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Spring 2020

## OSMOSIS

## **Illuminating the Coronavirus**

Enlightening our minds, and relaxing our thoughts.



Also in this Issue:

Brains on Batteries Our Future in a 3-D Printer What's the Hang-Up on Hangovers?

Cover Design: Lily Dickson

## Letter from the Editor Dear Readers,

We thank you for supporting us as this is our 8th issue of Osmosis! Even in times as rough as these, I've been proud to work with a team of editors, writers, and designers who have been willing to continue talking about science. I hope you enjoy this issue and take it as an opportunity to read about some fun science. I wish the future teams on Osmosis the best of luck and

I know you'll do us proud!



As always, Science on! Anthony Isenhour

## A Big Thanks from our Executive Team!



Editor-in-chief: Anthony Isenhour Associate Editor: Joseph McEachon Managerial Editor: Cassidy Hilton PR and Social Media: George Qiao

Good luck to upcoming executive team! Ryan Shah, Lily Dickson, Ryan Cvelbar, and Caterina Erdas

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#### By Rilyn McKallip

Biological weapons, as defined by the Federation of American Scientists, are "toxins and microorganisms, such as viruses and bacteria, used to deliberately inflict disease among people, animals and agri-

culture."<sup>1</sup>Biological weapons have been used for hundreds of years on varying scales, from the catapulting of plague-infected corpses into enemy cities in the 14th century, to the testing of infectious diseases in China during WWII, to the 2001 anthrax attacks. These weapons act discreetly, as it is hard to trace an outbreak to a particular attacker and it takes several days for an infected

individual to show signs of the disease. Moreover, because biological weapons are often highly infectious, their effect on society is far reaching. While state actors have made use of biological weapons in the past, the discreet and wide-reaching aspects of biological weapons make them increasingly appealing for terrorist groups, as they have the capability to disrupt society and cause panic.

A biological weapon can be developed in three steps—selecting a pathogen, growing and developing the microorganism, and preparing the disease for delivery. When selecting the pathogen, the designers of the weapon must consider how the biological agent spreads, how long it incubates, and how destructive it is. Generally, weapon developers aim to use biological

agents that are highly contagious and have relatively short incubation periods, high mortality rates, and the potential to cause public panic. Some agents that fit these characteristics, and are hence popular choices for

biological weapons, include anthrax and the plague.<sup>2</sup> Anthrax is the bacteria Bacillus anthracis, and it traditionally infects people who work with animals, but it can also be spread through aerosol. Gastrointestinal anthrax has a mortality rate of 25-75%, while inhaled anthrax can have a mortality rate of over 80%.<sup>3</sup> Another common pathogen used as a biological weapon, Yersinia pestis( plague) is a bacteria that causes painful, swollen lymph

nodes, fever and extreme exhaustion. Though outbreaks traditionally began with rat-to-human transmission, plague bacteria can also be released through aerosol, and the infection easily spreads from person to person. Plague mortality rate is around 50%.<sup>3</sup> Both of these diseases are commonly used as biological weapons because of their ease of spread and high mortality rates. Scientists can obtain these biological agents from the environment, but they are more commonly acquired from pathogen banks. Individuals also donate samples of the pathogen, which scientists can genetically modify into a biological weapon.<sup>1</sup>

After choosing and acquiring the biological agent, scientists use genetic engineering technology to

alter the pathogen to be more resilient and lethal. Using gene editing technology, scientists can change the genetic material of pathogens by either inserting genes, deleting genes, or altering existing genes to produce pathogens with desired traits. Bacterial agents may also be altered to be resistant to antibiotics, which makes infections resulting from these bacteria difficult to treat.<sup>4</sup> This biotechnology is expensive, however, and acquiring it is a hurdle for groups attempting to develop effective biological weapons.

Once the pathogen is edited, scientists must choose a method of delivery. The most common methods of spreading biological weapons are through the air using bombs or sprays, through the water supply, and through the food supply. The Japanese commonly used aerosol pathogens in their tests on China in World War II, and there are documented instances of salmonella and E. coli being deliberately added to food, such as salad bars.<sup>5</sup> The chosen method of transmission will depend on how widespread or controlled the attack is intended to be.

