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About EUMR

Mission Statement:

The Emory Undergraduate Medical Review is for Emory undergraduates interested in medical or health related careers to engage in scholarly discourse with their peers and medical professionals. EUMR publishes semesterly hard-copy and online-copy journals in addition to shorter blog posts throughout each semester. Each semesterly issue primarily features reviews on interesting and cutting-edge topics in medicine, while medical opinion articles are also welcomed. All semester pieces are reviewed by doctors and researchers from around the country who are featured on our Advisory Board. Blog posts are more succinct and accessible pieces in recurring areas including ethics, biotechnology, public health, nutrition, and more. EUMR also endeavors to put on educational events relevant to students interested in medical or health careers.

Our Advisor

Dr. Michael Crutcher, PhD

Emory

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

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

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Considering Sex as a Relevant Biological Variable

Authored by: Preethi Reddi
Edited by: Nivedita Potapragada **Reviewed by: Dr. Tyler Cymet**

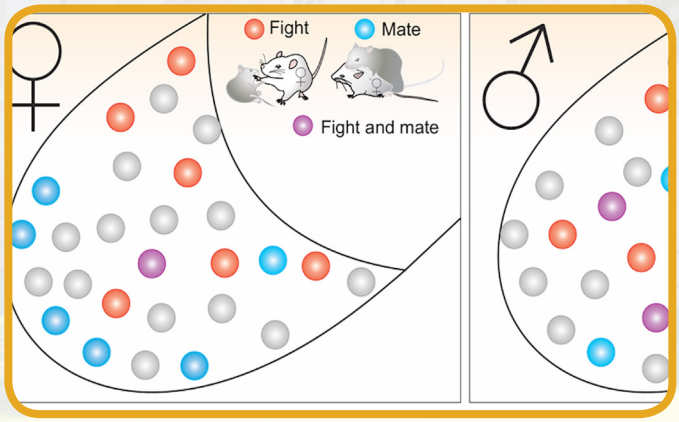
Females are twice as likely as males to develop Post-Traumatic Stress Disorder (PTSD) (Tolin and Breslau, 2007). However, the reasoning behind this statistic has been unclear. A study conducted by Maddox et al. showed that estrogen plays a role in increased risk for development of PTSD in female mice and women (2015). As a result of this study and many others suggesting the importance of females in translational research, the National Institute of Health (NIH) recently mandated that sex must be considered a significant biological variable in the experimental design of basic and preclinical research. In the past, sex has not been commonly studied as a significant biological variable in preclinical research because of the costs of time and money associated with studying both sexes. However, the role of sex in basic research has the potential to bring important insights into science and medicine.

...with an over-reliance on male animals and cells, preclinical research neglects to account for sex differences that could potentially guide clinical studies. This gap in knowledge hinders the likelihood of reproducibility in clinical research.

The Sex as a Biological Variable (SABV) policy was announced by the NIH in June 2015 with the objective of accounting for the potential influence of sex on the results of preclinical studies. For the purpose of this policy, the NIH defines "sex" as the "biological differences between females and males, including chromosomes, sex organs, and endogenous hormonal profiles" (National Institute of Health).

In 1993, the NIH mandated that women must be included in NIH-funded clinical research. As a result of this requirement, over half of the participants in NIH-funded research are women (Clayton and Collins, 2014). However, with an over-reliance on male animals and cells, preclinical research neglects to account for sex differences that could potentially guide clinical research. This gap in knowledge hinders the likelihood of reproducibility in clinical research. Therefore, through the SABV policy, the NIH aims to address this gap between preclinical and clinical research.

While the inclusion of sex as a variable in preclinical and clinical research allows for greater coherence and reproducibility, studying both males and females imposes hurdles involving the costs of conducting a study. Kathleen Gardiner is a neuroscientist who studies the role of sex differences in Down syndrome in mice at the the University of Colorado school of Medicine. According to Gardiner, studying both sexes doubles the cost of an experiment. Gardiner states, "If you need 15 mice for a study, but want to use both sexes, that means you need 15 males and 15 females" (Krisch, 2017). Although the costs of conducting a study are doubled, the SABV policy does not include additional funding for these experiments. Therefore, researchers will most likely have to use a smaller population size for studies. Although costs may be increased over the course of collecting preliminary data, the potential benefits of understanding sex difference in preclinical research outweigh the costs.



Sex differences are significant in preclinical research. Differences in activation of the ventrolateral part of the ventromedial hypothalamus in male and female mouse brains during mating and fighting ("Diagram of mouse brain (far left) and the ventrolateral part of the ventromedial hypothalamus").

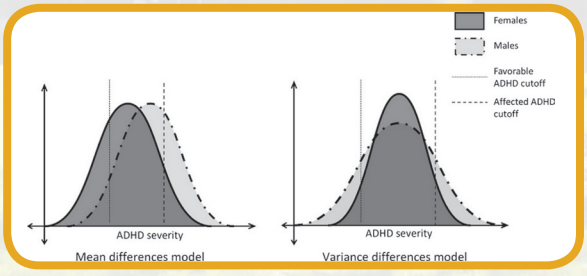
In addition to monetary costs, the SABV policy imposes potential costs in time. To eliminate the potential confounding variable of the female estrus cycle, an extra step must be taken in order to

synchronize estrus cycles (Krisch, 2017). With the consideration of these additional costs, the SABV policy allows for studies to use only one sex under the circumstances of strong justification of no sex influence in scientific literature and preliminary

Balancing usage of both sexes in preclinical research (Scott, 2014).

data. While using females in scientific studies may be more taxing at first, the eventual costs may decrease in the future depending on the relevance of sex in these studies.

The inclusion of sex as a biological variable in preclinical studies may offer important insights into clinical research based on the effects of findings from previous preclinical studies. Females are more susceptible than males to multiple sclerosis (MS), and late pregnancy decreases the severity of MS. A study conducted on mice showed that the because of the protective effect of testosterone in males decreased susceptibility for experimental



As an example of sex differences in clinical research, ADHD severity is shown to differ between males and females (Arnett et al., 2014).

autoimmune encephalomyelitis (EAE), used as an animal model for MS. In addition, this study showed that high levels of estriol reduced severity of the disease during late pregnancy (Voskuhl and Palazynski, 2001). Based on the results of this preclinical study, Wisdom et al. tested a clinical treatment using the estrogen receptor-β ligand after the onset of MS. The results of this study showed that the treatment may be neuroprotective, decreasing the severity of MS symptoms (Wisdom et al., 2013). These corresponding studies illustrate the importance of the concordance between preclinical and clinical research.

The NIH SABV policy brings sex differences to the forefront of research, hoping to align preclinical and clinical studies. Overall the benefits of catching sex differences earlier on in the research process outweigh the costs. This mandate not only allows for greater reproducibility and coherence in research, but also has the potential foster greater understanding of the underlying biology of females.

Images:

Arnett, Anne & Pennington, Bruce & G. Willcutt, Erik & C. DeFries, John & Olson, Richard. (2014). Sex differences in ADHD symptom severity. J Child Psychol Psychiatry. Journal of Child Psychology and Psychiatry. 56. . 10.1111/jcpp.12337.

[Diagram of mouse brain (far left) and the ventrolateral part of the ventromedial hypothalamus]. (n.d.). Retrieved from https://medicalxpress.com/news/2017-09-sex-aggression-female-animal-brains.html

Scott, K. (2014, May 14). Policy: NIH to balance sex in cell and animal studies. Retrieved from http://www.nature.com/polopoly_fs/7.17287.1399893449!/image/Final-KS-NTR-03.jpg_gen/derivatives/landscape_630/Final-KS-NTR-03.jpg

References:

Clayton, J. A., Collins, F.S. (2014, May 14). Policy: NIH to balance sex in cell and animal studies. Retrieved from http://www.nature.com/news/policy-nih-to-balance-sex-in-cell-and-animal-studies-1.15195

Krisch, J. A. (2017, February 24). How Much Do Sex Differences Matter in Mouse Studies? Retrieved from https://www.the-scientist.com/?articles.view/articleNo/48616/title/How-Much-Do-Sex-Differences-Matter-in-Mouse-Studies-/

Maddox, S. A., Kilaru, V., Shin, J., Jovanovic, T., Almli, L. M., Dias, B. G., . . . Smith, A. K. (2017, January 17). Estrogen-dependent association of HDAC4 with fear in female mice and women with PTSD. Retrieved from http://www.nature.com/articles/mp2016250

National Institute of Health. (n.d.). Sex / Gender. Retrieved from https://orwh.od.nih.gov/research/sex-gender/

Sterling, J. (2017, July 05). Considering Sex as a Biological Variable in Biomedical Research. Retrieved from https://www.genengnews.com/gen-exclusives/considering-sex-as-a-biological-variable-in-biomedical-research/77900936

Tolin, D. F., & Breslau, N. (2007, September). Sex Differences in Risk of PTSD. Retrieved from https://www.ptsd.va.gov/professional/newsletters/research-quarterly/v18n2.pdf

Voskuhl, R. R., & Palaszynski, K. (2001, June 07). Sex hormones in experimental autoimmune encephalomyelitis: implications for multiple sclerosis. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11499404?dopt=Abstract&holding=npg

Wisdom, A. J., Cao, Y., Itoh, N., Spence, R. D., Voskuhl, R. R. (2013, April 30). Estrogen receptor-β ligand treatment after disease onset is neuroprotective in the multiple sclerosis model. Retrieved from, http://onlinelibrary.wiley.com/doi/10.1002/jnr.23219/

Implications of Gut Microbiota in Parkinson's Disease Pathology

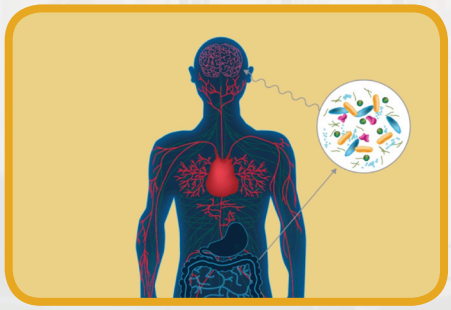
Authored by: Hannah Kelly
Edited by: Christopher Keyes **Reviewed by: Dr. Arri Eisen**

Considered the most common movement disorder and the second most prevalent neurodegenerative disorder, Parkinson's disease (PD) affects 7-10 million people worldwide. With a steady rise in the elderly population, researchers predict this statistic will double in the next 20 years. In diagnosing PD, pathological features primarily include the degeneration of dopaminergic neurons in the substantia nigra and the abnormal aggregation of alpha-synuclein (α-synuclein) fibers into Lewy bodies in the central nervous system (CNS). Several classic motor symptoms—such as dyskinesia, muscular rigidity, tremor, slowness of movement, and gait disorder—characterize PD. But PD patients also exhibit a wide array of non-motor symptoms (NMS), including depression, dementia, hyposmia, orthostatic hypotension and, most commonly, gastrointestinal (GI) dysfunction such as constipation (Nair, Ramachandran, Joghee, Antony, & Ramalingam, 2018). PD is a multifactorial disease with a complex interaction of genetic predisposition and environmental factors leading to its onset, and recently researchers have shifted their focus away from the hallmark motor symptoms affecting dopaminergic neurons. Instead, recent research examines early NMS that potentially originate in the gut to investigate claims that PD originates in areas outside of the substantia nigra (Erro et al., 2018).

