, describes the achievement by citing: "Eight years ago an article in Science magazine talked about adaptive immunity of bacteria against viral attacks and described CRISPR. And how important is this? All of it! Here was the most powerful gene editing tool that would pave the way for research into revolutionary treatments for genetic diseases and a myriad of other applications."

However, although the technique plays an indispensable role in today's biotechnology, the leading researchers of the project themselves emphasize the importance of establishing a code of ethics preventing the inappropriate use of the procedures, since the hasty application of the method can cause, besides damage to the patients' health, widespread negative social impacts.

Ethics

Representing a technology with revolutionary capacity within the sciences, as it enables the manipulation of nature on a biological scale, directly related to the factor responsible for all the adaptive characteristics, resulting from long evolutionary processes of each living organism. Genetic engineering conquers at the same time support from various scientists and apprehension from institutes and part of this community.

"Certainly, this is a very complex issue. If we take into account only the techno-scientific issues, imagination is simply the limit. However, if we take into consideration human welfare, the dignity of the person, the survival and the future of humanity, the limit that must be honored as an imperative, is the implementation of ethical values that direct the experiments in this scientific area." (Sganzerla, Anor and Pessini, Leo, 2020)

Among the benefits offered by this technique, especially from its simplification with the use of CRISPR Cas9, it is inevitable to mention the industry of genetically modified foods, products which are questioned about their consequences not only to human health, but also about their economic impacts. It is notable, however, that they present traits that make them more resistant to certain climatic and environmental aspects that are commonly considered unfavorable to planting, as well as to various species of pests; additionally they can also have their nutritional value increased, ensuring health and nutrition, especially for people living in food insecurity.

Moreover, with the technology that has been developed, there is, of course, the opportunity to investigate treatments for numerous diseases, both genetic and acquired, which have long been present in society. This area, however, is the one whose application is most closely dependent on a controversial discourse. On the one hand, these procedures can allow for an intense improvement in the quality of life of individuals affected by these diseases, so for more radical scientists, using them for the benefit of society would be a moral obligation for researchers. As Julian Savulescu, philosopher and bioethicist, member of the Oxford Uehiro Centre for Practical Ethics, and collaborators state: "editing experiments on embryos are not only necessary, but "a moral imperative". According to these authors, to refrain from engaging in life-saving research is to be morally responsible for predictable and preventable deaths.

On the other hand, most researchers recognize the potential of somatic cell gene therapy for the treatment of disease and have specific reservations when it comes to genome modifications of embryonic and germ cells. This position is mainly due to the fact that these characteristics will become part of the human genetic lineage. "For Reiter (1992), the technical-genetic intervention on the fertilized egg, even if performed for medical purposes, does not have the meaning of treatment of the person but of manipulation of his identity" (AZEVEDO, ELIANE S.).

Even before CRISPR was experimentally used for the editing of human DNA in embryos, several members of the scientific community got together in order to publish an article entitled "Don't Edit the Human Germ Line" in the journal Nature. Based on applications of techniques to modify the genome of different animals, the researchers argued against expanding and permitting the use of these techniques in human embryonic cells. The main justifications for the position claimed that the risks of the procedure included "random mutations that would occur in the modified genome, harmful consequences for future generations, extrapolation of the procedure to non-therapeutic purposes, and negative impact on the social perception of somatic cell editing. Given this scenario, the authors recommend the establishment of a voluntary moratorium aimed at discouraging human germline modification." (SGANZERLA, ANOR and PESSINI, LEO, 2020)

In contrast, recognized scientists highly engaged in the area, such as Jennifer Doudna herself, along with Paul Berg, and David Baltimore, also a Nobel Prize winner in Medicine in 1975, wrote an article for Science magazine, rebutting some positions reported in the previous

publication, by exposing possible benefits of gene editing for research purposes, citing, among them, the reconfiguration of the biosphere.

Numerous international research institutions have also expressed their intentions, favorable or unfavorable, regarding the use of this technique, in an attempt, in general, to balance its advantageous aspects and the risks involved. Thus, the International Bioethics Committee of the United Nations Educational, Scientific and Cultural Organization (UNESCO) reinforced that "gene therapy could be a watershed in the history of medicine and genome editing is undoubtedly one of the most promising endeavors of science, for all mankind", affirming additionally, however, that "the human genome underlies the fundamental unity of all members of the human family, configuring the heritage of humanity. As a consequence, interventions should be admitted only for preventive, diagnostic and therapeutic reasons, and without making modifications for the descendants. It is up to society then to establish a moratorium for the genomic engineering of the germ line."

Within the council's resolution, a warning is included regarding the use of scientific resources developed by private companies, aiming to maximize their profits from the exclusive, and mostly unregulated, application of the technology. It highlights in this context, the abuse of legislation in countries that have weak restrictions on this scientific field; emphasizing, therefore, the relevance of building a documentation containing universal standards that should be presented as examples for the inspection of these practices by the proper governmental body of each nation.

Conclusion

Recognizing all the advances capable of innovating current medicine and the relationship of human beings with nature on a biological scale, it is impossible to disregard the opportunities provided by the development of genetic engineering. The techniques, which can be implanted in various living organisms from the specific study of the genome of the species, make possible an infinite number of applications aimed at various objectives. The improvements in the technologies used within this scientific field represent, therefore, the possibility of creating more complex, but safe procedures, guaranteeing more precise and efficient research results.

Based on the information presented, CRISPR Cas9, along with the mapping of all human genetic sequences project (HGP), should be highlighted as huge revolutions in biotechnology,

since they become the safest method to promote the manipulation of genetic material. In this context, although the limits of DNA strand modifications are still widely discussed, especially when it comes to altered characteristics in embryonic or germ cells, it is noteworthy that benefits are also offered to the health of individuals through the techniques performed, which can also be restricted to the tissue directly affected when used for the treatment of specific diseases.

For this reason, the investment in studies within this area, accompanied by a growing debate among professionals in the scientific community should be highly encouraged, considering that its consequences will be perceptible within current and future society. However, no research should be allowed if it threatens the safety of the individuals involved and disregards norms adopted by governmental and international authorities, developed with the purpose of ensuring the beneficial and controlled use of these resources.

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Rousseau's Thoughts of Education and New Solutions of Korean Education By Nayeon Park

Introduction

What do you think freedom is? Many philosophers thought 'freedom' can provide true human nature and equality to people. One of those famous philosophers is Jean-Jacques Rousseau, who wrote *Discourse of Inequality* (1755), *The Social Contract* (1762), and *Emile, Or Treatise on Education* (1762). Across these works, Rousseau's definition of 'freedom' changed. At first, he thought that the human form of nature is the best human form in terms of 'freedom'. But afterwards, he realized and admitted that humans have to live under the control of a government. However, he knew that if humans live under a government, then they will lose their freedom and will, leading him to write, "Man was born free, and everywhere he is in chains."[5] This was Rousseau's pessimistic view of human society, and he tried to change this restricted society through his idealistic education system.

In imagining this new system, Rousseau emphasized that children can grow up with their human nature, yet still be a part of a civilized society. Rousseau's ideas are explained through the eyes of Emile in the book *Emile, Or Treatise on Education*, who is taught how to think, act and solve problems by himself. Through such a system, Emile is able to grow up to be a free, but well-educated and well-behaved young man.

The reason Rousseau wanted changes in the education system is clear: children grow up to become members of the society, and thus education's change would cause the conversion of the corrupted society. Only children who were taught under free education are able to make a fair and virtuous society, because children who never experienced 'freedom' would not know about what a 'free society' is. Children would never know how to make a free and fair society if they were taught in a confined and restricted education. This endless cycle of unenlightenment, in which people are locked in inequality and restricted from society's ideal view, makes people lose their true self. Rousseau's new idea of education would change the children and furthermore society. Therefore, modern education should be changed in a more free way, in which children can learn and experience independence.

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[5] Jean-Jacques Rousseau, *Discourse on Political Economy: And, the Social Contract (Discourse on Political Economy ; And, The Social Contract)* (Oxford University Press, 1999), 45.

The first section describes Rousseau's general preoccupation with freedom, presenting both and tracing his definition of freedom across his career. The second section focuses on the idea of freedom in the *Emile*, analyzing how Rousseau implements freedom in the authoritative relationship between tutor and tutee. The last section considers the advantages of his educational philosophy today with a specific focus on the Korean school system.

Rousseau's Overall Theme and Ideas of Freedom

Before turning to Rousseau himself, it is helpful to understand him in the broader context of the Enlightenment. Immanuel Kant, one of the central Enlightenment philosophers, defined enlightenment as when people think by themselves and try to understand the reason for phenomena rather than explaining it by just using God or religion. In his essay "What is Enlightenment?"[6] (1784) he described enlightenment as man's release from his self-imposed tutelage and his inability to make use of his understanding without direction from another. Heavily influenced by Rousseau, this definition of enlightenment is crucial to understanding Rousseau's philosophy of freedom.

Rousseau was one of the most famous philosophers of the Enlightenment. Born on June 28, 1712, he grew up in Geneva, Switzerland but lost his citizenship when he converted to Catholicism at the age of sixteen and fled the city. This might be the reason why he started to have an interest in inequality and freedom. At the age of thirty, he met Denis Diderot, one of the editors of the *Encyclopedia*, the iconoclastic and anticlerical centerpiece of French Enlightenment thought. Through his collaboration with Diderot, Rousseau became famous, particularly for his refined and unique writing style. His books were all about freedom and the state of nature, but he faced severe hostility about passages in *Emile* and *The Social Contract* that eighteenth-century audiences considered irreligious. But even with these controversies, he continued to attract attention and influence until his death in 1778.

Among Rousseau's books, he had a specific focus on 'freedom.' His books usually talked about nature and modern society. In*The Discourse on Inequality*, he claimed that social people are suppressed by society's view, while savage people live within themselves. It shows that he thought people are dependent on, and dominant towards, each other. They judge others, put

[6] Immanuel Kant, *Foundations of the Metaphysics of Morals, and, What Is Enlightenment?*, 2nd ed., rev., The Library of Liberal Arts 113 (Upper Saddle River, NJ: Prentice Hall, 1995).

themselves into the frame, and are restricted by society. And by doing so, people feel their existence as part of society. *The Social Contract* continued to criticize modern society's confinement, emphasizing that people cannot be free in society. They are always restrained by the influence of a leader or government, and lose their freedom. After trying to imagine a government that could favor freedom in *The Social Contract*, he wrote a book on pedagogy named *Emile, Or Treatise on Education*. Again, he blamed modern society's way of education and the necessity of freedom of learning. He wanted people to learn something by themselves without others' help and be independent. By reading these books, the definition of freedom that he offered is not just that people should express themselves without restriction, but that they need to know how to live on their own independently. People should not rely on others; they must be able to handle the world on their own.

The Discourse of Inequality most strongly expresses how the state of nature is the best human form. The book focuses on property as the major reason for the inequality and corruption of the society. What Rousseau tried to say through this book is that rich people dominate poor people in order to gain happiness and power. However, this oppression of the poor people under the rich people destroyed natural liberty and made the law of property and inequality. As society developed, the range of wealth became larger, and there were some people who could not follow the development of society because they were lazy. Those people became poor and couldn't have any property. They just depended on wealthy people, leading to slavery, which is inherently unequal. In this book, the meaning of 'freedom' is the state of nature. Rousseau claimed that every person cannot be free when they are in society because they are restrained by property and inequality. Eventually they will dominate and depend on each other, and make themselves a slave, forgetting their true nature. Therefore, in order to be free, he suggested that the people should go back to their state of nature, which cannot be dominated by others. He asserted that no one can restrain the men in nature. However, as Rousseau would come to realize in his later work, this solution is too idealistic for the real world. People have already developed a lot and can't go back to their natural state. Therefore this theory is only a theory.

In *The Social Contract*, his most famous book, he again argued that men are born free and they are independent from others. Rousseau's main view of the society is the corruption of individuals. He claimed the government should guarantee freedom to people. In his book, he had two statements: humans are independent under the state of nature, and society makes humans

complicated and suppressed. God gives the most simple and pure state of the world to humans. However, people built a society with various artificial things, which made humans stray far away from their natural state. This is why Rousseau said that as society develops, it corrupts people and makes them dependent on others. Rousseau cites the example of enslaved people's dependence on wealthy people or owners. Slaves can't do anything by themselves, and just be tamed by their owners. They tried nothing to be changed and independent because they don't want to. Society is so complex that it makes people lose their wills and keep living in an unwilling state. This is the problem of society according to Rousseau. He claimed that those slaves should fight back against their masters and gain their freedom. However, Rousseau didn't mean that there should be no restrictions at all. No restrictions means anarchy: people can do literally anything that they want. It will cause chaos and serious problems in society such as murder, theft, and trespassing. Society has to have at least some limits, but it is difficult to determine how. If the limits go too far, people would have no freedom as Rousseau described. If they are too small, society would be in chaos. What Rousseau has offered as a solution is that people give up all their rights and move together as the entire community. There is no leader, and everyone would have a fair position. In *Social Contract*, he wrote, "One of the most important things for a government to do, therefore, is to prevent extreme inequality in wealth, not by depriving the rich of their possessions, but by denying everyone the means of accumulating them;"[7] He suggested that wealth be distributed from rich people to poor people, so everyone can have the same amount of property. He claimed this will create the best fair society and eliminate the dominant relationship, which results from dependence on rich people and the inability to take care of oneself. Rousseau's definition of 'freedom' in society is thus fairness: not to harm anyone with authoritarianism or dictatorship in their community. Through this book, he wanted to demonstrate modern society's corruption, being suppressed by rules and losing people's freedom, and suggest a possible solution to this different idea of government. However, this solution is also idealistic because it is hard to form a society where everyone has the same amount of property.