International treaties have been implemented to slow or prevent the development of biological weapons. The 1925 Geneva Protocol banned use of biological weapons in warfare, and the 1972 Biological and Toxin Weapons Convention (BTWC) went a step further to prevent development, production, stockpiling, and acquisition of biological weapons.<sup>1</sup> However, it is nearly impossible to make sure that countries follow these treaties, and underground biological weapon programs continued, even in signatory countries. For example, the Soviet Union signed the BTWC but then started Biopreparat, a well-funded biological warfare research project. Through the pro-

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4 van Aken, J., & Hammond, E. (2003). Genetic engineering Page Design: Lily Dickson

gram, the Soviet Union stockpiled anthrax bacteria and smallpox viruses undetected until the program's dissolution in 1992.<sup>5</sup> In addition to non-compliance in state actors, non-state actors have made use of biological weapons. The anthrax attacks of 2001 were carried out by a non-state actor, as was the spread of salmonella through salad bars by a religious sect in the 1990s.<sup>5</sup> The ease of access to biological agents makes bioterrorism, the use of biological weapons by a nonstate actor to reach a political goal, a real and growing threat.

What can be done to combat the threat of bioterrorism? Perhaps the most important step is being prepared for an attack. The U.S. can invest in stockpiling vaccines for diseases like anthrax and the plague, researching possible new pathogens that could be used as biological weapons, and modeling possible outcomes of a biological attack. We can use what we know about the development of biological weapons to learn how to best protect ourselves from them, through modeling various diseases in different formats and mutations, and using these models to form plans to combat these pathogens. Additionally, there is the growing field of bioterrorism forensics, which aims to use DNA evidence to identify pathogens that could be developed into biological weapons.<sup>6</sup> While it is impossible to predict the exact timing and details of an attack, it is possible to prepare for possible attacks. Additionally, good hygiene practices, such as washing hands and staying up to date in vaccinations, can help individuals avoid contracting illnesses released by biological weapons. The threat posed by biological weapons and bioterrorism is present and growing, but there are measures that can be taken to protect us from a deadly attack.

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## Brains on Batteries: The Potential of **Deep Brain Stimulation**

#### By Joshua Pandian

For 40 years of her life, Edi Guyton could not experience happiness. Despite having a family and a successful career, she still struggled to feel happy. She tried various therapies and medications, but to no avail. Then, in 2007, Edi Guyton underwent an experimental procedure that allowed her to smile genuinely for the first time in her life. Due to two electrodes implanted in her brain and a small battery pack near her collar bone, Edi is now able to experience the joys surgery.<sup>3</sup> This phenomenon occurs because the periof life like everyone else.<sup>10</sup> Deep brain stimulation (DBS), the process of implanting electrodes into the brain to lessen the symptoms of neurological diseases, began as an experimental idea based on early pain-processing theories. Today, DBS is used to treat various neurological disorders, including Parkinson's disease, depression, OCD, and chronic pain. While major advancements have been made in recent years, DBS is still in its infancy and possesses a tremendous potential to advance human well-being as our knowledge of neuroscience increases.

#### The History of Deep Brain Stimulation

The discovery of deep brain stimulation began in 1965 when Ronald Melzak and Patrick Wall proposed their gate-control theory of pain. Through their studies, Melzak and Wall discovered that nerve fibers that transmit information about touch and vibration are more myelinated, and therefore faster acting than nerve fibers that transmit pain signals. In the dorsal horn of the spinal cord, these fast-acting nerve fibers can inhibit pain signals from reaching the brain. The gate-control theory explains why we tend to rub our head when we hit it on a doorframe or grab our foot when we step on a Lego. Increasing touch signals helps inhibit pain.<sup>3</sup>

The gate-control theory of pain gave rise to ideas about how pain can be controlled from a bottom-up

process, in which pain signals are processed via the spinal cord before reaching the brain. Then, in 1969, D.V. Reynolds discovered a top-down process in which the brain receives pain signals first and proceeds to inhibit them. In his study, Reynolds stimulated the periaqueductal gray regions in the midbrain of rats and performed surgery on them without anesthesia. The rats felt no pain for the duration of the aqueductal gray region has associations with nerve fibers that send signals to the dorsal horn of the spinal cord, the same area where pain is inhibited during gate-control.<sup>2</sup> Reynold's study demonstrated that the brain also has the ability to inhibit pain.

With the knowledge that pain can be inhibited from the spinal cord or from the midbrain, researchers attempted to cure chronic pain using two approaches. The first approach is spinal cord stimulation, which involves placing electrodes in the spinal cord to generate a pulse to keep pain signals from reaching the brain. This method of treating pain was originally believed to work due to gate-control theory, but currently research has shown that there may be more factors at play. Essentially, the added electrical signals from the electrodes inhibit the pain signals from reaching the brain.<sup>5</sup> As a result of its success, spinal cord stimulation was FDA approved and used as a method for pain relief.<sup>3</sup>

The second method used to cure chronic pain was DBS, which was originally proposed in the 1970s. Electrodes were placed in the thalamus, the part of the brain responsible for directing pain signals for the somatosensory cortex for processing. Unfortunately, clinical trials did not produce convincing evidence for the effectiveness of DBS.<sup>3</sup> Today, we know this is because the original trials were poorly executed,<sup>4</sup> but at the time, it appeared DBS had reached an end.