Further, α-synuclein aggregation in the ENS may begin up to 20 years before the degeneration of dopaminergic neurons in the CNS causes motor symptoms in PD.

Interestingly, the olfactory system and the enteric nervous system (ENS) in the GI tract also display Lewy body pathology, and thus α-synuclein pathology may arise in these areas before spreading to the CNS. Further, α-synuclein aggregation in the ENS may begin up to 20 years before the degeneration of dopaminergic neurons in the CNS causes motor symptoms in PD. In addition, constipation, the most prevalent premotor symptom in PD, can appear 10 or more years prior to disease onset. Neuronal degeneration in the ENS because of α-synuclein accumulation can explain the high incidence of constipation among PD patients, and as a result Lewy body accumulation in the ENS may trigger GI dysfunction in PD (Minato et al., 2017). Identifying risk factors and early biomarkers by investigating the association between gut microbiota profiles of PD patients and the early NMS will lead to a more comprehensive understanding of PD pathology and advance the search for a cure (Nair et al., 2018).

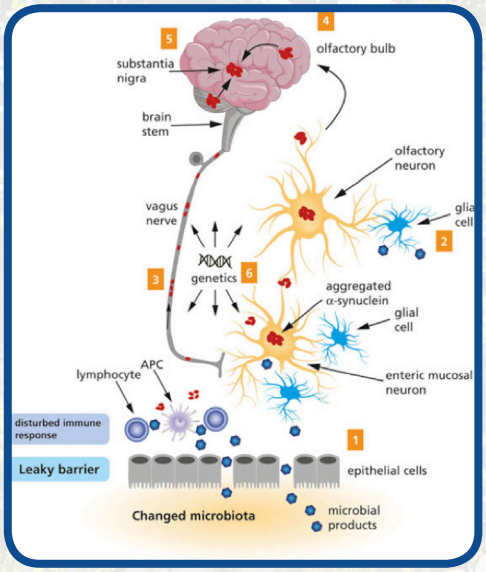
Although the exact causes behind the initiation of PD pathology remain unresolved, environmental factors and inflammatory responses likely contribute in significant ways. The fact that the GI tract becomes involved in PD pathology quite early supports both the presumed role of environmental factors influencing PD progression through the gut and GI tract inflammation leading to eventual neurodegeneration. For example, constipation remains the most common GI issue among PD patients and the second most common NMS. Up to 80% of patients report having constipation, and these symptoms may occur before motor symptoms by more than 10 years (Perez-Pardo, Hartog, Garssen, & Kraneveld, 2017a).



Initial PD pathology may spread from the gut to the brain via the microbiota-gut-brain axis, a bidirectional communication between the intestine and the CNS ("Parkinson's and the microbiome", 2017).

Mounting evidence reveals that PD patients may display an aberrant and pro-inflammatory gut microbiota composition because of the common early occurrence of constipation and other GI abnormalities in PD patients. Recent studies theorize that changes in gut microbiota conditions affect brain function through the microbiota-

gut-brain axis; a bidirectional communication system between the CNS and the GI tract that alters digestion, the immune system, perception, and emotions. Contributing to both brain and GI function, the axis consists of afferent fibers that



According to Braak's hypothesis of PD, microbial products interact with olfactory and/or enteric neurons, causing α-synuclein accumulation that spreads to the CNS through the olfactory bulb and vagal nerve (Rietdijk et al., 2017).

project from the gut to cortical centers of the brain and efferent fibers that reach the gut from the brain (Nair et al., 2018).

In recent PD research, growing evidence reveals that PD patients exhibit a pro-inflammatory gut microbiota profile that may increase gut permeability. Development of a "leaky gut" resulting from malfunctions in intestinal tight junctions causes bacteria and pro-inflammatory substances to leak into circulation and upset the balance of the inflammatory immune response. For example, colonic biopsies of PD patients demonstrate higher levels of pro-inflammatory cytokines and additional activation of glial cells in the ENS that play a role in the immune response (Perez-Pardo et al., 2017a).

Such pro-inflammatory activity in the immune system from oxidative stress in the gut might in turn initiate α-synuclein accumulation in the ENS that will eventually spread to the CNS. Researchers in several studies observed elevated levels of α-synuclein in the intestines of individuals with PD in comparison to healthy controls (Perez-Pardo et al., 2017a). These findings remain consistent with Braak's hypothesis, a proposed staging of PD presented by Braak and colleagues in 2003. According to the hypothesis, gut microbiota influence the activity of olfactory and/or enteric neurons, triggering α-synuclein accumulation in these areas from toxins or bacteria (Rietdijk, Perez-Pardo, Garssen, van Wezel, & Kraneveld, 2017). As early α-synuclein pathology often occurs in brain structures that provide parasympathetic innervation to the GI tract, the vagus nerve may offer a way for α-synuclein aggregates in the ENS to reach the brain. In fact, a recent study detected an association between a vagotomy and a lowered risk of developing PD, supporting the notion that the vagus nerve may facilitate the spread of PD from the gut to the brain (Perez-Pardo et al., 2017b). In short, GI dysfunction and inflammation—characterized by constipation, over-expression of enteric α-synuclein, gut dysbiosis, and higher intestinal permeability—occur up to 20 years before motor symptoms in PD patients. In turn, prolonged inflammatory conditions linked to gut microbiota profiles can trigger both systemic and neuroinflammation (Nair et al., 2018).

In support of the proposed mechanisms relating the gut microbiota to PD pathology, an abundance of studies reveal altered gut microbiota profiles in PD patients in comparison to healthy controls. Scheperjans et al. conducted the first study characterizing alterations in fecal bacteria profiles between PD patients and healthy subjects. In PD patients, the researchers detected higher counts of Enterobacteriaceae that related to the intensity of postural instability and gait troubles. They also identified a decreased abundance of Prevotella, a bacterial species essential to the synthesis of thiamine and folate: two vitamins often present in reduced concentrations in PD patients. Scheperjans et al. further argue that the decrease in Prevotella may be associated with increased intestinal permeability. Gut leakiness in turn can lead to toxin exposure, a possible environmental cause of PD through the induction of α-synuclein aggregation in the colon (Scheperjans et al., 2015).

While the Scheperjans study was the first investigation to describe the differences in gut microbiota profiles of PD patients, a more recent project led by Minato et al. became the first to consider the effects of gut microbiota on the progression of PD. In a two-year follow-up, they studied the intestinal microbiota of patients divided into "deteriorated" and "stable" groups and assessed the effects on progression of PD. Throughout the study, total fecal bacterial counts and the counts of six of the ten measured intestinal bacterial groups decreased in all PD patients, thus signifying the presence of gut dysbiosis. Furthermore, the C. leptum and B. fragilis group counts decreased over two years only in the stable group, possibly because

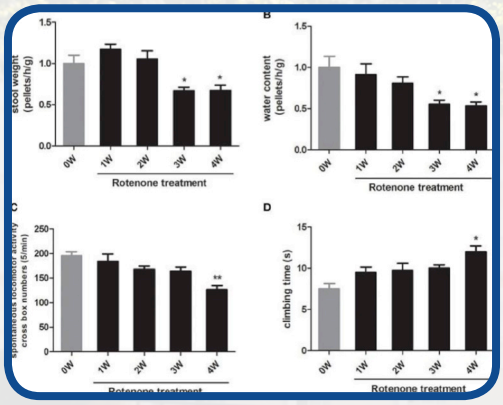
the deteriorated group may have already met the low plateau values for these bacterial species at the start of the study. The varying degrees of change in the counts of bacterial groups among the deteriorated and stable patients imply that gut microbiota profiles may already be significantly implicated in PD pathology by the time of actual clinical diagnosis (Minato et al., 2017).

In a longitudinal study published in January of this year, Yang et al. investigated the link between PD and fecal microbiota composition by examining the change in fecal microbiota before and after the oral administration of rotenone in mice. Rotenone, an inhibitor used to model PD in animals, causes degeneration of dopaminergic neurons, accumulation of α-synuclein in the CNS, and GI dysfunction. After three weeks of rotenone treatment, mice began to exhibit GI dysfunction, with reduced colon motility and stool water content compared to week zero. Also, the researchers detected an increased expression of α-synuclein in the colon of rotenone-exposed mice starting at week three. In open field and pole tests used to measure motor capacity, rotenone-treated mice displayed deficits at four weeks of treatment, demonstrating that rotenone triggers GI dysfunction and changes in fecal microbiota content before the onset of motor impairments and the hallmark CNS pathology of PD.

The data from Yang et al.'s experiment, moreover, show abnormal microbiota profiles in rotenone-treated mice, with significant shifts in fecal bacteria content at weeks three and four in comparison to the start of the experiment. Researchers detected an increase in the Firmicutes/Bacteroidetes ratio, which is related to many inflammatory conditions. Also, starting from weeks two and three, respectively, the relative abundance of Desulfovibrio decreased and that of Lactobacillus increased. Reduced levels of Desulfovibrio correlated with increased intestinal permeability, and higher amounts of Lactobacillus correlated with impaired GI and motor functions. Importantly, as the study found evidence of fecal microbiota aberrations prior to the onset of motor deficits and CNS pathology, disruptions in fecal microbiota may contribute to rotenone toxicity or accelerate the start of PD pathology (Yang, Qian, Xu, Song, & Xiao, 2018).

Despite decades of research and progress on decoding the biological mechanism underlying PD, treatment for PD remains difficult because of the challenges of both making definitive early diagnoses and managing late-stage symptoms. The available PD drug therapies, especially Levodopa, possess limits in terms of effectiveness and safety (Nair et al., 2018). While Levodopa subdues motor symptoms and increases dopamine production, patients experience dyskinesia and motor fluctuation after prolonged use (Perez-Pardo et al., 2017b). Today, no PD therapies can halt the progression of the disease or completely eliminate motor symptoms. Levodopa fails to prevent further loss of dopamine cells, and patients may even acquire drug resistance in late stages of PD. Also, none of the currently available therapies specifically target the gut-brain axis to reduce NMS in addition to motor symptoms.