[7] Rousseau, *Discourse on Political Economy*, 21.

Emile, Or Treatise on Education

Emile was written in 1762 by Jean-Jacques Rousseau. Since the book included the section named "Profession of Faith of the Savoyard Vicar," which questioned the existence of God and the legitimacy of Catholicism, the book was banned in many countries. Nevertheless, it was widely read, especially for its idea of a new system of education to obtain innate human natural characteristics but also be a part of a corrupted society.

Emile, the title character, was an imaginary child that Rousseau teaches. In the book, Rousseau focused on teaching Emile how to be independent from other people and how to think by himself without any help from others. But I think Rousseau's interference was too much in this book. Rousseau tried to control Emile by a hidden guide. On the outside, Rousseau looked like he was giving full freedom to Emile. However, on the inside, he actually manipulated every single situation to lead Emile to a way that he wanted. For example, a cake race. Rousseau wanted to teach Emile how to estimate and find the shortest or efficient distance, so he held a race contest, in which only the winner could eat the cake. "Continuing with him to mark in different places the points from which each boy was to begin at the same time, without his noticing it I made the distances unequal."[8] And when Rousseau made this race contest, he forged every course for Emile. If everything is made by Rousseau, then is Emile really free? There is a contradiction between Rousseau's first promise, which is freedom of Emile, and what he really did in the book.

"No one likes to make a useless effort, not even children. They are obstinate in their attempts; but if you are more constant than they are stubborn, they get weary and never return to crying again."[9] There are some parents who do whatever their child wants because they can't beat their child. Rousseau criticizes those parents in this book. Children are not stupid, he claims, and they know that their parents will grant their desires. This is why children whine to their parents to get what they want. However, parents should show that they are more powerful and stronger than them in order to stop their pestering. If the child realized that they can't control their parents, they would give up because they don't want to waste their energy and they already know their parents will not grant their favors. The parent's role is to make them realize that fact and their position. Then, there is a question, why should children be restricted? The answer

[8] Jean-Jacques Rousseau, *Emile: Or, On Education*, trans Allan Bloom (New York: Basic Books, 1979), 142.
[9] Rousseau, 69.

would be children don't know how to be responsible. If children have no restrictions and do whatever they want, what would be the consequences of those actions? Chaos, confusion, and mess. They have to be limited during the protection period and they should learn how to limit themselves in order to become a civilian and how to be responsible for their actions. Even a free society has some basic rules, and people have to live under those rules. In order to become those people, children should be restricted and learn how to follow those rules.

However, Rousseau hated when someone taught or told a child what they should do. He wanted the children to think and solve by themselves, not by adults, and realize what is efficient for them on their own. The children never learn without their own experiences. They should keep trying and know what is good for them and what is bad for them. In the book, Rousseau gives the example of teaching Emile about gardening. Emile wanted to plant, so he destroyed the melon farm and planted his beans. However, that farm was owned by a gardener. So, the gardener rooted out all the beans that Emile planted with great care. Through this painful experience, Rousseau taught the concept of 'property' to Emile. Each land is owned by an owner and Emile can't do planting without that person's permission. Rousseau taught that responsibility of property through making Emile feel sadness, despair, and despondency.

Through this educational system, Rousseau wanted to create a person who is a member of society, but still has human nature. Rousseau made Emile himself have fun in education and did not force him to do what he hated. Rousseau gave him freedom of learning and respected his opinion. Rousseau tried to show what is the most idealistic education. Although Emile is a virtual character, his new way of education was very impressive to people. And also I think, this idea is the most realistic and achievable in the real world, and able to change the world in a more free society.

In "The Constraints of Liberty at the Scene of Instruction," Diane Berrett Brown describes Emile as a sleepwalker, guided by Rousseau, the tutor: "in a state of ignorance, he can wander in safety, unaware of the dangerous precipices that surround him."[10] If Emile awakens suddenly, he would be exposed to full danger. So, Emile had to gradually adapt to danger, learning about the real world. Brown wrote Rousseau's writings are marked by this tension of liberty between necessary protection and freedom. Children are naturally dependent on their

[10] Diane Berrett Brown, "The Constraints of Liberty at the Scene of Instruction", in *Rousseau and Freedom* (Cambridge University Press, 2010), 159, https://doi.org/10.1017/CBO9780511712098.010.

parents, but dependence is only needed as long as children need protection. What freedom actually means is learning how to be responsible, so they no longer need protection from others. Brown questions whether Emile is ever truly free, but it is clear that Rousseau's goal is to move him gradually from this state of sleepwalking to full freedom.

Although Rousseau's educational system is appealing, it is important to note that he thought women were different from men. He thought that women should depend on men and exist for men. He claimed that women and men have a naturally different purpose, therefore women don't have to take the same education as men because their purpose is being a mother. There was a character named Sophi, who is going to be the wife of Emile. She only appeared in chapter 5, and she got a different education compared with Emile. Rousseau taught her that she has to be calm, kind, good at household chores, and support her husband well. There are some quotes about her, "She is a pupil of nature just as Emile is, and she, more than any other, is made for him. She will be the woman of the man,"[11] "Women are made to yield to man and to endure even his in- justice."[12]

I agree with his plan of a new education system, but I claim that he had the wrong conception of women. It's true that women and men are naturally different. However, that doesn't mean that they should learn different things. Every child should have the freedom to learn whatever he or she wants. Gender alone should not be an element in deciding what children should learn. In fact, his idea about separate gender roles contradicts his idea about free education. He claimed that children should follow their own will or natural passion to learn. Enforcing a gender-specific education curriculum exactly opposes this idea. Mary Wollstonecraft was a philosopher who criticized this aspect of *Emile* in *A Vindication of the Rights of Woman* (1792). In this book, she claimed Rousseau's education was unfair for women because Rousseau asserted women and men should have different education: "to enable the individual to attain such habits of virtue that will render him or her independent… This was Rousseau's opinion regarding men: I extend it to women."[13] She claimed that women are not inferior to men. They are naturally born the same, but women are given worse educations, leading to the educational difference between men and women.

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[11] Rousseau, *Discourse on Political Economy*, 417.
[12] Rousseau, 403.
[13] Mary Wollstonecraft, *A Vindication of the Rights of Woman: An Authoritative Text, Backgrounds, Criticism*, 1st ed., Norton Critical Edition (New York: Norton, 1975), 14.

Many people assert Rousseau is paradoxical. He claimed his own opinions, but at the same time, he claimed another opinion that was against his original claim. The representative examples are Emile and Sophie, and Emile's freedom. He claimed that every child has to be independent and free, however, he claimed that women are different from men so they have to be dependent. Through this claim, I guess his term of 'child' means only for the men. Also, at first he said he would guarantee Emile's freedom, but it was not. Like this he has some paradoxical sights and opinions, but he still provided and improved a lot the idea of freedom.

How Can These Books Change Today's Society?

Even two and a half centuries later, many people still rely on each other and don't think for themselves. This is the problem of the Cramming method of education. The current Korean education is the opposite of the best education that was suggested by Rousseau. Teachers always have to teach something to their students, or else, the students can't do anything alone. For example, when I was in an elementary school in Korea, my teacher didn't allow students to solve problems before the lecture even if students already knew the answers. I think the reason is just a respect for the teacher or in order to prevent one student from being advanced alone. Korean education never provides any opportunities or chances to really experience learning or being independent. It's just authoritarianism or a dictatorship of teachers.

The educators should try to raise the students' motivations. As Rousseau suggested, students have to think on their own. Without this skill, when they grow up, they will just sponge off to rich people and never be able to live independently. Rich and powerful people will dominate most of the world and in consequence the gap between rich and poor will be severe, which means extreme inequality. Therefore, they need freedom and motivation from learning. They need to be fascinated to study on their own. Just forcing study would never motivate the students because it is not their own will. Teachers' role should be to encourage and provide some sources to students to make them interested in studying. Directing every single way is never truly helpful and motivates students. When teachers do a lecture, they should first give out problems and give students a chance to try to solve them. Before the lecture, students will not know how to solve problems, so it leads them to think: "What should I do first?" and "How should I solve it?" These questions would eventually lead them to solve problems, or they can at least try and then

be motivated to listen to the lecture. This method will provide the chance to think on their own, rather than just listening to the lecture and being taken out of their chances to think.

Also, the government needs to increase the opportunities that students can learn about the world by experiencing it. They need to experience the world with their body. For example, they can plant their own plants as Rousseau did, and make students learn how to take responsibility on their own. Overprotection is never good for children. It rather makes children weak, irresolute, and dependent. Also, sometimes they need to experience the bad side of the world. So, I think it will be good if there are some chances to meet the real criminals, but surely they should be rehabilitated, and talk with them to ask some questions about their lives, and what they did. And through these special classes, students will learn and can be more alert about the crime.

Schools have to change one more thing that Rousseau himself supported: gender discriminative education and society's view of women. It is true that a lot of discrimination has disappeared, but there are still some that remain. For example, a lot of women are still housewives who just care for their children and do houseworks. Some of them would like their jobs, but some of them are kind of influenced by society's pressure so they became housewives. Some men are suffering from society's view that they should have a sustainable job so they can keep their house. Also, Korean education has some differences between boys and girls. For example, in P.E. class, the running limitation is different. Girls only have to run two laps of the schoolyard, whereas boys have to run three laps. Girls and boys are physically different, but that should not make a difference in their education, as Wollstonecraft said. In order to have a free society, the government has to change this first. Adults should not limit a student's ability. There are some solutions to change this education, such as school can teach girls that they don't have to be housewives or boys that they don't have to work in a company. So, schools can provide more opportunities for students to choose their jobs depending on what they really want and like to do, not by society's pressure.

Some people have the opposite opinion with me. They argued that Korea developed a lot from the twentieth century because of their education system. According to Tim Thompson's "The Strengths and Weaknesses of the Korean Education System," Korea's current status is mostly achieved rather than inherited, and amount of education is a determinant of status independent of its contribution to economic success.[14] So, the author claimed that the current

[14] Tim Thompson, "AN INSIDER'S PERSPECTIVE", January 13, 2018.

Korean educational system led to the huge development of Korea. That is true; however, the era has changed. This educational system has worked until now, but the future should be different. The people didn't have to think so far because they needed to just work in a factory and do whatever their boss ordered them to do. But there are no more factories in our future because robots will replace people. If the current education style keeps going on, then in the future, a very few people who are able to think on their own, will dominate the whole world. And it will create severe inequality. So, the education system has to be updated as well to avoid the inequality situation. Everybody has to take a fair and the same education from the school, which is not just solving problems, but teaching them how to think.

Conclusion

There is no doubt that freedom is very important to humans. This is claimed by most of the philosophers, not only by Rousseau. But many people still argue about what freedom is, drawing on *The Social Contract* and his other books. But in my opinion, the most practical idea of freedom is the one Rousseau presents in *Emile*. I think it was very impressive that Rousseau brought people the concept of what is a fair society and what is a free education.

It is true that society has corrupted a lot. So, our current society has to be changed, starting from the education system. The students need to be more motivated and get excited to study on their own, not forced by educators. Educators have to offer opportunities for students to think. Children are our future, and there is still a hope that society can be changed little by little. I believe that Rousseau's books were a big step towards building a free society.