DBS seemed to be a failed idea until the 1980s, when it was found to be effective in countering motor symptoms associated with Parkinson's disease.<sup>3</sup> Increased knowledge of the brain regions associated with Parkinson's disease allowed scientists to better target areas to stimulate to help counter irregular activity. Even today, our knowledge of these brain regions continues to expand. For instance, a 2018 study on the interactions between the basal ganglia and thalamus revealed that in low dopamine environments, inhibitory output from the basal ganglia can cause rebound firing in the thalamus, leading to motor symptoms associated with Parkinson's disease.<sup>6</sup> Modulating basal ganglia output or the rebound firing can help eliminate involuntary muscle contractions, so DBS can potentially be the answer to this problem.

#### Where is DBS Today?

After DBS was first approved in 1997, the applications of it have expanded beyond Parkinson's disease. One example of this is the use of DBS to treat certain types of depression. In 2005, Dr. Helen Mayberg used DBS on Brodmann area 25, a part of the brain that has been identified as overactive in individuals with treatment resistant depression. According to the study, stimulating this region with electrodes can help decrease activity in the region, which in turn affects the hypothalamus and the brainstem. For patients receiving this treatment, this means better sleep, motivation, and energy. As this study shows, DBS is effective because it modulates multiple functions in the brain by changing processes in the target site and downstream.<sup>7</sup>

Patients suffering from obsessive compulsive disorder (OCD) may also be able to benefit from DBS. A recent study showed that targeting one of five possible brain areas can relieve OCD symptoms. However, it appears that stimulating the different regions have different impacts on the brain, so a more personalized approach must be taken to provide the appropriate treatment to each patient.<sup>8</sup>

Advances in using personalized DBS techniques have led researchers to again attempt combating chronic pain with DBS. Dr. Shirvalkar, an associate professor of anesthesiology at UC San Francisco, is using the technology available today to monitor neural activity over time in order to create DBS with varying electrical pulses depending on the situation.<sup>9</sup> Studies such as these show promise for DBS to be more accurate and effective in the future.

#### What still needs to be done?

Although DBS is becoming more effective over time, there is still plenty of room for improvement. One of the biggest challenges facing the advancement of DBS is the current lack of understanding about how certain brain functions interact. While research can often get general ideas for what different brain regions do, it is still difficult to target which area to place the electrodes in order to have effective DBS. This is seen from the studies of DBS on OCD, where treatments of multiple brain regions appear to ease symptoms, but in different ways.<sup>8</sup> Also, in some cases, a patient's brain can become used to the deep brain stimulation, thus rendering the treatment ineffective. More research must be done in order to understand why DBS may cease to work in some patients.<sup>1</sup> As research on the topic expands, patients will benefit from having DBS that is more personalized and effective in treating their specific condition.

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## Coronavirus is spreading fast,

### but what is spreading faster?



By Dana Morcillo



The term coronavirus refers not to the newest, mysterious disease that is slowly spreading globally, but rather a family of viruses. These viruses are the source behind common illnesses such as the common cold to the more recent outbreaks of the coronavirus disease 2019 (COVID-19). Other more severe diseases have occurred before then such as the Severe Acute Respiratory Syndrome (SARS) in 2003 and Middle East Respiratory Syndrome (MERS) in 2012. However, both had a combined number of only 29 cases in the United States.4Coronaviruses are animal-borne diseases meaning they begin as diseases in mammals or birds. Although animal-borne viruses are usually not able to transfer to humans, a virus can mutate allowing it to be transmitted to humans. Once transmitted to humans, the coronavirus often causes an upper respiratory infection with mild symptoms, but certain types such as MERS and SARS will have more severe symptoms.2

COVID-19was first discovered in the Huanan Seafood Wholesale Market in Wuhan, China, in December of 2019.1,2The Huanan Seafood Wholesale Market is a wet market where live animals are bought and sold. Through the close proximity of the animals and humans, the virus would have been able to jump from animals to humans. While the disease is believed to have originated from the bats, pangolins -an armored nocturnal mammal -are believed to act as an intermediary before passing over to humans.3Studies into past coronaviruses have found similar transmittance with SARS being transmitted from civet cats to humans and MERS being transmitted from dromedary camels to humans.1



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How does it spread and what are the symptoms?