Recent evidence hints at the potential power of using nutritional interventions in combination with traditional PD therapies to address GI symptoms. Dietary treatments, such as phospholipid membrane precursors, may target the gut-brain axis by influencing neuronal activity in the ENS and the CNS. For example, rodent studies indicated that administering the nutrient combination of uridine, DHA, and choline elevated the amount of synaptic



Rotenone-treated mice showed GI dysfunction starting at week 3 and displayed motor deficits at week 4 (Yang et al., 2018).

proteins and might offset synaptic losses and lower membrane pathogenesis in the CNS and ENS in PD patients. Various types of probiotic bacteria, moreover, have been found to lower GI dysfunction and increase intestinal motility by altering microbiota composition. Researchers in a clinical study discovered that the probiotic Lactobacillus salivarius reduced markers of inflammation in healthy patients. Overall, nutritional therapies may improve GI symptoms and increase Levodopa absorption, permitting the prescription of smaller doses to patients and helping lower the drug's many negative side effects (Perez-Pardo et al., 2017b).

In addition to concerns regarding the efficacy and safety of current PD therapies, the diagnostic methods for PD require further research to enhance efficacy and accuracy. Traditional clinical diagnoses primarily entail detecting hallmark motor symptoms

in patients. However, because severe neurological harm can occur prior to the onset of these motor symptoms, novel methods for earlier diagnosis will allow for quicker treatment and proactive means to safeguard brain function and slow PD progression. To accomplish this, the discovery of consistent biomarkers will help anticipate the onset of PD pathology, and because constipation is one of the most frequently reported NMS in PD patients, bowel dysfunction and other GI issues are especially promising PD biomarkers (Nair et al., 2018). Similarly, recent evidence proposes the use of GI tract biopsies as early biomarkers of PD, a potentially favorable method of sensing α-synuclein pathology before it occurs in the CNS. The Scheperjans study, moreover, further emphasizes the urgent need to use microbiota analysis in the development of PD biomarkers. Results from the study highlight that high fecal expression of Prevotellaceae stands as a possible biomarker to exclude PD diagnosis. Overall, this area of research has significant promise for the future of PD treatment, as gut dysfunction occurs prior to the manifestation of motor symptoms and thus could help diagnose PD earlier (Scheperjans et al., 2015).

Recent advances in genomic analysis have allowed researchers to more thoroughly study fecal and intestinal bacterial compositions in PD patients. In investigating microbiota profiles, researchers have detected several consequences of microbiota fluctuations in PD patients, including the activation of harmful inflammatory pathways. Based on these findings, much of PD research now proposes the gut as the site of initial PD pathology and emphasizes the association of gut microbiota dysfunction to a cycle of increased intestinal permeability, GI and neural inflammation and, finally, neurodegeneration (Erro et al., 2018).

Such proposed mechanisms of neurodegeneration in PD as a consequence of events originating in the gut are consistent with evidence highlighting the high prevalence of GI-related NMS in PD. Most PD patients display GI dysfunction, characterized by constipation, high levels of enteric α-synuclein, and inflammation associated with increased permeability, and these NMS occur prior to motor symptoms by up to 20 years (Nair et al., 2018). The microbiota-gut-brain axis is especially pertinent to understanding PD pathology, as it may offer the necessary path linking the spread of initial PD pathology in the gut to regions of the brain such as the substantia nigra. The current research shedding light on the role of gut health in PD pathology has promising implications in the search for clinical biomarkers such as GI symptoms for earlier diagnosis of PD and in the development of novel therapies, including dietary interventions, to treat NMS and prevent the disease spread (Erro et al., 2018).

Images

[Parkinson's and the microbiome: A gut(-brain) reaction]. (2017). Retrieved from https://magazine.caltech.edu/post/gut-brain-reaction

Rietdijk, C. D., Perez-Pardo, P., Garssen, J., & van Wezel, R. J.A. (2017, February 13). [A schematic representation of the Braak's hypothesis of Parkinson's disease (PD).] [Map]. Retrieved from PubMed database.

Yang, X., Qian, Y., Xu, S., Song, Y., & Xiao, Q. (2018, January 8). [Figure 2] [Chart]. Retrieved from PubMed database.

References

Erro, R., Brigo, F., Tamburin, S., Zamboni, M., Antonini, A., & Tinazzi, M. (2018). Nutritional habits, risk, and progression of Parkinson disease. Journal of Neurology, 265(1), 12-23. Retrieved from PubMed database.

Minato, T., Maeda, T., Fujisawa, Y., Tsuji, H., Nomoto, K., Ohno, K., & Hirayama, M. (2017). Progression of Parkinson's disease is associated with gut dysbiosis: Two-year follow-up study. PLoS ONE, 12(11), 1-14. Retrieved from PubMed database.

Nair, A. T., Ramachandran, V., Joghee, N. M., Antony, S., & Ramalingam, G. (2018). Gut microbiota dysfunction as reliable non-invasive early diagnostic biomarkers in the pathophysiology of Parkinson's disease: A critical review. Journal of Neurogastroenterology and Motility, 24(1), 30-42. Retrieved from PubMed database.

Perez-Pardo, P., Hartog, M., Garssen, J., & Kraneveld, A. D. (2017). Microbes tickling your tummy: The importance of the gut-brain axis in Parkinson's disease. Current Behavioral Neuroscience Reports, 4(4), 361-368. Retrieved from PubMed database.

Perez-Pardo, P., Kliest, T., Dodiya, H. B., Broersen, L. M., Garssen, J., Keshavarzian, A., & Kraneveld, A. D. (2017). The gut-brain axis in Parkinson's disease: Possibilities for food-based therapies. European Journal of Pharmacology, 817, 86-95. Retrieved from PubMed database.

Rietdijk, C. D., Perez-Pardo, P., Garssen, J., van Wezel, R. J. A., & Kraneveld, A. D. (2017). Exploring Braak's hypothesis of Parkinson's disease. Frontiers in Neurology, 8(37), 1-9. Retrieved from PubMed database.

Scheperjans, F., Aho, V., Pereira, P. A.B., Koskinen, K., Paulin, L., Pekkonen, E., . . . Auvinen, P. (2015). Gut microbiota are related to Parkinson's disease and clinical phenotype. Movement Disorders, 30(3), 350-358. Retrieved from PubMed database.

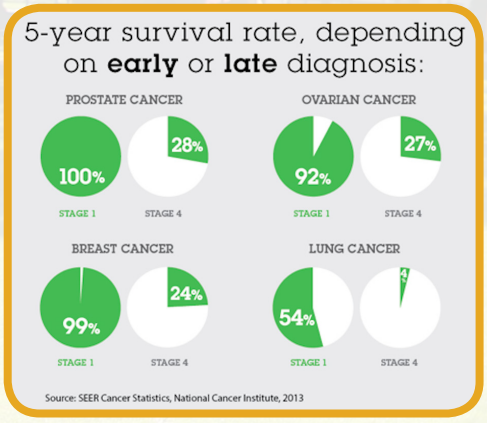
Yang, X., Qian, Y., Xu, S., Song, Y., & Xiao, Q. (2018). Longitudinal analysis of fecal microbiome and pathologic processes in a rotenone induced model of Parkinson's disease. Frontiers in Aging Neuroscience, 9(441), 1-12. Retrieved from PubMed database.

Cancer Screening in the 21st Century: A Double-Edged Sword?

Authored by: Aditya Jhaveri
Edited by: Soumya Mandava
Reviewed by: Dr. Gregg Orloff

I knew something wasn't right.

Nancy Crawford told her husband, Frank Crawford, to see a doctor because of her concerns about his health. As a Vietnam veteran, Frank was exposed to agent orange, precipitating health issues at the age of 42. An X-ray screening at Dekalb Medical revealed an issue in one of Frank's lungs, and he was subsequently diagnosed with lung cancer. Unfortunately, while removing the tumor, the surgeon stopped the operation as he found that the cancer had actually reached both lungs. Dekalb Medical employed an aggressive chemotherapy treatment and radiation (to shrink the tumors) followed by the removal of a lobe from each lung. Thankfully, he was declared cancer-free within a year of his diagnosis, which was largely credited to early detection through screening. For each success story, however, there are just as many failures stemming from missing cancer in earlier stages. Thus, the recent development of blood-based detection techniques—for early cancer detection and precision oncology—has tremendous potential



Many publications and figures showcase detecting cancer earlier seems to result in longer survival, but lead time bias potentially affects statistics relating to diagnosis and screening (National Cancer Institute, 2013).

to help diagnose and guide treatment decisions for patients like Frank but raises questions of whether increased cancer detection is truly a silver bullet.

Cancer screening holds significant value in oncology. The frontier for cancer screening is in finding a more specific and sensitive targeting mechanism to detect cancer earlier, so it can be treated and its spread prevented. Enthusiasm for cancer screening is high, as 87 percent of American adults consider cancer screening almost always beneficial and 74 percent of American adults believe finding cancer early saves lives most or all the time (Schwartz, Woloshin, Fowler, & Welch, 2004). Support for cancer screening can be seen globally: in Great Britain, for example, cancer screening is seen as overwhelmingly positive with nearly 90 percent believing that "screening is almost always a good idea" (Waller, Osborne, & Wardle, 2015). Both studies (Schwartz et al. and Waller et al.) warn that widespread enthusiasm for cancer screening may obscure the reality that cancer screening also carries a number of disadvantages. However, if cancer screening can be used with proper understanding of its advantages and disadvantages, the potential to save lives—especially with newer screening techniques—heightens the urgency to develop better treatment plans.

Enthusiasm for cancer screening is high, as ... 74 percent of American adults believe finding cancer early saves lives most or all the time (Schwartz, Woloshin, Fowler, & Welch, 2004).

Currently, tissue biopsies remain the standard diagnostic procedure for many cancer types. According to a 2017 report by the National Cancer Institute, however, there are pervasive complications with tissue biopsies that stem from their "invasive, risky, costly, and painful" nature. Furthermore, because of their static nature and the potential to miss mutations as tumors evolve, tissue biopsies are not considered an accurate, reliable detection method. The adoption of liquid biopsies (a range of tests examining blood, saliva, cerebral spinal fluid, etc.) for cancer detection has become increasingly important.

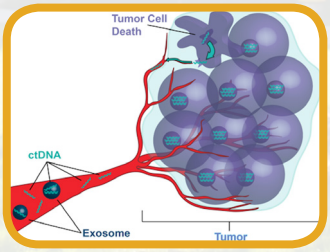
A new blood-based liquid biopsy focuses on evaluating circulating tumor DNA (ctDNA), which is released in exosomes or when cancer cells die.