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Highlighting the Large Global Health Impact and the Underfunding of Research Related to Giardiasis: A Neglected Parasitic Disease That Disproportionately Affects the Poor By Brinda Srinivasan

Abstract

Giardiasis is an intestinal disease caused by the microscopic parasite, Giardia duodenalis, which is endemic worldwide (number of cases approaching 184 million/year, US cases estimated 1 million/year), prevalent in underprivileged communities with low sanitation and poor access to clean drinking water. The common symptoms of the disease are stomach cramps, bloating, nausea and bouts of watery diarrhea, and some less common symptoms include vomiting and blood in the stool. The 5-nitroimidazoles and benzimidazoles derivatives-based standard of care drugs have historically been effective but their tolerability is poor and treatment failures are being reported globally. In 2004, the World Health Organization (WHO) added Giardiasis to the "Neglected Diseases Initiative" because of the human health burden it imposes and its association with poverty. Despite this, Giardiasis research remains largely underfunded by global agencies (WHO, European Commission, US NIH, Wellcome Trust, UK MRC, Gates Foundation and others), and there is no meaningful pharmaceutical industry research on this disease either. Outside of the 3 main or well-funded infectious diseases (Malaria, tuberculosis, HIV/AIDS), in general, the funding for all other infectious diseases combined amounts to a very low allocation (2.1% of the total development assistance to healthcare). Since the US contributes to more than a third of all health-related world-wide developmental assistance, it is relevant to discuss the funding priorities of the US NIH. We report here that the NIH in the period 2017-21 allocated a meager $16 million to Giardiasis research as compared to other infectious diseases like Gonorrhea (with a similar disease burden) receiving $272 million and conditions like lung cancer receiving ~$9 billion annually. As a result, drug resistant giardiasis infections are emerging and giardiasis related childhood malnutrition is worsening, with its own long-term healthcare costs and consequences. Common sense solutions to address this emerging global problem, including how to direct policymakers' and funding agency's attention to this disease, versus other major global health concerns, is discussed. Overall, the goal of this publication is to bring awareness to a prevalent but neglected disease in the hopes of improving coordinated research funding response to Giardiasis

Introduction

Giardiasis is an intestinal disease caused by the microscopic parasite Giardia duodenalis (formerly known as G. lamblia and G. intestinalis) which is found worldwide, especially in areas with limited sanitation and unsafe ground water usage. Common symptoms include stomach cramps, bloating, nausea and bouts of watery diarrhea; less common symptoms include vomiting and blood in the stool. (1) It is a leading cause of infectious gastroenteritis disease worldwide, with a reported prevalence of 2-7% in high income countries and 2-30% in low-income countries. (2) The WHO has added Giardiasis to the "Neglected Diseases Initiative" given its burden and association with poverty. (3)

Giardiasis is one of the most common causes of waterborne disease in the United States. The Centre for Disease Control (CDC) estimates that each year Giardia causes a total of more than 1.1 million illnesses in the U.S in total, with a vast majority of cases going unreported. (4) This parasite is commonly found in backcountry streams and lakes, but also in public water supplies, swimming pools, spas and ground wells. Giardiasis usually spreads through the consumption of contaminated food and water, and through human contact. Approximately 50% of infections are asymptomatic. (5-6) Since 1993, Giardiasis has been designated as a nationally notifiable disease in the U.S., and therefore the data on disease prevalence is collected through passive surveillance, which means that healthcare providers and laboratories voluntarily report any positive case to the local and state health departments. (5) This data is then voluntarily reported to the CDC by respective agencies via the National Outbreak Reporting System (NORS). The definition of a confirmed case has evolved over the years and today laboratory-confirmed Giardiasis is defined as the "detection of Giardia organisms, antigen, or DNA in stool, intestinal fluid, tissue samples, biopsy specimens, or other biological samples". (5)

Since 2011, the incidence of reported and confirmed giardiasis cases in the US has been <7.0 cases per 100,000 population. In the latest 2019 CDC report, there were 14,887 reported giardiasis cases in the U.S. (96.6% confirmed and 3.4% unconfirmed). The reported U.S. disease prevalence varies across states. Giardiasis incidence ranged from 2.0 per 100,000 population in Arizona to 14.4 per 100,000 population in New York City. (5) By US region, incidence of reported giardiasis cases ranged from 4.4 cases per 100,000 population in the South to 7.6 cases per 100,000 population in the Northeast. (5) Differences in incidence rate is potentially due to observed differences in risk factors, modes of transmission, magnitude of individual outbreaks,

and most importantly, the screening capacity across states. Another study estimates that Giardiasis results in 3,584 hospitalizations per year. (6) The disease, however, is often unrecognized and under-reported globally because 50% to 75% of Giardia infections are fully asymptomatic. (6) Furthermore, there are several non-reporting states in the U.S., which include Illinois, Kentucky, Mississippi, North Carolina, Oklahoma, Tennessee, Texas and Vermont. Taken together, it indicates that the current reporting of Giardiasis vastly underrepresents the magnitude of the disease burden in the U.S. because of the asymptomatic nature of the disease, limited diagnosis, and the current CDC policy of voluntary reporting.

1.0 Estimation of Giardiasis Global Disease Burden

Globally, the prevalence of giardiasis is reported to be high: in the range of 20 to 30% in developing countries and 3 to 7% in developed countries. (6) Since accurate data on the burden of parasitic diseases like Giardiasis can assist policy makers, in 2007, the WHO established the Foodborne Disease Burden Epidemiology Reference Group (FERG) to estimate global and regional burdens of foodborne diseases. (10) One of the main FERG established thematic task forces was the Parasitic Diseases Task Force (PDTF). This task force estimated the burden of three parasitic diseases: cryptosporidiosis, entamoebosis and giardiasis. Using this data as reference, the global impact of the Giardiasis is listed in table 1. (10) Table: 1, Median number of total and foodborne illnesses, Disability Adjusted Life Years (DALYs) and Giardiasis cases as a proportion of all global food borne illnesses

Disease	**Median # of Global Illnesses**	**DALYs**	**Proportion of total food borne illnesses**
Giardia	183,842,615	171,100	15%

Table 2: Median rate per 100,000 of foodborne illnesses and Disability Adjusted Life Years (DALYs) by global region

Geography	**# Illnesses**	**DALYs**
Africa	809	0.8

Americas	309	0.3
E Mediterranean	670	0.6
Europe	54	0.03
SE Asia	159	0.1
W Pacific	354	0.3
Global Totals	410	0.4

2.0 Pathophysiology and Transmission of the Disease

The life cycle of Giardia lamblia has two stages: infectious cyst and a vegetative trophozoite. The disease transmission is mainly by the fecal-oral route and through oral consumption of giardia cysts through fecally contaminated water or food. Person-to-person transmission and, rarely, animal-to-person transmission has been reported. (6) Giardia levels have been measured to be as high as 100,000 cysts/L in untreated sewage, 100 cysts/L in treated sewage, and 10 cysts/L in surface water sources and in tap water. These reported levels are usually higher in water sources near agriculture (e.g., cattle or dairy farming) or municipal and residential wastewater discharges and even in public places like preschools or theme parks where a greater fecal-oral transmission through contaminated surfaces and food/water is possible. Unfortunately, giardia is highly infectious with ingestion of as few as 10 cysts causing a symptomatic infection and is often known to easily spread between family members. (7) Thus, the high prevalence zones are usually the underprivileged rural areas with relatively poor sanitation (and who often use untreated groundwater), who live in close quarter housing conditions, and where both early diagnostic and treatment facilities are often unsatisfactory. The relative contribution of unsafe food handling versus contaminated water source as the origin of disease transmission has been difficult to discern. Initial estimates indicated that approximately a median of 15% of Giardia infections were transmitted via contaminated food. (10) In general, this was considered higher than expected for an enteric protozoan. Investigators initially estimated that only 7% of Giardia infections acquired in the U.S. were of foodborne origin. (11) However, a more conclusive 40-year summary of outbreaks of Giardiasis reported to the CDC identified that 16% of 242 outbreaks were the true result of foodborne transmission.

(12) How much of this CDC data on the origin of infection can be extrapolated to assess the global disease is unclear, considering that most endemic zones lie in areas that have poorer water purity and sanitation standards.

Sexual transmission of Giardia through oral-anal transmission or fecal-oral transmission among men who have sex with men is well documented. (15) The prevalence rates of giardiasis among men who have sex with men is reported to be as high as 30%. (15-16) Although giardiasis related diarrhea is not a major AIDS-associated symptom, the prevalence of giardiasis in patients with AIDS is higher in developing countries. (17) Overall, immunocompromised patients are clearly more susceptible to the development of chronic giardiasis as compared to the general population. (18)

3.0 High Prevalence of Giardiasis in Children and Its Consequences

G. duodenalis infection has been reported in approximately 15% of children aged 0–24 months in the developing world. (22) This contributes to the global burden of diarrheal diseases that collectively constitute the second-leading cause of death in children under five years of age. (23, 6) In the U.S., 7-54% of children attending day-care centers are reported likely infected, but these cases are largely unreported because either the children remain asymptomatic or undiagnosed. (7)

In the developing world, the high prevalence of giardiasis in children is a public health concern. (3) The long-term impacts of persistent giardia on children's growth and development are not yet fully understood. (8) Unfortunately, what is known is that giardia and infection in early childhood is associated with poor cognitive function and failure to thrive. (13) Giardia infections can be detected repetitively in over 40% of the infected children suggesting that persistent infections are also relatively common. The chronic infection has been associated with damage to intestinal permeability and is known to cause malabsorption of nutrition. (13) This evidence is captured in the MAL-ED birth cohort study, where the persistence of Giardia before 6 months of age was associated with a 29% deficit in weight-for-age and at 2 years of age a 29% deficit in length-for-age. (9) As few as 3 episodes of chronic diarrheal disease per year, in the first 24 months of life, is associated with significant reductions in both height (approximately 10 cm) and IQ (10 points) by the time the children reach the age of 7–9. (21). In summary,

Giardiasis likely adds to the burden of childhood malnutrition in regions where poverty related poor diet problems preexists (discussed in detail in the next section).

Giardiasis induced changes in the gut can last long after G. duodenalis infection is cleared both in children and adults (24), irrespective of whether the patient is symptomatic or asymptomatic (22). So, this parasitic infection is a risk factor in the etiology of major non-communicable diseases such as irritable bowel syndrome, chronic fatigue, obesity, and type II diabetes (25, 26). The above observations show that persistent giardiasis, either due to lack of diagnosis or resistance to administered treatments, combined with poor childhood nutrition, is a global childhood developmental and wellness concern. The cost of these resulting chronic conditions is far greater than recognized and could constitute a major healthcare related global socioeconomic challenge. A lack of recognition of this fact, and a lack of coordinated global health response thus constitutes a basic human rights and equitable healthcare access challenge.

3.1 Trifecta Problem: Poverty, Hunger and Giardiasis in Children

In addition to poor sanitation in underprivileged parts of the world, lack of nutrition also can also contribute to the global incidence of giardiasis in children. It is well known that food rich in Zinc and vitamin A have a protective effect against giardiasis among children. (9) In one randomized study in Brazil (in a region where approximately one-third of children had at least mild vitamin A deficiency) of 79 children aged 2 months to 9 years of age, those who received vitamin A had significantly fewer new Giardia infections compared with those treated with placebo over a three-year period. (33) In another study in Mexico, treatment of children aged 6 to 15 months with zinc and/or vitamin A was associated with decreased incidence of giardiasis. (34) The above data, though sparse, starts showing a correlation between lack of proper early childhood nutrition, poor sanitation and access to healthcare with higher disease burden (as shown in figure 1 below). The long-term impact of this trifecta problem will result in an unhealthy transition to adulthood and may be the cause of the high DALY observed with Giardiasis.

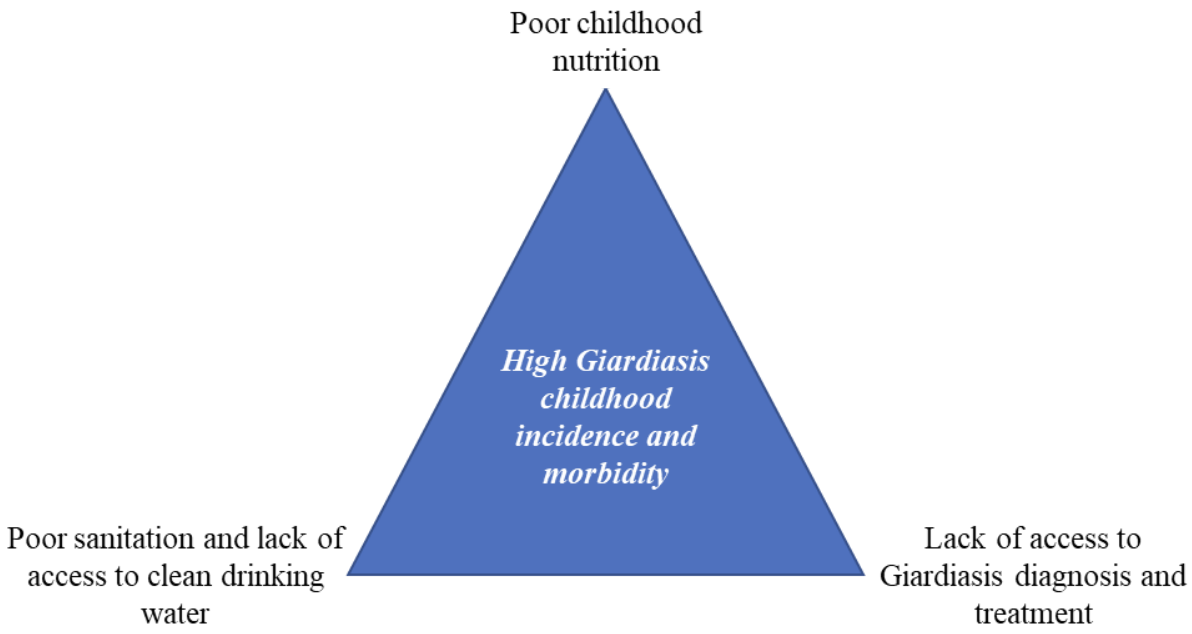


Figure 1: Trifecta of causes worsening the childhood Giardiasis crisis

3.2 Disease Diagnosis Technical Challenges

Globally, patient fecal sample microscopy remains the "gold standard" for detecting parasites and a definitive diagnosis is achieved by detection of Giardia trophozoites or cysts in stool specimens. While progress has been made in developing diagnostic tests that involve non-morphological methods, such as immunofluorescence microscopy, ELISA and parasite DNA related PCR tests that provide a more sensitive disease diagnosis, their associated cost has prevented them from becoming the standard of care.