Due to the novelty of COVID-19, how it spreads is mostly based on previous coronaviruses such as the common cold, SARS and MERS. There are two believed paths in which transmission for COVID-19 occurs: person-to-person and contact with infected surfaces and objects. Person-to-person transmission is the most likely route according to the CDC.2This can happen through close contact within 6 feet or coughing and sneezing which produces infective respiratory droplets. Contact through infected surfaces and objects is a less likely route. It occurs through an individual touching an area with the virus present and then touching their mouth, nose, or eyes.2

If infected, symptoms may appear between 2 to 14 days after exposure. A mild infection includes symptoms of fever, cough, and shortness of breath or difficulty breathing. A severe infection leads to severe illnesses such as pneumonia.1,2Moreover, it's believed that infected individuals are most contagious when they exhibit the most symptoms or are most sick. However, it's possible for individuals to still spread the coronavirus without showing symptoms, but this isn't believed to be the main way the disease is spreading.2

So, what is spreading faster than coronavirus?

Stigmas. COVID-19 is the official name used by the CDC, but often -and even now -the virus was referred to as the "Wuhan virus" or the "China Virus." While COVID-19 did originate in Wuhan, China, the words and language used when speaking about the virus are important. They carry power. More importantly, they carry the power to hurt. Globally, there has been an increase in xenophobic and overall, racist attacks. In Australia, parents refused to let their children be treated by Asian doctors.5 In Canada, a petition was formed and signed by over 10,000 residents to track and name Chinese-American students after any travel to China.6 In America, Chinese restaurants are struggling to stay afloat after business has gone down and racist attacks have been seen on public transits from the West to East Coast.7 A survey by the Asian Pacific Policy & Planning Council (A3PCON) has received over 1,100 reports of racist attacks from being coughed or spat at to physical assault.8 However, these racist attacks don't only affect Asians and Asian Americans but other minorities as well.

While the CDC has officially recommended that all Americans wear face masks, minorities are afraid of the larger implications at hand.9 Historically, bandanas when worn by Hispanics or African Americans have been strongly associated with gang involvement and violence. The worry then becomes that minorities wearing masks made of bandanas or other materials will be stereotyped and targeted. The most recent instance being two African American men who claim to have been escorted out of Walmart for wearing masks.10

Going forward, it's important that all individuals feel safe and accepted during such a fearful time. COVID-19 does not discriminate. All individuals are susceptible to it, especially our medical and essential workers. While we can do our duty of social distancing and staying at home to protect others, we also have a greater duty. To speak accurately and empathetically when it comes to COVID-19 and those affected by it. By knowing and understanding the facts can every individual prevent the spread of stigmas and hate, but instead foster compassion and understanding.

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## **Wolves and Ravens**: Defining a unique relationship

#### **By Caterina Erdas**

barely felt the cold, dry Montana air pierce my lungs as I looked through my scope for an iconic animal in our culture: a wolf. While the dramatic thermal features on the south side of Yellowstone National Park attract the most visitors, the north is quiet and rich with life. The Lamar Valley is a stunning stage for Yellowstone's wildlife to interact with one another. As the sun rises and hits the mountain tops, the cold air rushes into the valley and creates a thick fog, a curtain. Backstage, the wooded mountain ranges slowly bleed into the tall grasses and sage bushes blanketing the valley ground. Finally, I saw a black wolf's head peeking above the tall grass. Another five followed, probably from the Junction Butte Pack who currently hold control over the Lamar Valley.

By the 1920s, wolf populations were completely culled at Yellowstone National Park (YNP) by park officials and licensed hunters trying to protect their prime attractions: elk and other big-game animals. Wolves are the number one natural predator of elks, and at the time, there was concern that wolves were a danger to big-game animals. However, after the wolves were removed, park officials and scientists started to notice over-grazing on young trees, rampant erosion, and unstable growth/crash cycles in elk populations. Therefore, in 1995, wolves from Canada were brought into YNP to balance the ecosystem. To what extent wolf reintroduction "saved" the greater Yellowstone ecosystem remains debated, but elk levels stabilized

after re-introduction and by extension, the rest of the ecosystem stabilized. One hundred years later, seven generations of wolves have lived in Yellowstone and the surrounding area. That's seven generations of wolf packs fighting to expand their territory, winning, defending, losing, and dissolving as new packs grow (yes, it's Game of Thrones with wolves). YNP's wolf sanctuary provides a unique opportunity to study wolf behavior and biology, wolf pack dynasties, and their effects on the local ecosystem.

Apart from their own pack, wolves interact with ravens more than any other animal. The ravens are the most obvious beneficiary from the wolfraven relationship. Studies have found that 100% of wolf kills are visited by ravens and nearly 2/3 of the carcass is consumed by the raven. The official term for their relationship is predator-scavenger interspecific kleptoparasitism, or, in English, a relationship between two different species where the scavenger benefits off the predator by stealing a portion of their food. The ravens stay close, recognize a wolf's hunting cry, and follow the hunt from above. Ravens cannot open a carcass on their own, so without the wolves' help, the eyes are the only edible part of the carcass for a raven. In this instance, the wolf is the predator being taken advantage of by the raven.