This altered screening tactic shows promise in providing a more detailed, specific picture of tumor progression (Yong, 2014). Another cancer detection technique, a protein biomarker-based liquid biopsy, suffers from limitations because of overdiagnosis

Tissue biopsies have significant downsides but continue to be the gold standard in diagnosing cancer because of their widespread adoption (VENTUS, n.d.).

and a high rate of false positives (Casillas et al., 2014). Protein biomarkers - depending on the protein - can stay in the blood for weeks while ctDNA has a half-life of fewer than two hours, so liquid biopsies should give a clearer view of a tumor in its current form, rather than in its past (Yong, 2014).

A breakthrough blood test utilizing ctDNA has come to the forefront of cancer screening in recent weeks, with headlines highlighting the ability of the test to detect eight different types of cancer. The biopsy examines the levels of eight proteins and indicates the presence of mutations in sixteen genes (Ledford, 2018). Functionally, it yielded a positive result "about 70% of the time across eight different common cancer types in more than 1000 patients whose tumors had not yet spread" (Kaiser, 2018). The data show that ctDNA-based detection methods



A blood-based "liquid biopsy" detects circulating tumor DNA (ctDNA) from tumors secreting fragments of DNA in order to find changes in ctDNA that allow for more targeted prognosis (Lovly et al., 2016).

have a promising future in cancer screening.

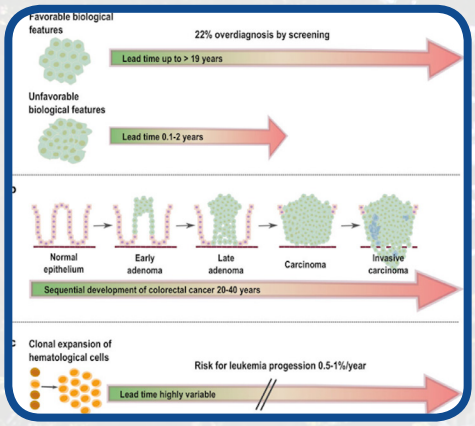
However, even though there is significant hope for liquid biopsy, researchers acknowledge that work must be done to address certain limitations in order to move the technology into the clinic. As a response to the prevalent concern of false positives, "Hopkins and Geisinger Health System in Pennsylvania have started a study of [liquid biopsy] in 10,000 Geisinger patients who will be tracked for at least five years" (Marchione 2018). Current studies have evaluated the success rate of liquid biopsies in patients that have already been diagnosed with cancer, but it is expected that the false alarm rate may increase in the general population. Additionally, further research is necessary in order to optimize the test to determine the threshold of circulating molecules sufficient to detect alterations in tumor progression (Di Meo et al., 2017).

Despite the widespread enthusiasm for cancer screenings and new liquid biopsies, it is important to take a step back and acknowledge the concomitant drawbacks, specifically the potential for misinterpretation of screening results. Primarily, screening with liquid biopsies has the potential to suffer from lead time bias, which gives the perception of longer survival of cancer detected in patients through screening compared to clinically diagnosed cases. Lead time bias, also known as zero time shift, occurs as screening places diagnosis forward in time and the cancer is detected earlier. Earlier diagnosis, however, does not necessarily promise better survival rates; "screening may therefore seem effective (even if ineffective) if survival from time of diagnosis is used as the outcome to compare screen detected cases with clinically diagnosed cases" (Barratt et al., 2002). If evaluating the success of cancer screening comes down to statistical manipulation, cancer screening may not actually be beneficial. Thus, in evaluating liquid biopsies, enthusiasm should not influence interpretation of data.

Furthermore, for liquid biopsies to be clinically useful, there should be evidence of patient outcome improvement. In a preliminary use of liquid biopsies to change the treatment plan of metastatic breast cancer patients, detecting an increase in circulating tumor cells resulted in a switch from first-line chemotherapy to second- and third-line treatments (escalating treatment in an effort to match the progression of the cancer); however, this did not improve overall survival of patients (Pan et al., 2017). Cancer screening must also account for unintended consequences. For example, if a cancer progresses slowly (the patient would die of something else first) or could potentially be resolved naturally, treatments would instead harm the patient (Chodosh, 2018). A startling example of this comes from an analysis of mammography that concludes that while mammograms find cancer in about 138,000 women in the U.S. each year, as many as 120,000 to 134,000 cases would not be resolved by

treatment since the cancers are lethal (late stage) or slow-growing (Kolata, 2011). With all the potential for cancer screening and the incorporation of liquid biopsy information in the near future, it is important to acknowledge the misconceptions surrounding cancer diagnosed by certain screening methods and the harms of unnecessarily aggressive treatment plans

The potential of liquid biopsies truly



Lead time is defined as "the length of time between when a cancer can be detected by screening and when it would have become clinically apparent without screening." Specific types of cancers can be treated upon clinical presentation making screening sometimes unbeneficial (Heitzer et al., 2017).

demonstrates the necessity of further research into precision oncology. With significant benefits over current cancer screening techniques, liquid biopsies appear to be a tremendous breakthrough. Nevertheless, enthusiasm must be tempered by pragmatism and caution as cancer screening can cut both ways.

Images:

Heitzer, E., Perakis, S., Geigl, J. B., & Speicher, M. R. (2017). The potential of liquid biopsies for the early detection of cancer. Npj Precision Oncology, 1(1). doi:10.1038/s41698-017-0039-5

Lovly, C., M. Berger, C. Vnencak-Jones. 2016. Circulating Tumor DNA. My Cancer Genome https://www.mycancergenome.org/content/molecular-medicine/circulating-tumor-dna/ (Updated February 8).

National Cancer Institute (2013). Seer Cancer Statistics. [Digital Image]. Retrieved February 25, 2018, from https://www.ohsu.edu/xd/health/services/cancer/about-us/early-detection-vision/why-focus-on-early-detection.cfm

VENTUS. (n.d.). Liquid Biopsy. [Digital Image]. Retrieved February 25, 2018, from http://www.ventuspm.com/product/liquid-biopsy/?lang=en&ckattempt=3

References:

Barratt, A., Mannes, P., Irwig, L., Trevena, L., Craig, J., & Rychetnik, L. (2002). Cancer screening Journal of Epidemiology & Community Health, http://dx.doi.org/10.1136/jech.56.12.899

Casillas, C. E., Fernández, J. M., Camberos, E. P., López, E. J., Pacheco, G. L., & Velázquez, M. M. (2014, July 23). Current status of circulating protein biomarkers to aid the early detection of lung cancer. Future Oncology, 10(8), 1501-1513. doi:10.2217/fon.14.21

Chodosh, S. (2018, January 19). We're getting better at screening for cancer, and that could be a problem. Retrieved January 30, 2018, from https://www.popsci.com/broad-cancer-screening

Dekalb Medical Cancer Center. (n.d.). Lung Cancer Survivor Story. Retrieved February 25, 2018, from http://www.dekalbmedical.org/our-services/cancer-care/atlanta-breast-lung-cancer-screening-and-diagnosis/lung-cancer-screening/lung-cancer-survivor-story

Di Meo, A., Bartlett, J., Cheng, Y., Pasic, M. D., & Yousef, G. M. (2017). Liquid biopsy: a step forward towards precision medicine in urologic malignancies. Molecular Cancer, 16, 80. http://doi.org/10.1186/s12943-017-0644-5

Ledford, H. (2018). Simple blood test detects eight different kinds of cancer. Nature, https://www.nature.com/articles/d41586-018-00926-5

Kaiser, J. (2018, January 19). 'Liquid biopsy' promises early detection for cancer. Retrieved January 30, 2018, from http://www.sciencemag.org/news/2018/01/liquid-biopsy-promises-early-detection-cancer

Kolata, G. (2011, October 29). Considering When It Might Be Best Not to Know About Cancer. Retrieved January 30, 2018, from http://www.nytimes.com/2011/10/30/health/cancer-screening-may-be-more-popular-than-useful.html?mtrref=www.google.com

Marchione, M. (2018, January 19). Blood test to detect 8 cancers early gives promising results. Retrieved January 30, 2018, from https://www.apnews.com/0206fab35bc2463aa1d1ac411f0a96a5/Blood-test-to-detect-8-cancers-early-gives-promising-results

National Cancer Institute. (n. d.). Liquid Biopsy: Using Tumor DNA in Blood to Aid Cancer Care. Retrieved January 30, 2018, from https://www.cancer.gov/news-events/cancer-currents-blog/2017/liquid-biopsy-detects-treats-cancer

Pan, Y., Ji, J. S., Jin, J. G., Kuo, W. P. & Kang, H. (2017). Cancer Liquid Biopsy: Is It Ready for Clinic?. IEEE Pulse. 8 (1), 23-27. doi: 10.1109/MPUL.2016.2630838.

Schwartz L.M., Woloshin S., Fowler, Jr. F.J., & Welch H.G. (2004, January 7). Enthusiasm for Cancer Screening in the United States. JAMA. 291(1), 71–78. doi:10.1001/jama.291.1.71

Waller, J., Osborne, K., & Wardle, J. (2015). Enthusiasm for cancer screening in Great Britain: a general population survey. British Journal of Cancer, 112(3), 562–566. http://doi.org/10.1038/bjc.2014.643

Yong, E. (2014). Cancer biomarkers: Written in blood. Nature, 511(7511), 524-526. doi:10.1038/511524a

Defining Differences: Perceived Reading Ability vs. Measured Reading Ability

Authored by: Shaily Patel
Edited by: Soumya Mandava **Reviewed by: Dr. Tyler Cymet**

Fundamental language skills are often culturally dependent and learned early in life. Prevalent in today's information-driven society, reading is considered an integral component of communication. Reading, however, is frequently thought of as a phenomenon that utilizes only the visual sensory modality. Counter-intuitively, it reaches far beyond sole visual input. As a cultural and biological phenomenon, reading integrates auditory and visual associations, combining phonology with orthography (Gabay et al., 2015). Phonology recognizes patterns of sounds within a language, whereas orthography involves the visual mapping of their arbitrary forms (Gabay et al., 2015). The brain combines auditory and visual sensory information, which are essential for conscious experience just as they are necessary for reading.

As a cultural and biological phenomenon, reading integrates auditory and visual associations, combining phonology with orthography

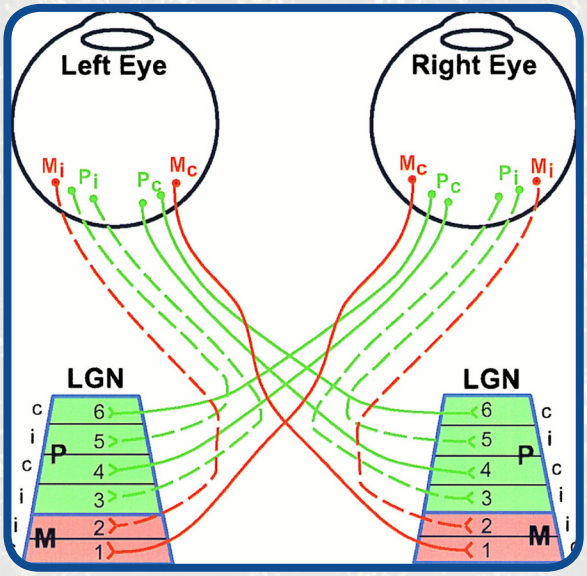
Reading involves the mapping of a combination of phonology and orthography.