The inherent problem with the microscopic diagnosis of giardia is the intermittent nature of excretion of intestinal parasites. So, a triple feces test protocol that combines three consecutive days of sampling and testing is required for conclusive Giardia detection (>90% sensitivity), as compared with single collection and microscopy of stool samples (sensitivity between 50-75%). (14, 19)

The collection, handling, transportation, and manual sample microscopic examination of patient feces samples can also be a challenge to achieve effective and large-scale testing for this disease. (19) So, wide application of fast biochemical and molecular assays testing could be a game changer for diagnosis and containment of disease outbreaks in vulnerable populations.

Unfortunately, PCR assays for specific intestinal parasites remain too expensive for diagnostic laboratory use in most geographies, especially in developing countries where the disease is endemic. So, general screening of stools for a variety of pathogens for achieving a differential diagnosis remains the standard of care. Implementation of definitive multiplex rt-PCR assay, allowing the simultaneous detection of multiple infections such as Entamoeba histolytica, Giardia and Cryptosporidium species and genotypes infections, should be a key global health priority. (19)

The other confounding factor is due to the shared symptoms with other GI conditions such as: viral gastroenteritis, food poisoning, lactose intolerance, irritable bowel syndrome, traveler's diarrhea, tropical sprue, Crohn disease, amebiasis, cryptosporidiosis, strongyloidiasis, and Dientamoeba fragilis infections, which require careful differential diagnosis by well trained physicians. (19)

3.3 Pharmacotherapies Available and Growing Clinical Drug Treatment Failures

Effective, approved drugs for giardiasis consist of six classes of compounds, namely 5-nitroimidazoles and benzimidazoles derivatives, quinacrine, furazolidone, paromomycin, and nitazoxanide. Nitroimidazoles (metronidazole and tinidazole) and albendazole are the drugs of choice for giardiasis, but lack of treatment compliance and side effects can result in treatment failures. (27)

Increasing number of drug treatment failures have been reported worldwide, which fall into 4 broad categories. (27):

1. **Drug Related**: failures due to poor treatment compliance amongst patients, either due to reducing symptoms or drug avoidance due to excessive side effects. Low dose or insufficient duration of treatment administered. Variations in drug systemic exposure (pharmacokinetics) due to interactions of coadministered drugs.
2. **Gut Microbial Related**: Dysbiosis in the microbiome of the patient (potentially due to diarrhea) leading to malabsorption of the drug
3. **Host Related**: immunodeficiencies in patients or co-administered immunosuppressant diet or drugs could increase drug treatment failures

4. **Parasite Related:** Reinfection due to poor sanitation, metabolic adaptation and stress response of parasite (non-genetically encoded), stable resistant microbe (gene mutations or lateral gene transfer)

3.4 Troubling Global Trend in Drug (Nitroimidazole) Resistance:

After 50 years of effective use of Metronidazole (MET), increasing resistance, and giardiasis has been reported. While evidence of parasite adaptation and drug(s) resistance is emerging, studies on the genetic mechanisms of resistance, extent of desensitization to drugs, as well as the development of multidrug resistance, are lacking. (20)

Many studies are reporting this generally unsettling trend: a study of 170 giardiasis cases in Madrid found that 10 (5.8%) failed one or more initial nitroimidazole drug regimens. (28) The frequency of nitromidazole treatment-refractory cases in giardiasis patients, referred to the Hospital of Tropical Diseases in London, increased from 15% in 2008 to 45% in 2013. (29) Infections originating from the Indian subcontinent were especially difficult to treat, with refractory cases reaching 70% (29). Similarly, in a retrospective study on 95 returned Spanish travelers attending a travel clinic, 21 (22%) had refractory giardiasis, particularly in those returning from Asian countries. (30) In a more recent study involving three specialized Tropical Diseases Units in Barcelona, Spain, patients with chronic giardiasis were prospectively analyzed, and around 20% were found to be refractory to the treatment with tinidazole or MET. (31) Also, this study confirms that refractory infections originating from Asia were more prevalent (70%) than infections originating from elsewhere. (31) A recent Czech study genotyping 47 patient samples also found that nine of these (19%) samples originate from patients clinically resistant to MET. (32)

4.0 Global Giardiasis Response

4.1 Development Assistance for Infectious Diseases from Major Donor Nations & Agencies

In the year 2016, Institute for Health Metrics and Harvard published a comprehensive report on the development assistance for health (DAH) disbursement over time, and the first to use past trends to estimate the assistance expected to be provided in the future. (38) DAH refers to financial resources transferred from primary funding channels to low and

middle-income countries for the purpose of improving the health of its citizens. (38) The study concluded that the era of major growth in DAH funding has ended. This observation has profound implications for poor people who live in countries where domestic resources fall well short of the minimum required to cover their healthcare needs. Using the metadata published here (37) we attempted to assess current and future funding levels for a neglected infectious disease like Giardiasis. There are a few important conclusions we derived from analyzing this data:

1. the US contributes close to a third of the all the DAH funding provided (shown in table 3) and so studying US NIHs commitment to Giardiasis research is important
2. total infectious disease allocation constitutes a healthy ~44% of the total DAH funding
3. vast majority of the infectious diseases allocation ($18.25 billion, ~94% of the total) is targeted to addressing only 3 specific diseases, namely, HIV/AIDS, Malaria and tuberculosis (shown in table 4)
4. all the other dozen or so infectious diseases (including Giardiasis) combined receive a meager $1.1 billion dollars in funding (6.1% of the total infectious diseases allocation), as shown in figure 2

Table 3: Year 2015 DAH disbursement towards research and treatment of different diseases provided by major international aid agencies and donor nations (in million US$)

DAH Funding Source	Newborn and child health	HIV/ AIDS	Malaria	Maternal health	Non-commun. diseases	Other infectious diseases	SWAPs/ HSS	TB	Other	Total	% of Total Funding
Gates Foundation	1,030	350	280	210	49	130	89	190	566	2,894	7.0%
Gavi	1,480	0	0	0	0	0	172	0	0	1,652	4.0%
Global Fund	0	1,740	917	0	0	0	57	607	0	3,321	8.0%
NGOs & US Foundations	1,180	3,480	501	1,010	181	145	375	218	2,810	9,900	23.8%
UN Agencies	1,360	348	40	787	101	245	442	52	1,140	4,515	10.8%
United Kingdom	1,100	659	452	429	66	94	335	145	789	4,069	9.8%
United States	1,360	7,530	1,000	1,090	45	332	329	473	953	13,112	31.5%
World Bank	402	143	35	58	30	163	910	29	389	2,159	5.2%
Total	7,912	14,250	3,225	3,584	472	1,109	2,709	1,714	6,647	41,623	

Figure 2: Allocation of funding from main multinational funding agencies and donor nations (in million US$) for different diseases in the year 2015

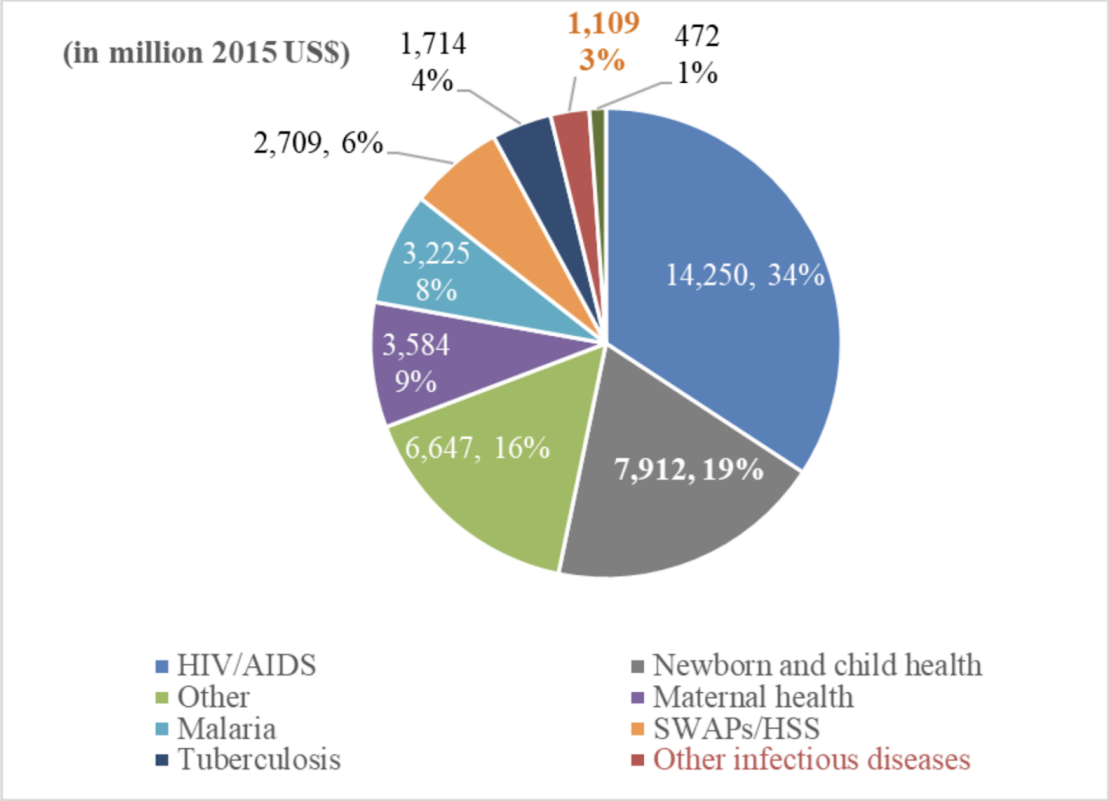


Table 4: Priority health focus areas for the major sources and channels of DAH (in million 2015 US$)

Disease	**(in million 2015 US$)**	**% Allocation of total DAH funding**	**% Allocation of total infectious diseases funding**
HIV/AIDS	14,250	34.2%	78.1%
Newborn and child health	7,912	19.0%	
Other	6,647	16.0%	
Maternal health	3,584	8.6%	

Malaria	3,225	7.7%	17.7%
SWAPs/HSS	2,709	6.5%	
Tuberculosis	1,714	4.1%	9.4%
Other infectious diseases	1,109	2.7%	6.1%
Non- communicable diseases	472	1.1%	
Total DAH Funding	41,622		
Total infectious diseases funding (TB, Malaria, HIV, Others)	18,256		
DAH: Global Development assistance for Health from main multinational funding agencies			
SWAP/HSS: sector-wide approaches and health system strengthening			

4.2 National Institutes of Health (NIH) Funding of Giardiasis Research: A Story of Indifference

The previous sections highlight the immense impact of Giardiasis on human health globally. The U.S., being the largest donor to global health initiatives, has the responsibility of addressing this scrouge on children, the immunocompromised, the poor and the elderly, which necessitates allocation of meaningful research investment towards development of next generation giardiasis vaccine and therapeutics. We present below a comparative analysis of the current state of research investment by the NIH on infectious disease, including Giardiasis.

The main source of information presented below comes from searches conducted in the months of May 2022 using the search feature of the RePORTER portal of the NIH Grants website (https://reporter.nih.gov/).