However, wolf and raven behavior doesn't perfectly fit the kleptoparasitism model. After a kill, wolves will only eat their preferred cuts of the meat and ignore the ravens and other scavengers pecking at the opened carcass by their side. If this were truly a competitive or parasitic relationship, the wolves would protect their meal like they often do against bears. Even more counter intuitive, ravens are scared or "shy" of large carcasses and won't feed on them unless a wolf is nearby. In addition. though wolves were gone from YNP for 70 years, ravens preferentially follow wolves significantly over coyotes or elk. If ravens were solely opportunistic, then a raven would choose a carcass without a wolf and would be equally likely to follow coyotes. These odd behaviors hint at an innate, ancient, and evolved mutualistic, not parasitic, relationship between wolves and ravens.

Wolves obviously don't mind ravens and have evolved with ravens, so what are they wolves getting out of their relationship? When wolves and ravens are preoccupied with feeding, the ravens remain extremely alert and will call out if danger is near. The ravens act as another set of eyes and ears, not only at a carcass, but in the sky. Ravens have on multiple occasions been observed locating, harassing, and yelling at injured elk to draw the attention of wolves.

Furthermore, there are numerous wolf-raven anecdotes that illustrate their special relationship. For example, a biologist studying wolves wrote about an interaction he saw of a raven pecking at the tail of a wolf and jumping away when the annoyed wolf snapped back in retaliation. A wildlife photographer saw a nearby wolf open up a bear carcass for a yelling raven who found the body. One wolf watcher noticed that ravens hang around wolf dens and play with three-week-old wolf cubs. Both ravens and wolves have the social abilities to form bonds between individual ravens and individual wolves. I have my own anecdote. Soon after spotting the wolves, I saw a raven. At first it was circling close above, but then it swooped down towards a wolf, taunting it. The wolf, in turn, jumped up and snapped its teeth at a safe distance from the raven. They repeated this dance a couple times. What at first looked like an aggressive interaction was actually two friends, playing. Watching the wolf and raven's unique relationship play out in the Lamar Valley is a moment I will never forget.

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Lamar Valley

## What's the Hang-Up on Hangovers?

#### **By Anthony Isenhour**

etting a hangover after drinking the night before can lead to varying regrets the next morning depending on a variety of factors including gender, weight, food consumption, and alcohol consumption. What a hangover feels like can vary a lot too: headaches, nausea, fatigue, etc.

Scientists are interested in understanding hangovers and how to prevent them because they experience them too. In order to better understand hangovers from a scientific perspective, a unifying definition needed to be set. In 2016, some scientists worked with consumer descriptions and experts to define a hangover from alcohol as referring "to the combination of mental and physical symptoms, experienced the day after a single episode Stress has been shown to bring on similar symptoms to of heavy drinking, starting when blood alcohol concentration approaches zero."<sup>1</sup> Nonethelss, scientists are still confused about how hangovers work, and why only about 75% of people report having ever experienced a hangover.<sup>2</sup>

There are a variety of potential factors that affect hangovers, stemming from how the body breaks down the alcohol, to other chemicals in the drinks, as well as genetics and personal factors. Studies have shown that some metabolic pathways other than just breaking down the alcohol (ethanol) seem to be involved in hangovers and involve molecules like vitamin B<sub>6</sub>, zinc,

and antidiuretics (which control how much water your body holds).<sup>3</sup> Similarly, drinks like red wine, rum, and whiskey have more of the other chemicals that may make hangovers more severe such as methanol.<sup>4</sup>

However, in delving into the personal and genetic factors that contribute to hangovers, studies have found that the sons of alcoholic parents (who are at greater risk for alcoholism) have more frequent hangovers.<sup>5</sup> This could stem from genetic factors, as well as environmental factors affecting diet and approach to alcohol consumption. Similarly, scientists have seen that guilt about drinking and higher levels of anger or depression are associated with experiencing more hangovers.<sup>6</sup> hangovers and the scientists who saw the above emotional ties to hangovers believe that this combination of different types of stress may be what is causing more hangovers. So if you're getting ready for a night out to relieve some stress, be wary of how you might feel the next morning.