Difficulty with reading has commonly been attributed to a failure of explicit identification of the basic phonemic units within speech (Perin, 1983). A phoneme refers to the smallest unit of sound in speech, resulting in perceptually distinct units of sound within a specified language (Liberman, 1957). For example, the word dash contains three phonemes: "d," "a," and "sh." Phonemes often allow one word to be distinguishable from another (Liberman, 1957). For example, replacing the phoneme "d" in dash with the phoneme "b" results in the word bash, which has a different meaning than the original word. Consciousness of the phoneme has often been studied and is a critical determinant for reading ability.

Within today's society, reading difficulty or disability is often attributed to dyslexia. Developmental dyslexia is a neurocognitive disorder that is diagnosed based on an individual's, typically a child's, expected reading skills (Brunswick et al., 1999). Individuals with developmental dyslexia are characterized by selective impairment in reading skill acquisition despite having conventional instruction, adequate intelligence, and sociocultural opportunity (Gabay et al., 2015). Developmental dyslexics generally have reading abilities that are lower than expected in comparison to their age-related intelligence levels or IQ scores. Children with developmental dyslexia have low-level visual and auditory deficits (Gibson et al., 2006). A critically acclaimed theory of visual deficits in dyslexia stems from the magnocellular (magno) deficit hypothesis. This hypothesis suggests that individuals with dyslexia have specific low-level deficits in the visual pathway, which originates in the retina and projects to the visual cortex via the magno layers of the lateral geniculate nucleus (LGN) (Gibson et al., 2006). Typically, the magnocellular and parvocellular layers of the LGN play a vital role in visual perception. The parvocellular layers process visual information about an object's color, shape, or size. The magnocellular visual stream, consisting of larger cells, processes information about the location and awareness of objects, such as detection of an object's movement, distance, or speed (Vidyasagar and Pammer, 1999). Since the magno pathway is crucial for focusing attention serially on objects within one's visual field, individuals with developmental dyslexia are associated with magno pathway deficits (Vidyasagar and Pammer, 1999). Psychophysical evidence for this magno deficit is corroborated by anatomical and physiological

Within today's society, reading difficulty or disability is often attributed to dyslexia.

evidence of reduced cell size in the magno layers but not in the parvocellular layers of the LGN within the brains of dyslexic individuals (Gibson et al., 2006). In an attempt to explain the pathophysiology of



Schematic of neuronal connection of the visual pathway between the eyes and the lateral geniculate nucleus (LGN) in the brain depicting the magnocellular and parvocellular layers (Meissirel, Wikler, Chalupa, & Rakic, 1997).

dyslexia, the magno deficit hypothesis proposes that selective attention, derived from magno processing, provides a neural mechanism that underlies reading (Vidyasagar and Pammer, 1999).

A more commonly accepted hypothesis for the resulting deficits in dyslexia, however, supports the theory originating with difficulties in phonological processing. Phonetic, commonly known as auditory, encoding generally correlates positively with reading ability. Many standardized tests used to diagnose developmental dyslexia examine phonological skills (Gabay et al., 2015). Phonological awareness, which tests the knowledge of the sound structures of words, and phonological processing, which assesses how an individual uses and manipulates this knowledge, are two examination criteria utilized to evaluate phonological impairment. Traditional dyslexia diagnostic standards include individual reading levels more than two standard deviations below expected age-related reading ability combined with normal intelligence levels (Gabay et al., 2015).

Because of discrepancies between reading and intelligence levels, disabilities such as dyslexia often result in disparities between self-perceived reading ability and measured reading ability. A subsequent question that arises, though rarely considered, comprises these two seemingly different proponents that encompass one's ability to read: is an individual's perceived reading ability correlated with his or her measured reading ability? Previous literature and scientific research hypothesize a positive correlation between perceived and measured reading abilities in typical adults. Because auditory and visual presentations interact

The unfavorable consequences of dyslexia can affect a variety of life skills and goals (Learning Ally, 2018).

to influence reading ability and skill, it is plausible for individuals who are aware of their sensory capabilities to subconsciously assume or associate these competencies with their perceived reading ability.

Understanding the causes behind the resulting disparities in perceived and measured reading abilities is pivotal for yielding insights for potential therapies to treat reading disabilities, such as dyslexia. Developmental dyslexia often results in life-long consequences, despite interventions that

Understanding the causes behind the resulting disparities in perceived and measured reading abilities is pivotal for yielding insights for potential therapies to treat reading disabilities, such as dyslexia.

boost reading skills (Gabay et al., 2015). These interventions often happen in adulthood, and the consequences that persist among dyslexics include reduced vocabulary, decreased motivation to read, and decreased background knowledge (Gabay et al., 2015 & Gibson et al., 2006). It is imperative to

know whether individuals actually read at the levels at which they perceive themselves to be reading; this information can be indicative of dyslexia, a disability with drastic reading difficulty yet normal intelligence levels, and has the potential to be beneficial for educational purposes by preventing dyslexia's unfavorable life-long symptoms and testing the efficacy of interventions at a young age.

Images

Learning Ally. (2018). What is Dyslexia? [Digital image]. Retrieved from http://www.learningally.org/dyslexia/what-is-dyslexia-definition

Meissirel, C., Wikler, K. C., Chalupa, L. M., & Rakic, P. (1997). Early divergence of magnocellular and parvocellular functional subsystems in the embryonic primate visualsystem. PNAS, 94(1), 5900-5905.

References

Brunswick, N., McCrory, E., Price, C.J., Frith, C.D., & Frith, U. (1999) Explicit and implicit processing of words and pseudowords by adult developmental dyslexics: A search for Wernicke's Wortschatz? Brain, 122, 1901-1917.

Gabay, Y., Thiessen, E.D., & Holt, L.L. (2015). Impaired Statistical Learning in Developmental Dyslexia. Journal of Speech, Language, and Hearing Research, 58, 934-945.

Gibson, L.Y., Hogben, J.H., & Fletcher, J. (2006). Visual and auditory processing and component reading skills in developmental dyslexia. Journal of Cognitive Neuropsychology, 23(4), 621-642.

Liberman, A.M., Harris, K.S., Hoffman, H.S., & Griffith, B.C. (1957). The Discrimination of Speech Sounds Within and Across Phoneme Boundaries. Journal of Experimental Psychology, 54(5), 358-368.

Perin D. (1983). Phonemic segmentation and spelling. British Journal of Psychology, 74, 129-144.

Vidyasagar, T.R., & Pammer, K. (1999). Impaired visual search in dyslexia relates to the magnocellular pathway in attention. NeuroReport, 10(6), 1283-1287.

Womb Transplantation: A Potential Treatment for Uterine Factor Infertility

Authored by: Soumya Mandava
Edited by: Christopher Keyes
Reviewed by: Dr. Katherine Heiden

In November 2017, doctors at Baylor University Medical Center delivered the first baby born via uterus transplant in America. The mother underwent the operation because she was born without a uterus, caused by a condition known as absolute uterine factor infertility (UFI) (Hafner, 2017). This condition affects 1 in 500 women and ranges in symptoms from having an unhealthy uterus to completely lacking the organ. It commonly results in infertility or obstetric complications

> The uterus transplant surgery, however, offers an avenue for women with UFI, or any other condition that causes infertility, to carry and give birth to a baby.

("Uterine Factor," n.d.). The uterus transplant surgery, however, offers an avenue for women with UFI, or any other condition that causes infertility, to carry and give birth to a baby. Although this procedure is in its early stages in America, womb

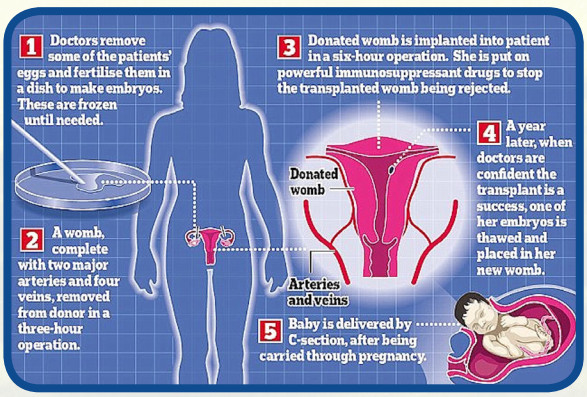
First baby to be born via uterus transplant (Marchione, 2017).

transplantation dates back to the late 1800s.

In 1896, Knauer documented an ovarian autotransplantation—transplanting an organ or tissue from one part of the body to another within the same organism—in a rabbit: a study that lead to numerous investigations conducted throughout the following century. In the 1960s, two notable researchers, Hamernik and Hardy, performed womb autotransplantations in a dog and successfully induced a pregnancy (Eraslan, Hamernik, & Hardy, 1966). Diaz-Garcia built on this work by conducting an allogenic transplant, which involved transplanting the uterus of one rat into another. The successful animal surgeries and healthy offspring led doctors to employ the transplant procedure with human patients (2010). In October 2014, doctors delivered the first human baby born to a uterus transplant recipient.

The process that the recipients must undergo, from embryo collection to hysterectomy, typically lasts 2-3 years. They first receive a fertility treatment consisting of daily injections of gonadotropin to increase egg production. Once the eggs have matured, they are collected and cultured with an augmented sperm sample. The eggs that become fertilized are kept in an incubator until they can be frozen in liquid nitrogen for later use in assisted conception after transplantation. In order to continue with the process, at least 10 viable embryos must be collected.

Recipients then wait for a donor uterus that is appropriately compatible with their bodies, to reduce the risk of rejection. Once one becomes available, the doctors will proceed with the surgery. In the surgery, doctors will place the patient under general anesthesia. A midline incision is made from the belly button up to the pelvic bone to provide access to the pelvis, blood vessels, and vaginal vault.



Stages of surgical transplant procedure ("Stages of Womb Transplantation", 2015).