4.2.1 Lung Cancer

We started by searching for the level of investment into major diseases like Lung cancer as a broad benchmark for a well-funded disease. This disease, understandably, received a major research investment from the NIH, with a 5 year (2017-2021) total research funding of ~$9.4 billion with 19,252 projects and subprojects funded during that period. The yearly investment shows a consistent increase over the 5 year period, starting at ~$1.7 billion growing to ~$2.1 billion. This data is shown in Table 5a:

Figure 5a: The Number of projects and funding of programs in **Lung Cancer** by the NIH from **2017 -2021** (5 years)

Fiscal year	**Projects**	**Funding ($ millions)**
2017	3,469	$1,679
2018	4,048	$1,698
2019	3,888	$1, 897
2020	4,071	$2,008
2021	3776	$2,109
Total	**19,252**	**$9,394**

4.2.2 Pruritus (Skin Itch)

We then continued by analyzing data about the level of investment into a condition like skin itch (pruritus) as an indicator of the level of funding a relatively minor ailment should receive. By referring to pruritus as a minor ailment, the author does not intend to devalue the suffering of patients with this condition, but rather only to draw funding parallels versus a major disease like Giardiasis. Pruritus, understandably, received a much lower research investment than lung cancer in comparison from the NIH, with a 5 year (2017-2021) total research funding of ~$272 million with 582 projects and subprojects funded during that

period, as compared to lung cancer. The yearly investment shows a consistent increase over the 5 year period, starting at ~$44 million growing to ~$57-67 million. This data is shown in Table 5b:

Figure 5b: The Number of projects and funding of programs in **Pruritus (Skin Itch)** by the NIH from **2017 -2021** (5 years)

Fiscal year	**Projects**	**Funding ($ millions)**
2017	106	$44
2018	115	$50
2019	139	$57
2020	119	$67
2021	102	$57
Total	**581**	**$272**

4.2.3 Gonorrhea

Below is an analysis of the level of NIH investment on an infectious disease like Gonorrhea. This disease has a similar disease burden (or DALYS) as Giardiasis and thus should be a good indicator of the level of funding an infectious disease should receive. Gonorrhea received a respectable research investment from the NIH, with a 5 year (2017-2021) total research funding of ~$400 million with 662 projects and subprojects funded during that period. The yearly investment shows a consistent increase over the 5 year period, starting at ~$66 million growing to ~$100 million. This data is shown in Table 5c:

Figure 5c: The Number of projects and funding of programs in **Gonorrhea** by the NIH from **2017 -2021** (5 years)

Fiscal year	**Projects**	**Funding ($ millions)**
2017	113	$67
2018	127	$70
2019	130	$67

2020	145	$95
2021	147	$101
Total	**662**	**$400**

4.2.4 Giardiasis

Below is shown the level of NIH investment into a Giardiasis, with a reported 180 million cases every year. The 5 year (2017-2021) total research funding allocation for Giardiasis was ~$15 million with a mere 42 projects and subprojects funded during that period. The yearly investment shows a < $5 million per year investment over the 5-year period. . The yearly investment shows a consistent decrease over the 5 year period, starting at ~$5 million ending at $2-3 million. *Giardiasis received ~4% of the research funding allocated by NIH to Gonorrhea, which is a disease similar in DALYs in the period of years 2017-2021.* The total investment in Giardiasis was just 5.5% and 0.16% of the funding received by Pruritus (skin itch) and Lung Cancer, respectively. This data is shown in Table 5d:

Figure 5d: The Number of projects and funding of programs in **Giardiasis** by the NIH from **2017 -2021** (5 years)

Fiscal year	**Projects**	**Funding ($ millions)**
2017	11	$5
2018	10	$4
2019	8	$3
2020	5	$2
2021	8	$3
Total	**42**	**$16**

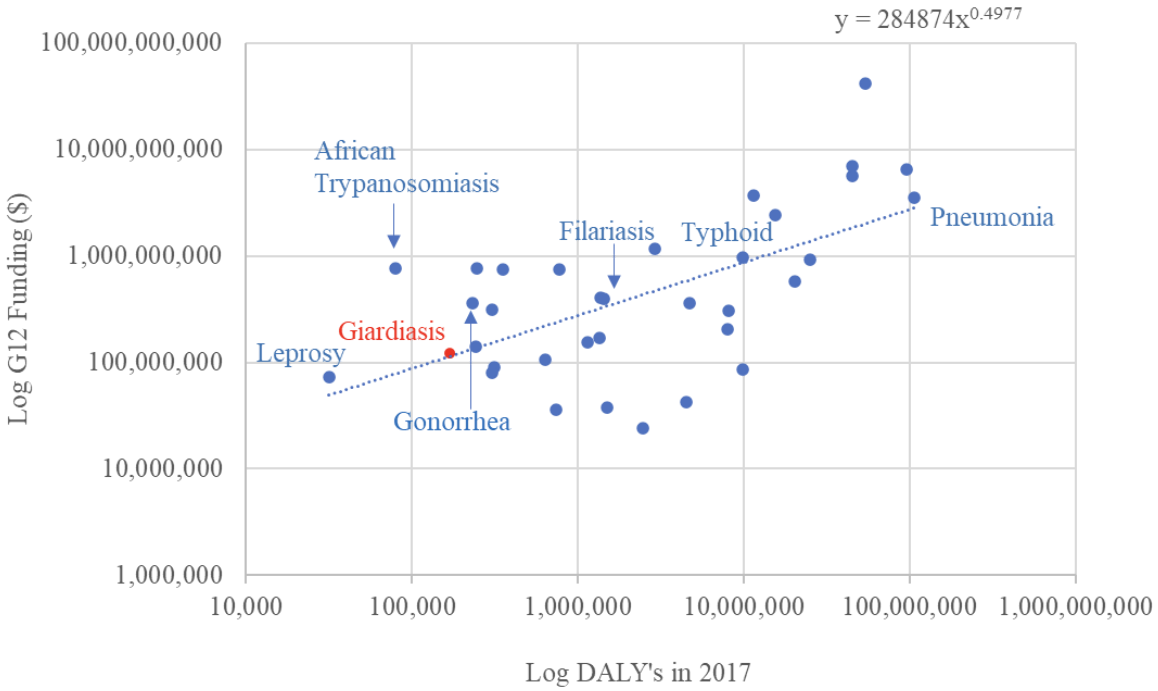
4.3 Giardiasis Funding by G20 Countries

The global public spending for infectious disease research and development, from G20 countries, between the years 2000-2017, is reported around US $105 Billion in the comprehensive study published in the journal Lancet in 2020. (35) These allocations involve

numerous stakeholders across the global health community, including funders, researchers, policy makers, and clinicians. The main sources of these funding's, as per the report, include Gates Foundation, European Commission, US NIH, Wellcome Trust, UK MRC and a multitude of other well-meaning philanthropic organizations across the large segment of wealthy G20 nations.

During this 18-year period (2000-2017), the allocation of funds to specific diseases has been compared to their respective global disease burdens, to identify potential areas of relative underfunding. Unfortunately, no data on Giardiasis is present in this comprehensive publication, which leads us to conclude that the funding for Giardiasis research and treatments must have been insignificant.

The plot below (Figure 3) adopted from the publication by Head MG *et. al.* (35) shows the log(DALY) versus funding (in US dollars) for major diseases, except that for giardiasis, the red circle, is a datapoint inserted by the author of this paper (based on the best fit line) and is absent in the original publication. Based on this analysis, if one were to consider the DALY of Giardiasis one should expect at least ~$115 million spending on Giardiasis research, to stay in line with other infectious disease allocations, as determined from the best fit equation shown in the graph. Unfortunately, the actual Giardiasis funding is ~10 fold lower than what the data indicates is minimally necessary (and is in the 10's of millions of dollars). Once again, this global funding allocation highlights a relative apathy towards supporting Giardiasis research and development. Figure 3: The plot indicating levels of funding of various infectious diseases versus their respective disease burdens (DALYs) (35). The red datapoint is not present in the original publication (35) and was added by the author to highlight the appropriate level of Giardiasis funding (from best-fit equation).



5.0 Conclusion

In general, infectious diseases, outside of HIV/AIDS, Malaria and tuberculosis, do not get the attention of global funding agencies and major donor countries (37). The other dozen or so infectious diseases combined, which includes many major diseases like Giardiasis, receive a small allocation for research and treatment budgets (2.1% of the total development assistance and 6.7% of the infectious diseases sub-allocation), which is not enough to deliver a meaningful solution in the foreseeable future. So, important research that will bring forth new vaccines and treatments will remain starved of funding and vulnerable patients will likely continue to suffer.

The earlier sections describe the large giardiasis disease burden (184 million cases/year and DALY ~171,000 years). Yet, the analysis of U.S. NIH (the major global donor to healthcare efforts) and G20 agencies show that this disease remains largely unnoticed and unfunded. There is also no meaningful private research funding support for this disease, as the authors could not find pharmaceutical industry involvement (either as an independent initiative or through a public-private/industry partnership) into development of diagnostics or therapeutics for Giardiasis. This is evidenced by the fact that none of the major (top 15) pharmaceutical companies, by market capitalization, mention any Giardiasis related research programs on their R&D pipelines on their respective websites or in press releases in the last 2 years.

The assessment of major pharmaceutical companies could be that there is little or no commercial opportunity to invest in the expensive endeavor of developing new drugs for Giardiasis, a disease that primarily affects the poor in developing countries. So, such disinterest in Giardiasis can be somewhat justified for a for-profit industry. The lack of allocation by public funding agencies to support Giardiasis research is harder to explain. The question is how can an effective strategy be developed to focus stakeholder's attention on Giardiasis and convince policymakers/stakeholders to act?

5.1 Advocacy and Awareness Building

Focusing the attention of decision makers at funding agencies has been a challenge so far, in an environment where research dollars, though appearing plentiful, is still insufficient to address all pressing global health needs. It is likely that the emergence COVID-19 pandemic has refocused global priorities for diagnosis, vaccination, and surveillance efforts, and away from already underserved parasitic diseases. The COVID-19 epidemic will likely continue to consume a significant portion of public policy experts' focus and government(s) health services and investment dollars for many years to come. In such an environment, Giardiasis' silent suffering patient's situation is only likely to worsen. The author believes that, despite the challenges Giardiasis advocates face, the following course of action has a reasonable chance of success (see figure 3):

Figure 3: The quadrangular approach to addressing Giardiasis

- Patient advocacy and outreach organization, through formation of **Giardiasis and neglected parasitic diseases foundation** in the U.S.
- **Build awareness** with policy makers, as we are attempting to do through publication of this paper, and through presentations at major public health scientific conferences
- **Incentivizing for-profit research** efforts by assuring an accelerated regulatory approval pathway for treatments. Unfortunately, Giardiasis cannot be considered a “rare” or “orphan” disease designation due to the history and relatively high prevalence. So, creation of a new category for accelerated regulatory approval should be considered.
- **U.S. Congress lobbying efforts to generate political support for minimum support pricing** of new therapeutic in Giardiasis, due to its large global unmet medical need

In conclusion, Giardiasis is currently underfunded and under researched despite its high prevalence throughout lower- and middle-income countries. It is a disease that has many long-lasting health effects, especially in children, and current standard-of-care treatments are encountering new and resistant Giardia strains. Despite this emerging threat, low visibility and support is to be expected from major public or private agencies in the foreseeable future. We hope that through this publication and related advocacy efforts, that we can start the dialogue on addressing the large unmet medical need in this disease and how we may find ways, together, to increase research and development funding for Giardiasis.

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Dissociative Identity Disorder By Anvitha Yalamanchili

Abstract

Dissociative Identity Disorder (DID) is a mental illness described as a disruption of identity characterized by distinct personality states. Borderline Personality Disorder (BPD) is another mental illness characterized by severe mood swings, impulsive behavior, and difficulty forming stable personal relationships. Meanwhile, dementia is a condition of the brain characterized by the impairment of two brain functions: memory loss and poor judgment. Although classified differently, DID and BPD have the same symptoms as dementia and affect the brain similarly. Symptoms of DID and BPD include behavior changes, shorter attention span, ongoing gaps in memory, and loss of time sense, personal info, and past traumatic events. Like DID and BPD, symptoms of dementia include behavior changes, shorter attention span, and lowered impulse control. Additionally, previous research has examined risk factors for neurodegenerative diseases. Understanding what contributes to the etiology of dementia may help us understand the causes and effects of DID and BPD. This could lead to advancements in treatments and therapy for these mental disorders. The present review will discuss the current literature surrounding dementia and mental disorders. It will also explore how the field's understanding of dementia might contribute to advancements in the diagnosis and treatment of DID and BPD.

Introduction

DID and BPD are both mental disorders; there is a large range of symptoms severity related to mental disorders, with DID falling on the severe end of this range (Gillig). DID and BPD are poorly understood disorders, which has led to controversies, misdiagnoses, and lack of proper treatments for individuals with the disorders. The current literature surrounding DID and BPD explains that memory loss and difficulty with decision making are major symptoms of these disorders. However, they are not discussed in the context of dementia, which is a group of conditions also characterized by the impairment of at least two brain functions, such as memory loss and poor judgment (*What Is Dementia? Symptoms, Causes & Treatment | Alz.Org*). Dementia is a better understood disorder, and using what is known about the framework of dementia can lead to better outcomes for patients with DID and BPD. This literature review will

explain how dementia and DID/ BPD are related and how BPD and DID can be better understood, diagnosed, and treated if considered in the context of dementia. It will also address the controversy surrounding DID and BPD by presenting its risk factors, symptoms, and neural and molecular substrates.