Not only do all of these factors contribute to hangovers, but it is found that gender does as well. Research shows that women reach a higher blood alcohol content (BAC) with the same amount of alcohol, but that men typically consume more alcohol in a single drinking session leading to typically higher negative consequences. When studies take all of these factors into account, it seems that men are less sensitive to the adverse effects of alcohol (aka hangover symptoms) at the same BAC.<sup>7</sup> However other studies find that there are little to no differences between men and women in regards to hangovers so no one is safe.<sup>8,9</sup> On another surprisingly positive note, a large-scale research project has found that hangover symptoms and severity tend to decrease as you age.<sup>10</sup>

While the likelihood that we may experience hangovers is clearly very variable, what about treating hangovers? A 2005 study compared a range of potential hangover cures--such as some various drugs, sugar, pickled vegetables, and fruits--only to find that none of them are effective hangover cures. However, a more recent study has shown that a diet rich in zinc and vitamin B<sub>3</sub> leads to less severe hangovers.<sup>11</sup> Both of these seem to be important in helping regulate the proteins in your cells that are breaking down the alcohol. This study did also mention that for the 20-25% of people lucky enough to experience no hangover symptoms there must be some other biological reason. Similar to popular belief though, clear alcohols and ones that are closest to pure ethanol are less likely to promote hangovers.

Scientists seem to conclude that a true hangover cure might be out there, but that traditional methods of moderation, diet, and basic symptom treatments are your best bet. Similarly, studies have not been able to identify a main cause for hangovers (other than drinking alcohol) that could help lead to lessening hangover severity. Instead, much like the rest of life, the pain comes from many a reason and many a place.

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#### Page Design: Mikayla Quinn

## Tree Man Syndrome

## By George Qíao

Imagine a condition in which lesions that grow on your appendages are so severe that you cannot use your hands and feet properly. Moreover, these lesions are large and painful, and prevent you from being able to perform daily activities. Surgery, a common answer for this condition, can temporarily control the growths, but the lesions continue to grow back after each surgical operation. Currently, there is no cure, and the treatments only offer a temporary fix. Therefore, you are faced with a lifelong condition that severely limits your ability to live a normal life. Though there are many debilitating diseases, few of them are not given much attention. For example, one extremely rare disease is Epidermodysplasia verruciformis (EV), or tree man syndrome, characterized by bark-like warts growing on the body.<sup>1</sup> Although the exact number of cases of EV is uncertain, about 200 cases in the world have been reported thus far.<sup>2</sup>

**D**iscovered in 1922, EV is an autosomal recessive disorder that increases one's susceptibility to the human papilloma virus (HPV) and is characterized by lesions that resemble wood. Furthermore, EV increases one's risk of developing skin cancer.<sup>3</sup> HPVs are non-enveloped, double-stranded DNA viruses responsible for many lesions and cancers, and are often sexually transmitted.<sup>4</sup> They infect the stratified epithelium of the epidermis, and do not lead to symptoms for most individuals, although some cases can involve development of warts. For infected individuals who show symptoms but are not suffering from EV, the warts are not as vast in number as those in patients with the mutations associated with EV.<sup>5</sup>

**R**esearchers have generally attributed EV to mutations in the EVER1 and EVER2 genes, also called TMC6 and TMC8, respectively. These genes code for transmembrane proteins of keratinocytes, which are epidermal cells targeted by HPV. The proteins bind to and form a complex with a zinc transporter protein called zinc transporter 1 (ZnT-1). The EVER-ZnT complex transports zinc from the cytoplasm into the endoplasmic reticulum of the cell, directly decreasing the amount of zinc in the cytoplasm and indirectly decreasing the amount of zinc in the nucleus.<sup>5,6</sup> Zinc is an ion vital for the function of AP-1 transcription factors which promote expression of the HPV genome. The EVER-ZnT complex limits the activity of AP-1 transcription factors by decreasing the concentration of zinc in the nucleus, thereby limiting the ability of HPV to replicate.<sup>7</sup> A mutation in either of the genes EVER1 or EVER2 would prevent the proper functioning of the EVER-ZnT complex and allow the proliferation of HPV. With the mutation, HPV infection can lead to uncontrolled division of keratinocytes, resulting in bark-like warts, especially on the hands and feet.<sup>1</sup> Immunohistochemistry with antibodies specific for HPV can detect HPV infection in keratinocytes and is used to diagnose patients with EV.<sup>2</sup>