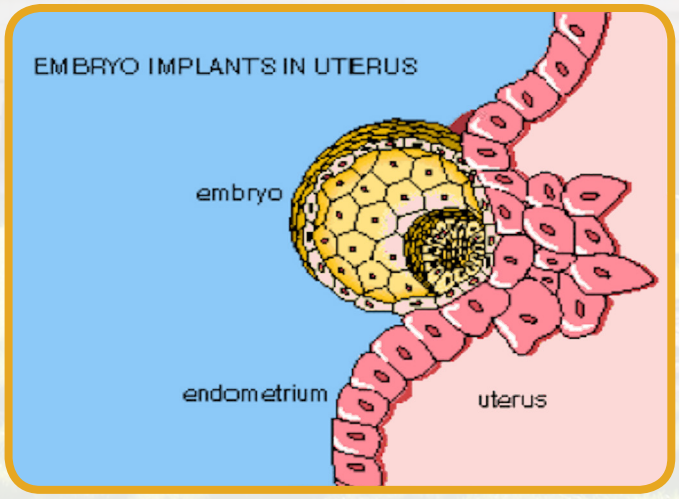
Once the blood vessels are prepared and the vaginal vault is separated from nearby organs, the donor uterus is implanted into the pelvis. It is finally joined with the existing blood supply in the pelvis and attached to the nearby ligaments and connective tissue for better support.

After the procedure, recipients take immunosuppressive medications and have frequent clinic appointments to reduce their chances of rejection. The physicians will gradually reduce the number of medications and the dosages to the lowest possible quantities. The treatment will need to continue (including throughout the pregnancy

...an embryo will be transplanted into the donor uterus through the cervix.

term) until the donor uterus is removed.The treatment is safe to use and has not been shown to cause any major structural or developmental abnormalities in the growing embryo.

One year after the uterine transplantation, doctors will begin attempting assisted conception. The previously stored eggs will be thawed and an embryo will be transplanted into the donor uterus through the cervix. Only a single embryo is transplanted to avoid the complications and risks of multiple pregnancy. Since there are



Surgical implantation of embryo into transplanted uterus ("Embryo implantation in the maternal uterus is enabling better knowledge by new technology," 2015).

multiple embryos prepared, the procedure can be repeated until successful conception. Following a complication-free pregnancy, the baby will be delivered via Caesarean section after about 36

...about 6 months after she has given birth she will undergo a hysterectomy to remove the donor womb

weeks.

If a family decides to have another child, then the recipient can undergo another In Vitro Fertilization (IVF) treatment, continue immunosuppressive medications, and deliver via Cesarean section. Once a recipient decides that her family is complete, about 6 months after she has given birth she will undergo a hysterectomy to remove the donor womb (Smith, Saso, & Jones, n.d).

Since this process is relatively new and could have various unpredictable complications, it is difficult to predict the likely success rates. Data from a Swedish uterus transplantation team, though, shows a 78% success rate with seven successful transplants out of their nine patients (Johannesson, 2016).

Aside from the potential risks and time commitment of this procedure, there are also many ethical issues raised by the community. In order to address them, McGill University developed the "Montreal Criteria for the Ethical Feasibility of Uterine Transplantation." The guidelines for the recipient, donor, and healthcare team are stated as follows:

1. The recipient is a genetic female, has obstetric complications that cannot be ameliorated via other therapies, can undergo a transplantation, and has personal or legal reasons that prevent her from utilizing other options (surrogacy, adoption, etc.). She must want a child, be suitable for motherhood, be psychologically healthy, be likely to follow treatment plan and instructions, and understand the risks of the procedure.

2. The donor is a female (within a healthy reproductive age), is able to undergo the procedure, and has given her consent to donate her uterus. She must be of able mind and should not be coerced or bribed in any way.

3. The healthcare team must receive informed consent from the donor and recipient, must not have any conflict of interests, and must protect the anonymity of both parties, unless it is waived (Lefkowitz, Edwards, & Balayla, 2012).

There are many young women who have medical conditions that prevent them from becoming

pregnant. They could use a surrogate or adopt, but many want the experience of carrying their own child. Studies also show that the mother's bond with the baby begins during pregnancy. The mother's attachment to the fetus not only is an indication of the extent to which she'll bond with the newborn baby but also will have a great impact on the child's future growth, development, and socialization ("Bonding With Your Baby During Pregnancy", 2018). In addition, while in the womb the fetus learns to recognize its mother's voice, and after birth the baby shows more physiological signs of comfort (e.g.,. more regular heart rate) when he or she hears the mom (Sorgen, n.d.). Therefore, despite it being a relatively new procedure, womb transplantation is still currently a notable option for providing considerable benefits to women with UFI and to their children.

Images

Marchione, M. (2017, December 04). First baby from a uterus transplant born in the U.S. [Digital Image]. Retrieved February 14, 2018, from http://www.chicagotribune.com/lifestyles/health/ct-first-baby-from-uterus-transplant-20171204-story.html

Observatorio Bioética. (2015, January 8). Embryo implantation in the maternal uterus is enabling better knowledge by new technology. [Digital image]. Retrieved February 14, 2018, from http://www.observatoriobioetica.org/2015/01/embryo-implantation-maternal-uterus-enabling-better-knowledge-new-technology/6104

[Stages of Womb Transplantation]. (2015, November). Retrieved from http://www.dailymail.co.uk/health/article-3317554/US-hospital-offer-womb-transplants-offering-hope-millions-women-born-without-uterus-left-infertile-cancer-treatment.html

References

Bonding With Your Baby During Pregnancy. (2016, January 17). Retrieved January 28, 2018, from https://www.myvmc.com/pregnancy/bonding-with-your-baby-during-pregnancy/#c1

Díaz-García, C. Akhi, S. N., Wallin, A. Pellicer, A. & Brännström, M.. First report on fertility after allogeneic uterus transplantation. Acta Obstetricia et Gynecologica Scandinavica, 89(11), 1491–1494.

Eraslan, S., Hamernik, R. J., & Hardy, J. D. (1966). Replantation of uterus and ovaries in dogs, with successful pregnancy. Archives of Surgery, 92(1), 9–12.

Hafner, J. (2017, December 4). Uterus transplant results in successful birth - the 1st in the U.S. Retrieved January 28, 2018, from https://www.usatoday.com/story/news/nation-now/2017/12/04/uterus-transplant-results-successful-birth-1st-u-s/920041001/

Johannesson, L., & Järvholm, S. (2016). Uterus transplantation: current progress and future prospects. International Journal of Womens Health, 43. doi:10.2147/ijwh.s75635

Knauer, E. (1896). Einige Versuche über Ovarientransplantation bei Kaninchen [An attempt at ovary transplantation in rabbits]. Zentralblatt für Gynäkologie (in German). 20, 524–528.

Lefkowitz, A. Edwards, M. & Balayla, J. (2012). The ontreal criteria for the ethical feasibility of uterine transplantation. Transplant International, 25(4), 439–447.
Smith, R., Saso, S., & Jones, B. (n.d.). The process of uterine transplantation.

Sorgen, C. (n.d.). Bonding with baby before birth. Retrieved February 14, 2018, from https://www.webmd.com/baby/features/bonding-with-baby-before-birth#2

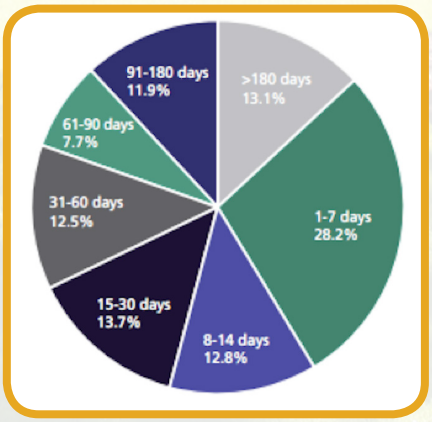
Uterine factor. (n.d.). Retrieved January 28, 2018, from https://www.azfertility.com/your-miracle/fertility-basics/causes-of-infertility/uterine-factor-infertility/

Resuscitating Palliative Care

Authored by: Sharvil Patel
Edited by: Alec Shannon
Reviewed by: Dr. Lynn O'Neill

As the baby boomer generation continues to climb in age, attention to the field of hospice care has risen significantly in recent years. Moreover, empirical literature has identified it as an essential medical service to mitigate suffering for the seriously ill, a force to reduce economic costs for society, and a potential enhancer of community health. Despite its plentiful advantages and need, hospice care continues to be an underutilized resource. Indeed, less than a quarter of Americans who die enroll as hospice care patients, and more than half of those patients spend less than a month receiving care (Finestone & Inderwies, 2008). Consequently, the current healthcare system must make an effort to incorporate more patients in the hospice system and to expand the existing infrastructure to accommodate these patients; any national movement promoting end-of-life care, however, faces multiple barriers. Systemic barriers to improvements in this specialized field of medicine are diverse in nature, ranging from cultural attitudes towards hospice treatment to insurance coverage shortages to specialist deficits. Understanding the way obstacles to hospice care manifest will be vital to magnifying its beneficial impact. Before society can truly benefit from the advantages of hospice care, we must first examine the impediments to its development and target these obstacles in order to inform the public opinion of its value.

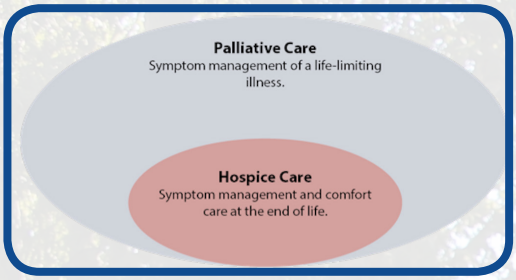
Before delving into hospice care's impediments, a thorough understanding of what hospice specialists do and do not do is vital. The National Hospice and Palliative Care Organization indicates that hospice care "focuses on caring, not curing" with "the belief that [everyone] has the right to die pain-free and with dignity" (2017). In this sense, hospice care differs from palliative care which "is focused on providing relief from the symptoms and stress of a serious illness…and can be provided along with curative treatment" (Center to Advance Palliative Care). While hospice care and palliative care are intertwined, they differ in their ultimate goals.



Proportion of Patients by Days of Care in 2015 (National Hospice and Palliative Care Organization, 2016)

One of the largest obstacles to delivering equitable hospice care is in cultural and racial disparities in attitudes towards end-of-life care. Statistically speaking, Caucasian households are significantly more likely to approve do not resuscitate (DNR) orders than other racial groups. Data from Medicare enrollees finds that white patients were 11.8% more likely to use hospice than African American patients, 8.8% more likely than Hispanic patients, 17.7% more likely than Asian patients, and 15.2% more likely than Native North Americans. The cause of the racial disparities in hospice care usage and DNR acceptance is complex and multifaceted, but attempts to identify the root of these disparities have recognized that hospice care often carries negative cultural stigmas, religious conflicts, or perceived losses of autonomy—factors that commonly deter patients from accepting hospice care (Finestone & Inderwies, 2008). In addition to its poor perception among minority populations, the quality of care that these patients receive is also documented to be lower: medical decisions frequently neglect patient preferences and patients are less likely to have access to medications often prescribed for pain and symptom management in serious illness (Johnson, 2013). Consequently, for minority patients, the desire and perceived necessity of hospice care is more likely to be outweighed by the financial and time costs associated with accepting care, especially since many minorities already harbor mistrust against the American healthcare system (Finestone & Inderwies, 2008). Understanding the racial context in which patients accept or deny hospice care is crucial for healthcare providers because they cannot ensure the safety and comfort

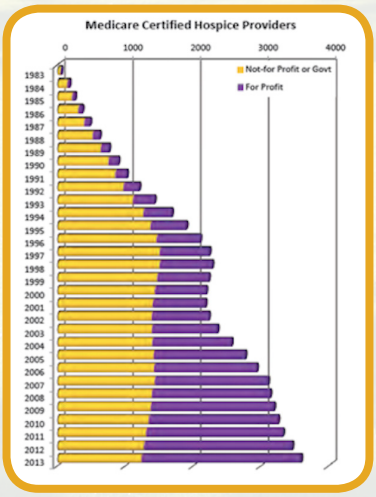
of their patients, as mandated by their oath, if their patients are averse to accepting beneficial treatment strategies. In the broader context of healthcare, combatting distrust of healthcare professionals on a new front will advance trust-building in other



Hospice care is a subsection of palliative care as a whole (Home Health and Hospice Care).

domains of healthcare.