Controversy

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, American Psychiatric Association 2013), DID is a well-established mental illness described as a disruption of identity characterized by two or more distinct personality states or an experience of possession. Despite this, many clinicians/caregivers have failed to properly diagnose and provide care for patients that meet criteria for diagnosis. Of 62 respondents who have treated patients with DID, more than 80 percent said they had experienced a range of reactions from their colleagues, including attempts to refuse their patients' admissions to hospitals and to force discharge of patients that the respondents felt were likely to commit suicide (Gillig).

Some researchers speculate that the emotional reactions to the diagnosis of DID stem from anxiety evoked by the disorder's unsettling clinical presence. Other reasons for the heated controversy surrounding the diagnosis of DID are the fear that criminals will get off by blaming their crime on the mental disorder of an alter ego, the rapid increase in the number of cases, and the great majority of cases being reported only in North America. Some doctors believe DID is created by therapists and clinicians who think a disorder exists even when it does not (Gillig).

Because of misdiagnoses, patients with DID do not get the proper treatment for the disorder, which negatively impacts their quality of life. Though DID and BPD present nearly the same symptoms, risk factors, and molecular substrates, there is less controversy surrounding BPD. Though less research has been done on either of these mental disorders compared to other disorders, BPD is much more prevalent than DID. The little controversy surrounding BPD and other similar mental disorders compared to DID suggests that the controversy surrounding DID is unfounded. According to the DSM, more than 70 percent of patients with DID have attempted suicide, and 10 percent of patients with BPD have died from suicide. This review will provide possible treatments for DID and BPD. If the neurobiological basis of DID and BPD is better understood, it may resolve the controversy surrounding their diagnosis, again leading to better treatments, and ultimately better outcomes for patients.

Symptoms

The symptoms section of this paper will describe, in detail, the set of symptoms for each of the three disorders: DID, BPD, and dementia. It will show how each of the disorders have unique symptoms but also several similarities and can therefore be considered as related disorders.

Dissociative Identity Disorder

DID involves a lack of connection among a person's sense of identity, memory and consciousness (Spiegel). It is classified as the existence of two or more distinct identities or ego states (Wang). An ego state is a set of behaviors and experiences that share similarities but are separated from each other by permeable boundaries. Although ego states are often referred to as alters, the alters/alternate personalities in DID have their own identities, each with different names, histories, characteristics, initiatives, and memories; they distinguish what they understand to be their own actions and experiences from those done and experienced by other alters (Gillig).

A known case example of DID is the case of Mary 1 (last name unknown), a quiet 30-year-old woman. She was talking to her therapist about some of the events of her past, which included severe sexual abuse starting at the age of 20 months. She began to tell her psychiatrist about a crying voice she heard constantly: "'Baby cries all the time—Baby—I hear her. She is sad all the time.'" While explaining this story, Mary stops talking suddenly and her posture and demeanor change so much that the psychiatrist felt as though there was a different person in the room. Mary (now a different alter ego, Edith) says, "'She is a wimp…I'll kill him. I'll kill him. I'll kill you too and [Mary] deserves to die.'" When asked to speak to Mary, Edith says that she doesn't have the guts to come back to where they are (Gillig). In this case example, Mary and Edith are shown to have completely different personalities and act and think independently of each other.

Symptoms for DID include sudden changes in mood and behavior or memory loss. Family members can usually tell when a person changes from one identity to another. These transitions can be sudden and startling; the person may go from being fearful, dependent, and excessively apologetic to becoming angry and domineering just as Mary did when she changed into Edith. They may report not remembering something they said or did just minutes earlier; they also may deny saying or doing things that family members witnessed (Spiegel). Lastly,

individuals with DID experience ongoing gaps in memory about everyday events, personal information and/or past traumatic events. These symptoms cause significant distress and problems in social, occupational or other areas of functioning (Wang). Other symptoms include amnesia and detachment (Gillig).

Borderline Personality Disorder

Symptoms associated with DID, including insomnia, sexual dysfunction, anger, suicidal ideations, self mutilation, drug and alcohol abuse, anxiety, paranoia, somatization, dissociation, mood changes, and pathological changes in relationships, are similar to those associated with BPD **(Fig. 1)** (Gillig). An additional symptom of BPD is an intense fear of abandonment; people diagnosed with this disorder may go to extreme measures such as suicidal threats or self-injury to avoid real or imagined separation and rejection. It also includes a pattern of unstable intense relationships, such as idealizing someone one moment and then suddenly believing that the person does not care about them or is cruel ("Borderline Personality Disorder - Symptoms and Causes").

Mary 2 (a different Mary) is a 26-year-old African American woman who was diagnosed with BPD; she presented a history of self-injury, specifically cutting her arms and legs, since she was a teenager. She has made two suicide attempts by overdosing on prescribed medications. When she is stressed, Mary says that she often blanks out in the middle of conversations or while at work. She states, '"I don't know who Mary really is,"' which shows a feeling of dissociation and describes a longstanding pattern of changing her hobbies, style of clothing, and sometimes even her job based on who is in her social group (American Psychological Association Division 12).

More symptoms are rapid changes in self-identity and self-image that include changing goals and values; these changes could happen within weeks **(Fig. 1)**. BPD patients might see themselves as bad or nonexistent. They might also have periods of stress-related paranoia and loss of contact with reality lasting from a few minutes to a few hours. Patients may demonstrate impulsive and risky behavior, such as gambling, reckless driving, unsafe sex, spending sprees, binge eating, drug abuse, or sabotaging success by suddenly quitting a good job or ending a positive relationship. Lastly, they can have wide mood swings lasting from hours to days, ongoing feelings of emptiness, inappropriate and intense anger, and physical fights (American

Psychological Association Division 12). These symptoms could cause them to make regretful decisions causing pain for them and their loved ones and could also ultimately lead to death.

Figure 1. Venn diagram showing the symptoms associated with Borderline Personality Disorder (BPD) and Dissociative Identity Disorder (DID). Though DID and BPD have unique traits and symptoms, they show several similarities; the differences and similarities in the disorders' symptoms are listed in the diagram above. *Created with biorender.com*.

Dementia

Patients diagnosed with dementia mainly experience memory loss, attention deficit, poor judgment, and confusion about everyday events; they might have difficulty reading, writing, speaking, understanding, and expressing thoughts as well. Patients with dementia may find themselves wandering and getting lost in a familiar neighborhood or having trouble handling money responsibly. Family members may notice someone with dementia constantly repeating questions, using unusual words to refer to familiar objects, or having problems with balance and movement; they may take longer to complete normal daily tasks or lose interest in them. Lastly, they might hallucinate, experience delusions, act impulsively, and not care about other people's feelings ("What Is Dementia?"). Therefore, those diagnosed with dementia often act in ways that are very different from their original personality, similar to those diagnosed with DID and BPD.

Relation Between DID/BPD and Dementia

In each of the cases presented above, Mary 1 and Mary 2 zone out in the middle of conversations, either presenting a new alter ego or a different version of themselves. Mary 1 is shown to not have any memory of what happened when Edith was speaking because they are two completely different personalities. In the second example, Mary 2, now in a different state, says that she does not know who Mary is. They both have a troubling past that affects their current and future decisions. Both of these patients also present progressive memory loss, poor judgment, and attention deficits which are all symptoms of dementia.

Neural and Molecular Substrates

The neural and molecular substrates section of this paper will describe the underlying processes in the brain that lead to the symptoms that occur in patients with DID, BPD, and dementia. Because the neural and molecular substrates are similar for both DID and BPD, they are grouped under the same section. It will show how each of the disorders have unique substrates but also several similarities and can, therefore, be considered as related disorders once again.

Dissociative Identity Disorder and Borderline Personality Disorder

Neural Substrates: Though there are many similarities between the neural substrates of DID and BPD, not all individuals with DID and BPD present in the same way; they show reduced gray matter volume in different brain regions. Magnetic resonance imaging (MRI) studies have demonstrated that people with BPD have reduced gray matter volume in the anterior cingulate cortex, bilateral hippocampus, bilateral amygdala, medial prefrontal cortex, and dorsolateral cortex (**Fig. 2A**) (Lis et al.). When compared to the brains of healthy controls, patients of DID show smaller cortical and subcortical volumes in the hippocampus, amygdala, parietal structures involved in perception and personal awareness, and frontal structures involved in movement execution and fear learning (**Fig. 2A and Fig. 2B**). These patients also show larger white matter tracts that are responsible for information communication between somatosensory association areas, basal ganglia, and the precuneus. These changes are associated with the previously mentioned symptoms such as host dissociation, neurotic defense mechanisms, and overall brain activation (Blihar et al.). Attention deficits are a defining characteristic of DID because regional cerebral blood flow in patients diagnosed with DID is reduced in the left orbitofrontal cortex regions (similar to what is seen in attention-deficit/hyperactivity disorder (ADHD)), and increased in median and superior frontal regions and occipital regions bilaterally (Gillig).

Molecular Substrates: Little is known about the molecular substrates of DID and BPD largely because there has historically been a lack of preclinical research using non-human animal models characterizing this class of disorders. Recently, there is a new focus aimed at summarizing the etiology, major symptoms, and symptom triggers of BPD. A blueprint is proposed for building an animal model of BPD by choosing key components of the disorder that can be implemented in rodents. In the proposed model, scientists use maternal abandonment to

alter maturation of the HPA axis and mild secondary adult stress to evoke behavioral symptoms such as increased impulsivity and impaired extinction, habituation, and social interactions (Corniquel et al.). Since the behaviors of those with BPD are similar to those with post-traumatic stress disorder (PTSD) and substance abuse, animal models for BPD are being made based on strategies that are currently used in animals to model PTSD. The major symptoms of BPD such as unstable self-image, unstable jobs/relationships, feelings of emptiness, and worries of abandonment are difficult to study in animal models because they are difficult to quantify. Some suggested symptom measures for inclusion in an animal model of BPD are poor impulse control, affect instability, suicidal behavior, worries of abandonment, and dissociation/paranoia. Existing models show poor impulse control and instability such as a decrease in response to a stimulus after repeated presentations (*Borderline Personality Disorder | MentalHealth.Gov*). Choice of small early rewards versus large later rewards and choice of small frequent rewards versus large infrequent rewards suggest poor impulse control in animal models; habituation to stimuli portrays instability (**Table 1**) (Corniquel et al.).

Table 1.

Symptoms and behavioral paradigms and associated measures that can be used in animal models for BPD. Table adapted from Corniquel and colleagues (2019) (Corniquel et al.).

Symptom	**Existing Animal Model?**	**Measures**
Unstable self-image	No	
Poor impulse control	Yes	Delay Discounting: Choice of small early vs large later rewards Choice of small frequent vs large infrequent rewards
Affect instability	Yes	Habituation to stimuli

		Extinction acquisition Extinction recall
Unstable jobs/relationships	Yes	Social interaction test 3-chamber social interaction
Suicidal Behavior	No	
Feelings of emptiness	No	
Worries of Abandonment	No	
Dissociation/Paranoia	No	

Dementia

Neural Substrates: Dementia is characterized by a progressive decline in two or more cognitive domains including memory, language, executive and visuospatial function, personality, and/or behavior. It is caused by significant damage to brain cells and a loss of neurons (*What Is Dementia? Symptoms, Causes & Treatment | Alz.Org*). This damage interferes with the ability of brain cells to communicate with each other. Connections between networks of neurons may break down, and many brain regions begin to shrink, causing significant loss of gray matter volume. The loss of neural connectivity in specific areas of the brain can result in behavior changes. For example, neural loss in the temporal lobe, specifically the entorhinal cortex and hippocampus, can cause a loss of memory and ability to learn because the hippocampus is the center of learning and memory in the brain (Przedborski et al.). In dementia, the brain cells in the hippocampus are often the first to be damaged. Neural loss in the frontal lobes of the brain can cause patients to be less focused and unable to plan; they also become less motivated and more passive because the frontal lobes control our impulses **(Fig. 2B)** (*What Is Dementia? Symptoms, Causes & Treatment | Alz.Org*).

Molecular Substrates: Dementia is characterized classically by two hallmark pathologies: beta-amyloid plaque deposition, which is a histopathological hallmark of Alzheimer's disease and other related diseases, and neurofibrillary tangles of hyperphosphorylated tau, which are aggregates of the protein that are most commonly known as the biomarkers of memory loss

diseases (Weller and Budson). When neurons are lost during dementia, there is a severe distortion of the shape and size of several organelles of the cell such as the cell body, nucleus, and cytoplasm, among other cellular structures (Przedborski et al.).