Several treatments exist to combat EV, although there still remains no cure. The condition can be treated with surgery, which can remove the growths. However, surgery only offers a temporary solution to the condition, as the warts often return after surgery. One man in Bangladesh suffering from EV underwent multiple surgical operations to remove his warts in 2016. Although the surgeries granted him the ability to use his hands and feet for a period of time, the warts returned. Since 2016, he has had 25 surgeries, and has not found a permanent solution to the condition.<sup>8,9</sup> Other treatments include cryotherapy, interferons, and

retinoids, all of which also offer temporary solutions to the problem.9, 10

**F**urther research on EV should be conducted so that the scientific community can come closer to a cure for this debilitating disease. One path to take is to determine different possible causes of EV. Despite the experiments performed to determine the role of the EVER genes, it is not certain that a mutation in these genes is the sole cause of EV. In a particular study involving 41 EV patients, mutations in the EVER genes were present in 75 percent of the patients but absent in the remaining 25 percent, suggesting that there are other possible causes of EV.<sup>6</sup> Thus, more research should be conducted to identify alternative causes of the condition. If we can determine the different mechanisms of action of this disease, we can come closer to a cure by directly targeting those mechanisms. Hopefully, in the future, we can find a solution that can help end the suffering of those affected by the disease.

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## Our Future in a 3-D Printe

#### By Ryan Cvelbar

CareCloud, a privately held technology company headquartered out of Miami, states that according to recent figures, the average cost of an organ transplant in the U.S. can reach well over \$1 million. Furthermore, according to the United Network for Organ Sharing (UNOS), more than 113,000 patients in the U.S. are currently waiting for an organ transplant. Anne Paschke of UNOS stresses this need for organs by expressing that only 1 to 2 percent of

the population dies in a way that makes them potential organ donors. Although the need for organs has yet to be met, bioprinting has the potential of saving lives by addressing this chronic shortage through various applications.

Many of you may have heard of 3-D printing, but have you heard of bioprinting? Bioprinting is a biotechnology that does not fail to excite optimists in the biotech industry. Specifically, bioprinting is "an additive manufacturing process where biomaterials such as hydrogels or

other polymers are combined with cells and growth factors, and then printed to create tissue-like structures that imitate natural tissues" (What). You may be mass-supplied prosthetics are likely to be a thing of wondering how exactly this printing process takes place. Futurity explains that bioprinting involves using a computer-guided pipette that takes up cell cultures and "prints" them out in gel layers onto biopaper. This biopaper degrades over time; leaving behind the printed structure. According to the Australian Academy of Science (AAS), every tissue in the body is naturally made up of different cell types, so the required cells are taken from a patient and cultivated until there are enough to create cell specific 'bio-ink' that is loaded into the printer. Moreover, the AAS explains how these cells seek out similar cells to join with much like the way cells in an embryo develop in the womb during embryogenesis, or tissue in an adult moves to repair damage. Because the parts are synthesized from the organ recipient's genetic matter and precisely match the tissue or organ being replaced, CareCloud states that there is less of a



tissue. Now that we have covered the basics of sourcing, growing, and implanting bio-prints, let's talk about bioprinting's potential applications.

From patient-specific surgical models and personalized medicines to replacement body parts and custom-made prosthetics, the possibilities of bioprinting are endless. A serious car accident that results in a passenger's nose being shattered serves as a great example of a situation in which bioprinting can

> be put to use. According to the AAS, bioprinting technology makes it possible to reconstruct this nose as a 3D model on the computer. A biopsy can simultaneously be performed on the patient while cartilage cells are extracted from the knee, finger, ear or splinters of the shattered nose. The cells are reproduced in the laboratory and mixed with a biopolymer, which is then used to print a new nose to be implanted during surgery. In this process, the biopolymer is used as a form of shaping mold that is gradually broken down by the body and replaced by its own cells. This re-

placement leaves the implant unrecognizable as it appears cohesive with the individual's own skin and cartilage. Moreover, Futurity forecasts that the past as 3D printing is increasingly used to manufacture prosthetics that are tailored to a patient's anatomy and needs. For example, Futurity explains that surgeons have to cut a patient's bone to fit the prosthetic in a hip-replacement, but in the future, it will be normal to 3D print a prosthetic to fit a patient. Additionally, bioprinting has extensive applications in the pharmaceutical industry with the potential to drastically reduce the need for animal trials in drug testing. Cellink contends that this technology offers the potential to test treatments for diseases using artificially affected tissues, eradicating organ donation and transplantation. Perhaps bioprinting's most significant application is the use of 3D printed models to practice surgical operations. According to Jason Chuen, Director of Vascular Surgery at Austin Health and a Clinical Fellow at the University of Melbourne, studies have shown that operations can be completed chance that the immune system will reject the foreign faster and with less trauma for patients and the potential cost savings alone are considerable. Although these ideas sound both exciting and feasible, professionals have a long way to go until these applications become reality.