Racial and cultural disparities are not the only barrier to hospice care access; economic inequalities, especially in housing, also exacerbate health inequalities. Despite aggravated health risks associated with homelessness, indigent communities have less access to hospice care because of logistical barriers. As Dr. Davis-Berman notes: "being homeless also causes logistical problems for end-of-life care providers, such as the inability to locate patients, or lack of reliable power supplies for equipment or refrigeration for medication" (2016). Moreover, Dr. Davis-Berman further notes that surveys conducted in low income communities recognized cost as another deterrent to accepting hospice care, and, unfortunately, public insurance may still prevent more widespread adoption of hospice care. Medicare rules state that patients



The number of total hospice care providers has increased, but the largest increase has occurred with for profit providers (AmerisourceBergen, 2014).

who want their insurance to cover hospice costs must be willing to forgo any disease-directed treatments (2017). For patients and families who wish to continue receiving any and all potential life-prolonging therapies, giving up on disease-directed treatments may seem like giving up on life itself. Thus, even if the economic opportunity cost does not dissuade enrollment into end-of-life care programs, the moral and value-based opportunity cost may be too hefty for patients and their families.

Causes of limited hospice care enrollment are not limited to patient and economic domains. A major contributor to low enrollment is a lack of medical emphasis on hospice care. A strong indicator of weak healthcare priority is in the shortage of hospice and palliative medicine (HPM) physicians; Lydia Zuraw writes that for every 20,000 chronically ill adults, there is only one HPM specialist (2013). This large deficit can drive up costs and strain existing physicians, preventing quality care for enrolled patients and limiting the total number of patients who can be treated at all. A novel solution would be to increase end-of-life care training for other specialists that deal with serious illnesses, such as oncologists or cardiologists. Doing so would not only reduce the strain on the scarce specialized doctors, but also reduce the number of physicians who avoid referring patients to hospice specialists because they see hospice admittance as failure (Scientific American, 2015). By increasing access to specialized care, whether it be from specialized physicians or any physician with medical training for end-of-life care, patients who are seriously ill will benefit from lower costs, equitable access, and individualized attention.

As the baby boomer generation continues retiring, the number of Americans seeking end-of-life treatment will continue to increase and ensuring access to equitable care will be a vital issue for American healthcare. Indeed, the hospice system in healthcare will permeate every imaginable domain of life: baby boomers will compose a large voting bloc, hospice care will either become a new market or strain the economy as more people attempt to enroll, the moral cost of unnecessary suffering will escalate, and so on. Consequently, it is imperative that hospice care becomes a cornerstone of healthcare education and strategy; thus, more resources need to be directed at combating institutional problems in hospice care. The most feasible place to start is at medical institutions, where all practitioners can be trained in general end-of-life care and taught about its importance. By doing so, hospice care can finally be resuscitated into a major dimension of American healthcare.

Images:

AmerisourceBergen. (2014). Medicare Certified Hospice Providers [Digital image]. Retrieved March 12, 2018, from http://www.amerisourcebergenphaservices.com/pharmacy-to-hospice/hospice-today

Home Health and Hospice Care. (2017). [Palliative Care vs. Hospice Care]. Retrieved March 12, 2018, from https://www.hhhc.org/resources/news/general/palliative-care-vs-hospice-care/

National Hospice and Palliative Care Organization. (2016). Proportion of Patients by Days of Care in 2015 [Digital image]. Retrieved March 12, 2018, from https://www.nhpco.org/sites/default/files/public/Statistics_Research/2016_Facts_Figures.pdf

References:

Center to Advance Palliative Care. (n.d.). What is Palliative Care? Retrieved March 12, 2018, from https://www.capc.org/payers-policymakers/what-is-palliative-care/

Davis-Berman, J. (2016). Serious Illness and End-of-Life Care in the Homeless: Examining a Service System and a Call for Action for Social Work. Social Work and Society International Online Journal, Volume 14, 1-11.

Doctors Are Poorly Trained in End-of-Life Care, but That Can Change. (2015, June 1). Scientific American. Retrieved January 23, 2018, from https://www.scientificamerican.com/article/doctors-are-poorly-trained-in-end-of-life-care-but-that-can-change/

Finestone, A. J., & Inderwies, G. (2008). Death and dying in the US: the barriers to the benefits of palliative and hospice care. Clinical Interventions in Aging, Volume 3, 595-599. doi:10.2147/cia.s2811

Fins, J. J. (2017, June 07). Who "Persists" in Opposing DNR Orders? Demographics Matter. Retrieved January 23, 2018, from https://www.thehastingscenter.org/persists-opposing-dnr-orders-demographics-matter/

Hawley, P. (2017). Barriers to Access to Palliative Care. Palliative Care: Research and Treatment,10. doi:10.1177/1178224216688887

Johnson, K. S. (2013). Racial and Ethnic Disparities in Palliative Care. Journal of Palliative Medicine,16(11), 1329-1334. doi:10.1089/jpm.2013.9468

Kaiser Family Foundation. (2017, December 07). Key Facts about the Uninsured Population. Retrieved January 23, 2018, from https://www.kff.org/uninsured/fact-sheet/key-facts-about-the-uninsured-population/

National Hospice and Palliative Care Organization. (2017, April). Hospice Care. Retrieved March 12, 2018, from https://www.nhpco.org/about/hospice-care

Zuraw, L. (2013, April 5). As Palliative Care Need Grows, Specialists Are Scarce. Retrieved January 23, 2018, from https://www.npr.org/sections/health-shots/2013/04/03/176121044/as-palliative-care-need-grows-specialists-are-scarce

The Opioid Epidemic

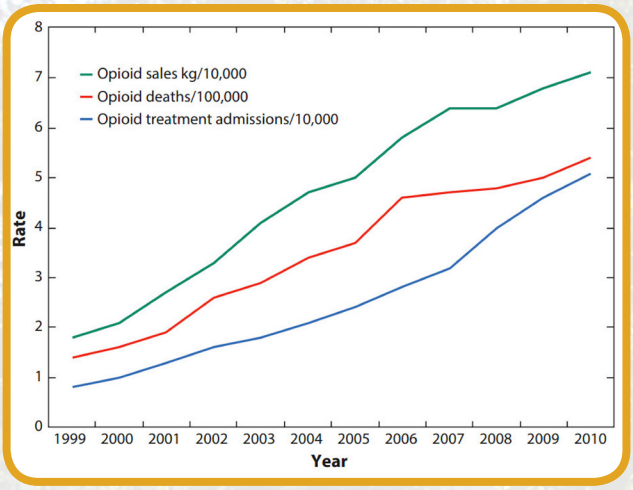
Authored by: Lisa Zhang
Edited by: Preethi Reddi
Reviewed by: Dr. Daniel Bell

Opioids have been prescribed with increasing frequency since the 1990s, which has contributed to an epidemic of opioid misuse, addiction, and related deaths. This epidemic has galvanized an ongoing public health initiative involving billions of dollars in prevention, treatment, and public outreach. These efforts have escalated only recently, including the institution of recovery services, experimentation with legalizing alternative medications, new technology to push the addicted towards sobriety, and increased overall awareness surrounding the extent and severity of the opioid epidemic.

By the time there was enough evidence to contradict the assumption that opioids were non-addictive, the epidemic had already grown substantially.

The term opioid describes both naturally occurring opiates from the opium poppy such as morphine and codeine, and other derivatives or synthetics such as heroin, dilaudid, fentanyl and methadone. Given opioid's known therapeutic value in treating acute pain, the medical community historically used it as such—in limited fashion. However, in the 1990s, pharmaceutical companies funded studies that concluded that more liberal use of opioids would greatly benefit patients and that opioid addiction was of minimal concern. What followed was a systematic campaign targeting both doctors and patients touting the benefits of opioids. Despite this clear conflict of interest, many of these studies and advertisements were published in prominent medical journals (Vowles et al., 2015). This resulted in a substantial increase in the number of prescriptions written by American medical professionals, with the misuse of opioids developing into a widespread issue (Rudd et al., 2016). By the time there was enough evidence to contradict the assumption that opioids were non-addictive, the epidemic had already grown substantially.

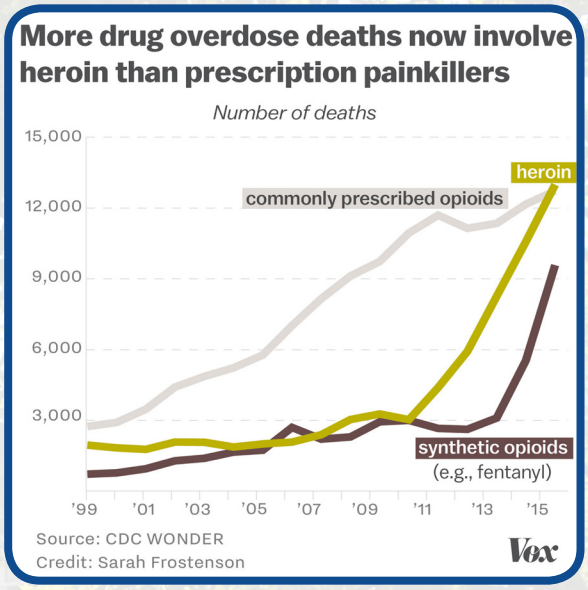
The opioid crisis has spread beyond an issue of the healthcare system and now holds consequences for the socioeconomic status of modern



The trends of opioid sales, deaths, and treatments has steadily increased since 1999 (Lopez & Frostensen, 2017).