Relation between DID/BPD and dementia

As shown above, there is a loss of neural connectivity in the frontal and temporal lobes of the brain in DID, BPD, and dementia, therefore causing patients with these disorders and disease to exhibit similar symptoms. Though not much research has been done before on the molecular substrates of BPD and DID, it is likely that they are similar to dementia because similar parts of the brain are being affected in both disorders. Since the disorders share many common neural and molecular substrates, their treatments could also be very similar. As such, understanding DID and BPD in the context of dementia may help diagnosis and treatment outcome.

Figure 2. Brain regions that are affected in dementia, Dissociative Identity Disorder (DID), and Borderline Personality Disorder (BPD). (a) Individuals with BPD show reduced gray matter volume in the anterior cingulate cortex, hippocampus, amygdala, medial prefrontal cortex, and dorsolateral cortex (Lis et al.). Individuals with DID show reduced gray matter volume in the hippocampus and amygdala and greater white matter tracts in the basal ganglia (Blihar et al.). (b) Individuals with DID also show reduced gray matter volume in the parietal lobe and frontal lobe (Blihar et al.). Individuals with dementia show reduced gray matter volume in all parts of the temporal lobe and frontal lobe (*What Is Dementia? Symptoms, Causes & Treatment | Alz.Org*). *Created with biorender.com*.

Risk Factors

Because of the similarities between BPD and DID, some studies have shown that the disorders can co-occur, and that individuals who meet the criteria for both disorders have more trauma than individuals who meet the criteria for only one disorder (Laddis et al.). The core symptoms for DID and the core symptoms for BPD are very similar and include identity confusion and memory problems.

Mental disorders are often caused by traumatic events that occurred in early childhood. For example, BPD is often a reaction to trauma as a way to help a person avoid overwhelming

experiences, traumatic experiences, and/or abuse that occurred in early childhood. Risk factors for BPD include abandonment in childhood or young age, disrupted family life, poor communication in the family, or sexual, physical, or emotional abuse (*Borderline Personality Disorder | MentalHealth.Gov*). The vast majority of people who have developed DID have experienced repetitive, overwhelming trauma in childhood and have been the victims of childhood abuse and neglect (Spiegel). BPD and DID are thought to be developed as coping mechanisms. The trauma-related perspective entails that DID is related to a combination of factors that include chronic emotional neglect, attachment disorder, and lack of relation with caretakers. In this view, DID is thought to be at the far end of the spectrum of trauma-related psychiatric disorders (Reinders et al.).

Dementia

Studies on risk factors for dementia have mainly focused on Alzheimer's disease (AD), as it is the most frequent cause of dementia. The most prevalent risk factor for dementia is age; the disease usually comes to those above the age of 65y. Smoking/alcolhol use and female sex also speed the process up and increase the risk of AD, especially at old age (*Epidemiology and Risk Factors of Dementia | Journal of Neurology, Neurosurgery & Psychiatry*).

Other risk factors for AD and dementia include genetic and vascular risk factors. People with a family history of AD are generally considered to be at a heightened risk of developing the disease themselves. Individuals with mutations in the prion protein gene are at a significantly higher risk of developing certain forms of dementia. Several recent studies have found that drinking and smoking increase the risk of mental decline and dementia as well. People who smoke have a higher risk of plaque buildup in their arteries (i.e., atherosclerosis) and of developing other types of vascular diseases, which may be the underlying causes for the increased dementia risk. Smoking is a significant risk factor for vascular dementia because it interferes with the delivery of blood to the brain and can lead to stroke. People with cholesterol and diabetes are also at a high risk for developing dementia (*Risk Factors*).

Relation Between DID/BPD and Dementia

Unlike the symptoms and neural and molecular substrates of the disorders listed above, the risk factors for DID/BPD and dementia are very different. While dementia usually is caused

by old age, DID and BPD are both likely caused by trauma at a young age. The difference between the risk factors is something to take into consideration when considering the treatment of the disorders. Even though the disorders look similar, they are classified as distinct disorders. Once diagnosed with dementia, a patient can no longer be diagnosed with DID and BPD; however, being diagnosed with DID and BPD could increase a patient's chance of developing dementia if more or different regions of the brain are affected. DID and BPD could be risk factors themselves for dementia (Deví Bastida et al.).

Diagnosis and Treatment

Dissociative Identity Disorder and Borderline Personality Disorder

The diagnosis of BPD and DID is based on symptoms. Personality continues to evolve throughout childhood and adolescence; because of this, healthcare providers do not typically diagnose someone with mental disorders like BPD and DID until after the age of 18. Mental disorders can be difficult to diagnose because most people with these disorders lack insight into their disruptive behavior and thought patterns.[3] A licensed health professional can diagnose BPD and DID based on a certain diagnostic criteria. The DSM-5 provides the following criteria to diagnose DID ("Dissociative Identity Disorder (Multiple Personality Disorder)"):

1. Two or more distinct identities or personality states are present, each with its own relatively enduring pattern of perceiving, relating to, and thinking about the environment and self.
2. Amnesia must occur.
3. The person must be distressed or have trouble functioning in one or more major areas of life because of the disorder.
4. The disturbance is not part of normal culture or religious practices.
5. The symptoms cannot be due to the direct physiological effects of a substance or a general medical condition.

The DSM-5 provides the following criteria to diagnose BPD ("9 Symptoms May Indicate Borderline Personality Disorder Diagnosis"):

1. Chronic feelings of emptiness
2. Emotional Instability
3. Frantic efforts to avoid real or imagined abandonment

4. Identity disturbance with unstable self-image or sense of self
5. Impulsive behavior in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating)
6. Inappropriate, intense anger, or difficulty controlling anger
7. Pattern of unstable and intense interpersonal relationships
8. Recurrent suicidal behavior, gestures, threats, or self-harming behavior
9. Transient, stress-related paranoid ideation or severe dissociative symptoms

Clinicians ask questions relating to personal medical history and family medical history, previous work and relationship history, and impulse control when diagnosing BPD or DID. Mental disorders have been historically challenging to treat; however, newer treatment can help people with mental disorders experience fewer and less severe symptoms, improved functioning, and better quality of life. Treatments for mental disorders like BPD and DID include psychotherapy (talk therapy), medications or both. The goal of psychotherapy is to help a patient uncover motivations and fears associated with his/her thoughts and behavior; it focuses on working through past trauma, managing sudden behavioral changes, merging separate identities, and learning to function and manage emotions that feel uncomfortable (*Borderline Personality Disorder - Diagnosis and Treatment - Mayo Clinic*). Though there is not a certain medication to treat mental disorders as a whole, a psychiatrist may recommend medications to treat specific symptoms such as mood swings or impulsive behavior or co-occurring mental health conditions such as anxiety and depression. Antipsychotic drugs help some people with BPD. Though mental disorders like BPD and DID are impossible to prevent, early detection and diagnosis of the disorders would help patients get treatment sooner ("Borderline Personality Disorder").

Dementia

In order to diagnose dementia and find its treatments, a doctor must recognize a pattern in the loss of skills and function of a person and determine what he/she is still able to do. Doctors review medical history and evaluate thinking abilities such as memory, orientation, reasoning, judgment, language skills, and attention. Lastly, they evaluate language, visual perception, movement, senses, balance, and reflexes. Brain scans such as MRI and positron emission tomography (PET) scans can also search for brain patterns that show signs of dementia (*Dementia - Diagnosis and Treatment - Mayo Clinic*). Medications like cholinesterase inhibitors

and memantine are used to improve dementia. Cholinesterase inhibitors work by boosting levels of a chemical messenger involved in memory and judgment while memantine works by regulating the activity of glutamate, another chemical messenger involved in brain functions such as memory (Livingston et al.).

Treatment and Diagnosis of DID/ BPD through Dementia

Our knowledge of neurodegeneration could help with an earlier detection of DID and BPD, and it could help with researching treatments for the disorders as well. Though the risk factors for both disorders are quite different, mental disorders like DID and BPD share common symptoms with dementia; the main three similar symptoms are attention deficits, poor judgment, and memory loss. Just as brain scans are used to diagnose dementia, they can also be used to diagnose mental disorders quickly. The current treatments for DID/ BPD are talk therapy, medication, and sometimes, hospitalization; though this treatment is sometimes effective in decreasing the severity of symptoms, it still causes major negative life changes (Grosjean and Tsai).

The medications mentioned previously such as cholinesterase inhibitors and memantine are used to treat certain symptoms of dementia like memory loss, attention deficits, and judgment; they affect certain parts of the brain like its receptors, its entorhinal cortex, and the hippocampus. Neural substrates show that similar parts of the brain are affected in both BPD, DID, and dementia. Therefore, trials could be performed to test the effectiveness of these medications in treating symptoms of these mental disorders as well. They can also be further and more deeply researched in relation to neurodegenerative diseases in order to form more effective forms of treatment.

Conclusion

Previous research explains the symptoms, substrates, and risk factors of dementia and mental disorders. However, because of controversy and lack of diagnosis in patients, little progress has been made in researching treatments for mental disorders. The lack of treatment has caused patients with mental disorders to commit suicide, practice unhealthy habits, and suffer from depression. This review addressed the controversy surrounding DID mainly and presented similarities between dementia and Borderline Personality Disorder and Dissociative Identity

Disorder. It also showed how the similarities between the disorders can help with their treatment and diagnosis. In the future, increasing treatment for mental disorders and dementia could decrease suicide risk and increase chances of a more normal lifestyle even after developing the disorder.

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The Risk Of Asthma Among Elite Swimmers By Mihika Reddy Kuchkulla

Abstract

This article was written to explore the notion that competitive swimmers are at a high risk of asthma despite the sport being promoted to improve asthmatic symptoms. This paper summarizes the possibilities of how elite swimmers are at risk of asthma as well as analyses data collected on US Olympic swimmers over the years. Overall, this paper's goal is to inform the audience on this concept not known to a majority of the public and offer a contradicting view to the accepted idea that swimming, including elite swimming, improves respiratory symptoms and justifies the importance of research needed in this topic.

1. Introduction

For several decades, Bronchial Asthma has been a health concern for both children and adults. This chronic disease causes airways in the human lungs to inflate along with tightening the surrounding muscles. Symptoms of asthma are common among a majority of the population, including: shortness of breath, cough, tightness in the chest, wheezing, etc. However, the disease is more likely to take over one's body when experiencing a 'trigger.' Although these 'triggers' may vary, common ones can include dust, smoke, pollen, infections, and more (Ratini,2021). The disease's severity and impact on the human body are significant while not being universally regarded as "dangerous" or "life-threatening," with an estimated 262 million individuals affected by it globally in 2019 alone (Asthma, 2022).

Asthma can sometimes occur at a more severe level, such as during episodes that cause the airways to expand more than usual and constrict the space where air can enter and exit the lungs. The formation of mucus, which clogs the airways and makes breathing more challenging, is another result of an asthma attack. This causes breathing to become challenging as the airways narrow, and the patient's condition may worsen. If this condition is not treated properly, the airways may remodel, scarring the lungs and making medication ineffective (Ortega, 2022). This demonstrates the severity of the condition, which is often overlooked.

However, advancing technology along with research, and scope for curing and reducing the effects of asthma have been introduced. One such treatment to control the symptoms of the disease is an inhaler; a device (pressurized canister) allowing one to breathe in the medicine.

Over the past several years, new developments and a range of inhalers have been made available on the market, allowing asthmatics to select the one that is best for them. Aside from inhalers. Other tablets and treatments are provided depending on the severity. Even with this technology, there is no cure, only an increasing number of triggers and more individuals vulnerable to it, such as swimmers.

Swimmers, in specific competitive swimmers, are prone to long hours of practice exposing them to byproducts of chlorine, a possible trigger. Unlike divers or athletes based on land, swimmers are exposed to long hours in these chemicals. Long-term exercise is known to have an effect on the respiratory system, and in the case of swimmers, it may have played a role in airway inflammation. Elite swimmers have even reported higher levels of leukotriene implying that they are experiencing neutrophilic airway inflammation. Other studies have even elaborated on the inducted sputum in swimmers with increased sizing of the eosinophils and neutrophils (Rasmussen, 2022).

However, the curious factor is, many choose to swim to improve their asthma and although there have been cases in which it does due to the frequency of aerobic fitness, there are also cases in which it worsens. This brings the question, “To what extent does swimming improve or deteriorate the respiratory health of a swimmer?”

Furthermore, exposure to disinfectants in a swimming environment can make swimmers more prone to asthma in multiple ways such as through inducing oxidative stress leading to symptoms of asthma. As chlorine concentrations are known to gradually decline due to environmental factors, most pools are over-chlorinated, causing increased absorption among swimmers who spend extended time in the pool. Evidence of the relationship between elite swimmers and asthma has been shown during the 2008 Olympic games, in which synchronized swimmers along with competitive swimmers had high rates of asthma (Doyle, 2015).