Aside from potential applications of bioprinting in the medical field, professionals are currently making progress in the development of bioprinting as it pertains to some similar applications. "In 2003, Wake Forest succeeded in printing the first fully functional mini-kidney, which was able to filter blood and produce urine. Since then, scientists have been working to develop more sophisticated organs like hearts, livers and uteruses" (Carecloud). Chuen explains that once inside the gel, cells can die in a matter of minutes. This isn't a problem for small structures like organoids, an artificially grown organ, that can be built quickly and then transferred back into a nutrient solution, but it is a problem when attempting to print an organ because the initial layers of cells will die before the organ is completed. Dave Fornell of Diagnostic and Interventional Cardiology argues that the Achilles heel of tissue engineering today is the need to create vascularity in the structure. He states that the key to printing vascularizable micro-organs involves chemical modifications of alginate hydrogels to promote organoid vascularity and suppress inflammatory responses. According to Fornell, what we can print right now are cardiac patches and small- to mediumsized blood vessels, skin tissue, soft tissue for reconstructive surgery, and vascularized micro-organs that can be grown in a bioreactor and used to supplement the function of a diseased organ like the liver.

Recent breakthroughs in bioprinting include a team from Swansea University's work that has developed a bioprinting process that can create an artificial bone matrix in the exact shape of the bone required. Mischa explains that, "Over a period of several months, the implants fuse with and are eventually replaced by a patient's natural bones with few, if any, complications." The AAS recognizes similar work at Wake Forest School of Medicine where researchers have successfully designed, built and tested a printer that can print skin cells directly onto a burn wound. Research engineer Monica Moya from Lawrence Livermore National Laboratory is also using bioprinting. The AAS explains how Moya is using the technology to create 'living' blood vessels by enabling small blood vessels to develop on their own. "Over a period of time, the self-assembled capillaries connect with the bio-printed tubes, thereby beginning to deliver nutrients to the cells on their own-mimicking the way these structures work in the human body" (science.org). Dr. Anthony Atala, director of the Wake Forest Institute for Regenerative Medicine, predicts that someday, perhaps in the span of a generation, you can have a heart made out of your own cell tissue. The biotechnology industry is growing at an unprecedented rate and the prospects of bioprinting applications like these give us a lot to look forward to.

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It is no secret that modern medicine has improved people's lives in virtually every are of healthcare. What is also not a secret is how expensive it is. Not only does the average American spend roughly \$5000 on healthcare, they also spend roughly \$1200 on pharmaceuticals. The candidates gunning for the U.S. presidency often bring up the topic of rising pharmaceuticals and what they would do to change it. Medical services and products as a whole are of concern for virtually all Americans, and many of them are considered overpriced. The development of these products isn't cheap, and it needs funding. On the other hand, citizens would rather spend that \$1200 on other commodities. Looking at the path of funding for pharmaceuticals and biomedical research as a whole can help people understand why.

Let's take a quick look at biomedical research as a whole. Though biomedical research in the United States is funded through multiple channels, the largest funder of federal research is the National Institutes of Health (NIH). Comprising of 27 institutes and centers in the U.S., it pours over \$40 billion into research, mainly in the form of grants. These grants are awarded to research institutions, mainly universities and medical schools, where some of the science is done, and about 10% of funding goes to in-house NIH research. NIH -funded projects cover a wide range of research areas. Some of their biggest in-house projects include cancer research; the National Cancer Institutes budget was \$5.098 billion. What's interesting, however, is that this number (just over \$40 billion) has remained relatively stagnant over the past two decades and has failed to keep up with inflation. As a result, less and less projects are being funded - approximately one in five and less research is able to be done.

Pharmaceutical research, on the other hand, is often done by private firms. These firms both raise money and perform the resulting research. For example, The Pharmaceutical Research and Manufacturers of America (PhRMA) report that \$97 billion was spent in 2017 by biopharmaceutical companies on research and development (R&D). This industry alone, then, spends more than double the NIH's research funding on their projects.

These two areas of healthcare are different in several ways, mainly that pharmaceuticals offer one product - drugs - while biomedical firms and institutes offer a variety of services. However, there is another key distinction:government institutes like the NIH are, well, publically funded, while private institutes like Novartis and Pfizer are for-profit. As much as these firms claim they are trying to save lives, at the end of the day they are also trying to maximize their profits and will sell their products at the price the market can bear. Unlike the NIH, private firms gather their research funds from their profits, meaning they can only produce beneficial drugs as long as they are making a profit. When that stops happening, they either raise prices or look for another way to make money.

The path for funding for biomedical research and pharmaceutical development is a complicated one. It has clear advantages: institutions across the country are diligently working to produce innovations, improvements, and efficiencies in the world of medicine. Funding a large number of research programs also results in a large number of different and varying ideas. The path isn't perfect, though. A shrinking NIH budget and increasing pharmaceutical company profits paired with increasing pharmaceutical drug costs are concerning many Americans who struggle to pay for healthcare.

#### **By Garrett Lang**

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