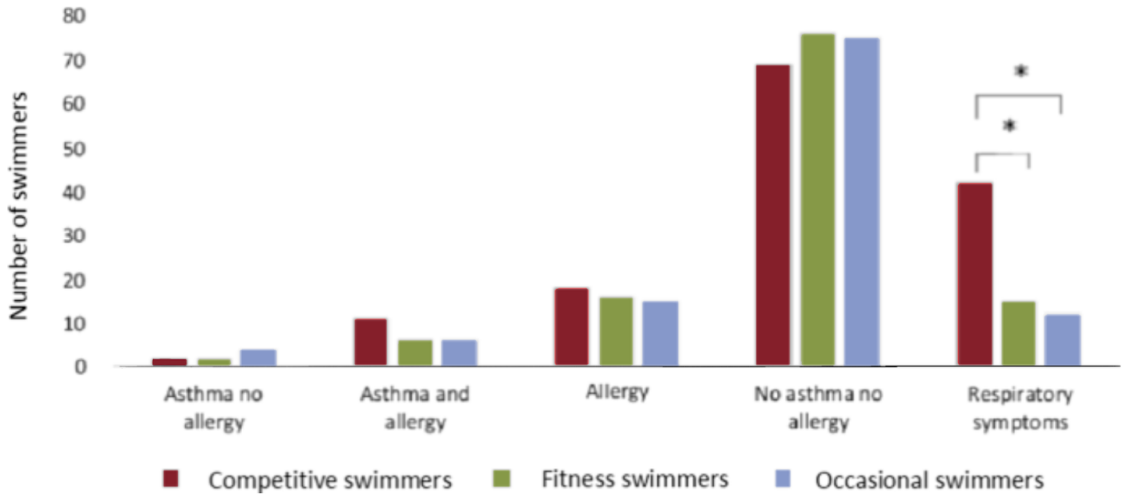

Figure 1: Reported respiratory symptoms and physician-diagnosed asthma and allergy in competitive, fitness and occasional swimmers (Päivinen, 2021)

1.1 Further Understanding

Olympic athletes and such elite swimmers are prone to regular swimming environments which have been known to be associated with developing asthma. This is due to the exposure to the chlorination by-products which not only contaminated the pool but the air as well. By-products including sodium hypochlorite are known to be disinfectants for pool treatment, which can react with swimmers' saliva and develop respiratory issues. Past research has shown that a concentration above 0.5 mg/m3 induced respiratory symptoms in swimmers based on the long period of practice they do (Haahtela, 2008).

Furthermore, swimmers inhale a significant amount of air during their rigorous practices, not only does this cause intake of contaminants within the air but also repetitive hyperventilation, possibly inducing airway narrowing.

Inflammation

The environment of an elite swimmer can also cause increased levels of fractional exhaled nitric oxide, which determines whether one has inflamed airways. In the past, this has been reported in multiple elite swimmers and the number may only continue to grow. In an analysis previously done, nonasthmatic elite swimmers showed an increase in the proportion of

eosinophils and neutrophils, suggesting an induced sputum (Haahtela, 2008). As airway responsiveness is more noticeable in elite swimmers, it is understandable that competitive swimmers may be more prone to asthma due to a variety of environmental factors including exposure to a pool environment which causes allergic inflammation and increased fractional exhaled nitric oxide, increased bronchial responsiveness, and more.

However, such airway inflammation is not only due to the exposure to the pool but also the endurance exercises that swimmers have to do multiple times on a daily basis. Through this, there is inhalation from droplets in the pool, and possibly even damage done to the airway based on the intensity of the workout.

Treatments

Athletes who seek treatment first require a thorough diagnosis; if the diagnosis is false, the treatment will fail. Asthma has similar symptoms to hyperventilation and other injuries causing more difficulty in the diagnosis. As swimmers take on strenuous and heavy exercise routines, they are more at risk of asthma along with respiratory tract infections. In addition, the treatment may also fail as heavy exercise can also influence the response to asthma medications and hyperventilation can cause the airway muscles to reduce the response to the beta2 agonists. The assessment of the diagnosis should also take into account the degrees of exposure, the intensity of training, and the time period. Thus, resulting in the best treatment (Haahtela, 2008).

Past Research

Previously completed research on induced asthma for elite swimmers has presented evidence shedding light on the effects of competitive swimming. Published in the *BMC Sports Science, Medicine and Rehabilitation*, research by Marja Päivinen, Kari Keskinen, Tuula Putus, Urho M. Kujala, Pentti Kalliokoski, and Heikki O. Tikkanen, elaborates on the aspects of induced asthma among elite athletes - including swimmers.

In this study, a total of 1,118 participants were involved with 133 being competitive swimmers, 734 swimmers focused on fitness along with 251 swimmers who swam occasionally. The data was collected from these three groups through a questionnaire regarding their medical history, their swimming experience, exposure to the swimming environment, and more. Specific

to the competitive swimmers, their pulmonary function was tested to assess their overall respiratory systems.

With competitive swimmers inhaling large amounts of air above surface water, they are exposed to chlorine derivatives, which suggests a possible reason for the increased risk of asthma. Based on this research, the risk of asthma increased from 36% to 79% showing bronchial hyperresponsiveness to histamine and methacholine.Through this research, it was concluded that 18% of swimmers had asthma symptoms and competitive swimmers had significantly more symptoms, due to longer exposure and more endurance-based workouts. The pulmonary function testing through the usage of a spirometer had even determined airway obstruction among 15 swimmers, which was 12% of all competitive swimmers.

This study suggests that competitive swimmers do in fact have a higher risk of induced asthma given the fact that they had no symptoms in their childhood. In addition, data from previous Olympic games have shown that swimming events had more participants and airway obstruction than any other sport, proving that there in fact is a possibility that elite swimmers are at risk of asthma.

Similarly, a study done in 2005, published in the European Respiratory Journal, reported that the prevalence of asthma among elite swimmers was found to be as high as 29%. This is significantly higher than the general population, where the prevalence of asthma is around 10% (Näsman, 2018).

Another study, published in the Journal of Allergy and Clinical Immunology in 2008, found that elite swimmers had a higher prevalence of asthma, exercise-induced bronchoconstriction (EIB), and respiratory symptoms compared to non-athlete controls. The study suggested that the high-intensity training and exposure to chlorine in the pool may contribute to the development of asthma and other respiratory problems in swimmers (K.LundMDa, 2008).

These studies are observational and don't prove that swimming causes asthma, but they suggest that swimmers may have a higher risk of developing asthma and other respiratory problems, particularly if they have a history of respiratory symptoms or atopy, a genetic predisposition to develop allergic diseases, such as asthma.

2. Variables

The concept of this report can address the relation in several ways, therefore to specify the aim and expectations further, specific variables have been chosen.

	Variable	Reasoning
IV	Year	The independent variable in this case will be the year of the olympic games, this will help determine the increase in percentage of asthma throughout the years for either sex and whether swimming and asthma truly has a correlaiton.
DV	Swimmers with Asthma	As the independent variable is different for each interval, the probability of them with asthma also changes. Therefore, the number of female and male swimmers with asthma through the last two decades with asthma is highly dependent on their exposure to the swimming environment.
CV	Swim team	For this report, a specific swim team will be looked into, it will be the US Olympic Team. Focusing on the changes experienced in one team will help provide a better understanding starting at a smaller scale. In addition to this, data will be looked into from different years, it is important to ensure all data was collected from the same years to provide accurate results.

Table 1: Focused Factors/ Variables taken into consideration for data analysis

3. Collected Data

One component of this paper is to determine whether swimming causes asthma among elite swimmers, by focusing on data regarding the number of olympic swimmers, in specific those suffering from asthma and which gender of athletes this disease is more prominent in. The

variation of this data over the course of two decades will be looked into, in order to provide scope in the increasing/decreasing number of olympic swimmers with asthma.

3.1 Data Collection Method

This data was collected through various sources such as past reports on asthma analysis, however some years the data was not presented, therefore extensive research was done to determine these percentages. By using USA Swimming, the number of olympic swimmers in the US team were determined, through research and articles, the number of swimmers with induced asthma were reported. With this data, the percentages were calculated. Aside from this method, some previous studies already included percentages which were directly imputed. However as this data was collected through secondary sources, there is a degree of uncertainty, but the general trend remains the same.

4. Results

Olympic games	Number of athletes	Number with Exercise Induced Asthma (± 5%)	Males with Exercise Induced Asthma (± 5%)	Females with Exercise Induced Asthma (± 5%)
1996	54	29.6%	13.2%	14.3%
2000	48	14.6%	5.7%	17.4%
2004	55	17%	10.2%	11.4%
2008	43	24.06%	9.9%	10.4%
2012	49	25%	12.2%	12.8%

5. Discussion

Although the data looks obscure, the percentage of Olympic US swimmers with exercise-induced asthma has been presented. Specific to females, it can be seen that as the years increase females consistently have a higher percentage of exercise-induced asthma in

comparison to men. This supports the notion that exercise induces different changes in both males and females. The theory remains that physiological changes are in fact triggered during exercise, however, the interaction among sex, sex hormones, and atopic nature varies. Specific to females, hormonal fluctuations and environmental changes influence the degree of severity experienced by asthma and the symptoms.

Past studies have shown that lung cells known as group 2 innate lymphoid cells, which make proteins that cause inflammation and mucus production within the lungs, are more prominent in women than men. The developed proteins make it more difficult to breathe, hence developing initial asthma symptoms. However, males naturally have the sex hormone of testosterone which has been discovered to hinder group 2 innate lymphoid cells, reducing the probability of asthma (Van Der Ploeg, 2020).

Furthermore, another trend identified is the percentage of female Olympic swimmers with exercise-induced asthma is reducing as time increases. One possibility for this trend is swimmers have taken on treatments for their presented symptoms, in some cases for swimmers who have swum in more than one Olympic meet, it is possible that they were able to get rid of their asthma through treatment, reducing the percentage. Although the swimmers are aging with each Olympics, there is no significant data presenting a correlation between ages 20-25 (mean age of swimmers) and asthma.

Male Data

Through the data collected, there is no significant correlation between the year and the percentage of male swimmers with endurance induced asthma, however the main correlation remains that given the median age of Olympic swimmers (21-26) males are less likely to experience induced asthma in comparison to females. This is in part with the fact that testosterone hormone hinders the immune cell linked with inflammation and the production of mucus in the lungs.

Overall

The data presented through past research as well as the collected data by the US Olympic team presents outliers, hence not providing inclusive evidence of the exact trend in asthma

throughout the years. In addition, there are numerous possibilities for the cause of induced asthma for competitive swimmers with possibilities that the cause varies for each swimmer.

Competitive swimmers show the highest exposure to a swimming environment and report significantly more respiratory symptoms than other swimmers. There are high airway obstruction findings for such swimmers with asthma suggesting that more medical care is required- this is only possible with a clearer understanding through research. Despite swimming having health benefits for many, data also provides that the swimming environment, level of endurance, and type of workout are factors in the development of asthma. However, there is no current research comparing the prevalence of asthma in olympic swimmers to normal swimmers with regards to their gender and level of competitiveness.

Similar results of a significant amount of induced asthma were also shown in a study conducted on the Finnish national swim team. The study focused on how high level sports affected airway inflammation and asthma. 42 swimmers were observed throughout 5 years by completing questionnaires, spirometry testing, and a histamine challenge test. Asthma was observed in 31% of the swimmers in the beginning of the study and 44% during the follow up. The change in the asthma among the studied group was significant and it was seen that the "differential cell counts of eosinophils and lymphocytes were increased during the follow up (Helenius, 2002).

6. Conclusion

Based on current findings, there is still no conclusive evidence determining whether asthma is a delirious effect of the rigorous routines and high exposures for elite swimmers. With many studies focusing on random sampling, the changes based on geographic location and the type of endurance-based workouts are not fully considered. Past research does show that exercise and endurance-based activities play a role in airway obstruction, however focus on competitive swimming and the specific causes are lacking. This paper collected data from previous databases and although the sources used to extract such information were authentic and reliable, there were no trials conducted and it was used under the assumption that the methodology for collecting the data was authentic. Another point to take into consideration is each year the coaches for the swim team along with the swimmers differentiate, leading to changing data, however the average

time spent practicing along with the drills and workouts done is relatively the same, therefore the data is not falsified.

With asthma increasing socially and becoming a real concern among athletes, including competitive swimmers, focused research is highly significant and necessary for the protection of these athletes. In 1984, 11% of the US Olympic team was using inhalers and each year this statistic continues to change with little progress in understanding why (Dickinson, 2005). The analysis in this report pointed out specific relationships between the variables and possible reasons for the changes that can be seen. By understanding the correlation of swimmers' asthma to the year and sex this report provides a deeper insight into data that is already known. Identifying the limitations opens up possibilities for future studies that can be undertaken in the years to come, giving a comprehensive grasp of the disease. Future research targeting the lead cause of asthma among elite swimmers for both men and women can provide clarity on what needs to be done to protect these swimmers and their immunity.

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