Americans. At first, opioid misuse and addiction disproportionately affected minority populations living in urban environments (Florence et al., 2016). Within the recent decade, however, the epidemic has expanded into suburban and rural areas involving largely young Caucasian populations. (Unich et al., 2013) . The method of consumption has also changed; rather than buying and misusing prescribed opioids, many have turned to heroin instead, as the drug tends to be cheaper, easier to find, and more potent (Carlson et al., 2016).

Opioids can activate a variety of opioid receptors around the body (e.g. mu, kappa, delta), each with varying physiologic effects. Mu opioid receptors specifically are responsible for not only pain control, but for positive feedback in our neurobehavioral reward system. Activation of Mu receptors releases the neurotransmitter dopamine, prompting the feelings of pleasure we feel during our daily lives and activities (evolutionarily adapted to encourage activities of survival, nutrition, wellbeing, and procreation). This delicate neurobehavioral reward circuit can be triggered to release the same rush of pleasure when taking opiates. Ideally, when used in limited dosage under supervision for the intended purpose of easing acute pain, a patient should have minimal risk of developing an opioid use disorder, or signs/symptoms of addiction. Though different people have different risk profiles/backgrounds that



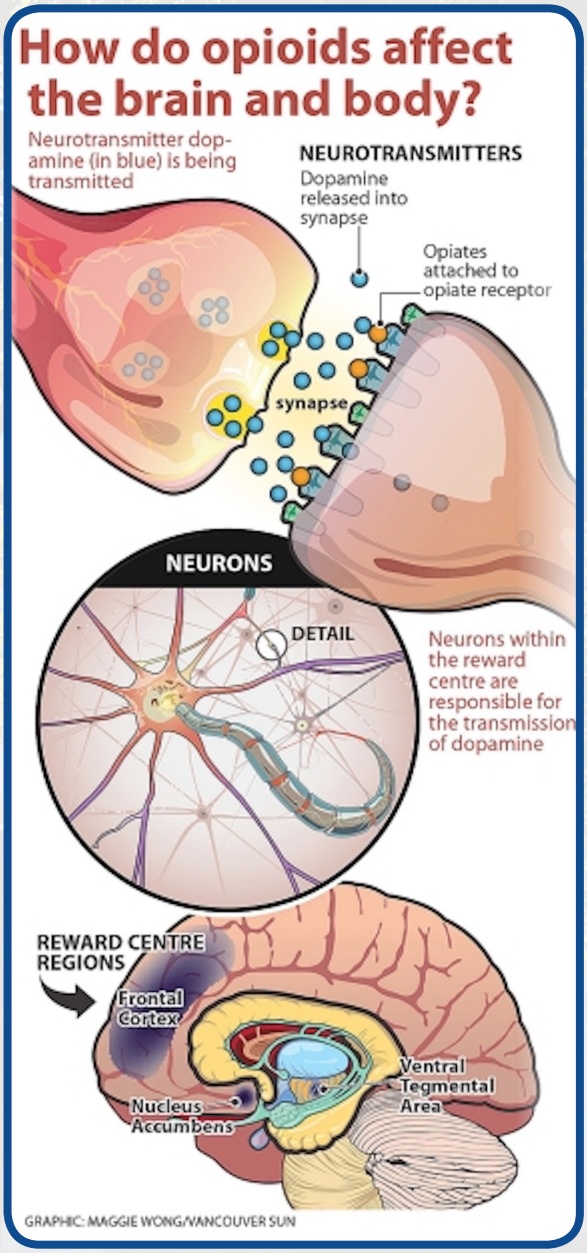
Since 2011, there has been a large increase in heroin related deaths. Now, there are more drug overdoses due to heroin than there are prescribed opioids (Lopez & Frostensen, 2017).

may increase their susceptibility to these issues. When prescribed or used improperly, either by taking too large of a dosage or taking a dosage even when there is no acute pain present, the opioids begin to stimulate the brain's mesolimbic reward system, which regulates the release of dopamine; this disruption of the system's homeostasis is key in the development of neurobiological, psychological, and behavioral manifestations of opioid addiction. The desire to use opioids over time generally increases following the pleasure given when the reward system is activated. Over time, the system becomes more expectant of opioids as fuel, and with it the person's expectation and need of

The desire to use opioids over time generally increases following the pleasure given when the reward system is activated.

opioid increases. At this point, the brain no longer functions normally without opioids present.

Opioid addiction is associated with a complicated neurophysiologic withdrawal process, as the addiction developed from the drug relies on a significant threshold of dependence and subsequent alterations within the brain (Vowles et al., 2015). Repeated exposure to high dosage levels alters brain function throughout multiple systems, and rehabilitating people with addiction requires both



The mechanism of how opioids affect the brain and body on a biological scale. It targets the reward areas of our brain via dopamine (Wong, 2014).

pharmacological and psychological treatment.

Pharmaceutical drugs used to treat long-term opioid addictions attach to the same Mu receptors targeted by opioids. However, the neurophysiologic effect can be more closely titrated, in an attempt to mitigate highs and lows, and resulting cravings and life-disruption. (Rudd et al., 2016). The majority are used to reduce instances of relapse and facilitate cooperation from the user so they can focus on improving their behavioral and physical health during rehabilitation. Without psychosocial treatment, the complex pathophysiology of opioid use disorder makes the disease almost impossible

to tackle. Effective programs to rehabilitate people suffering from opioid use disorder must include a holistic implementation of pharmacological and behavioral therapies. Hopefully, as more attention and resources are placed on the opioid epidemic, the United States will bolster efforts to involve a combination of therapeutic disciplines.

Images

Lopez, G., & Frostenson, S. (2017, March 23). Drug companies have made a lot of money from opioids. [Digital image]. Retrieved from https://www.vox.com/science-and-health/2017/3/23/14987892/opioid-heroin-epidemic-charts

Lopez, G., & Frostenson, S. (2017, March 23). More drug overdose deaths now involve heroin than painkillers. [Digital image]. Retrieved from https://www.vox.com/science-and-health/2017/3/23/14987892/opioid-heroin-epidemic-charts

Wong, M. (2014, May 30). Graphic demonstrates how opioids affect the brain and body. [Digital Image]. Retrieved from http://www.vancouversun.com/Graphic+demonstrates+opioids+affect+brain+body/9894365/story.html

References

Alexander, G. C., Frattaroli, S., & Gielen, A. C. (2015). The Prescription Opioid Epidemic: An Evidence-Based Approach (Rep.). Baltimore, MD: Johns Hopkins Bloomberg School of Public Health.

Carlson, R. G., Nahhas, R. W., Martins, S. S., & Daniulaityte, R. (2016). Predictors of transition to heroin use among initially non-opioid dependent illicit pharmaceutical opioid users: A natural history study. Drug and Alcohol Dependence, 160, 127-134. doi:10.1016/j.drugalcdep.2015.12.026

Cicero, T. J., Ellis, M. S., Surratt, H. L., & Kurtz, S. P. (2014). The Changing Face of Heroin Use in the United States. JAMA Psychiatry, 71(7), 821. doi:10.1001/jamapsychiatry.2014.366

Florence, C. S., Zhou, C., Luo, F., & Xu, L. (2016). The Economic Burden of Prescription Opioid Overdose, Abuse, and Dependence in the United States, 2013. Medical Care, 54(10), 901-906. doi:10.1097/mlr.0000000000000625

Ruhm, C. J. (2018). Corrected US opioid-involved drug poisoning deaths and mortality rates, 1999-2015. Addiction. doi:10.1111/add.14144

Vowles, K. E., Mcentee, M. L., Julnes, P. S., Frohe, T., Ney, J. P., & Goes, D. N. (2015). Rates of opioid misuse, abuse, and addiction in chronic pain. Pain, 156(4), 569-576. doi:10.1097/01.j.pain.0000460357.01998.f1

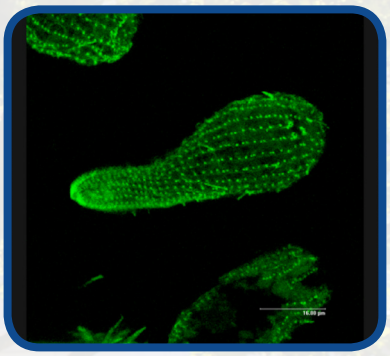
Unick, G. J., Rosenblum, D., Mars, S., & Ciccarone, D. (2013). Intertwined Epidemics: National Demographic Trends in Hospitalizations for Heroin- and Opioid-Related Overdoses, 1993–2009. PLoS ONE, 8(2). doi:10.1371/journal.pone.0054496

How Nanotechnology is Poised to Make (Little) Big Waves in 2018

Authored by: Han Li
Reviewed by: Nivedita Potapragada **Edited by: Dr. Katherine Heiden**

Sixty years ago, Richard Feynman lectured on the potential of nanotechnology, daring the world to bring forth the day when humans could manipulate the atomic orbitals, treat diseases with microscopic machines, and store entire libraries on chips smaller than sugar cubes. Nanotechnology has since edged ever closer to the physicist's dream, manifesting in cancer therapy particles, diagnostic imaging agents, and drug delivery vehicles. This past year saw dozens of interventions entering the intersect between nanotechnology and medicine, with exponentially growing literature and clinical trials. Now more than ever before, we find ourselves at the exciting forefront of a new frontier—the practical adaptation of molecules out of range of the strongest light microscope. With nanotechnology's growing prevalence, one can't help but to ask, "What's next?" We attempt to answer this question by examining nanomedicine's history, reasons biomedical scientists have invested so much in the technology, and some of its most promising applications that may soon arrive in the clinic.

The concept of nanotechnology is nothing new. What distinguishes current study at the nanoscale, however, is our growing capability to assemble, manipulate, and visualize nanoparticles (Tibbals, 2017). Many emerging techniques, derived largely from growing computer power, have fueled our breakthrough into this new frontier. Confocal microscopy, for example, has improved immensely as an imaging tool in recent years. Confocal microscopy works by shining highly focused beams of light at small portions of a sample, then using software to reconstruct a 3D image of the specimen. With more efficient computing power, this technique has provided a powerful means to image noninvasively and to section living specimens optically, forming a solid backbone for quantifying nanoparticles' uptake into cells. Another example includes the proliferation of electron microscopy. Frens' 1973 refinement of the synthesis of gold nanoparticles, a prominent and highly influential publication, demonstrates this technique in action; Frens and company harnessed electron micrographs to assess their synthesis yields in terms of the average size, distribution, radii of his nanoparticles. (Frens, 1973). Likewise, developing new therapeutic nanovectors frequently involves electron microscopy and HPLC to analyze key parameters such as particle diameter and drug entrapment efficiency (Saadat et. al., 2014; Patil & Jadhav, 2014). Such techniques afford us a tremendous amount of control and accuracy in designing structures even at the nanoscale, and have played a major role in nanotechnology's emergence as a powerful platform for improving drug delivery.



Confocal microscopy, patented in 1957, has played a major role in imaging at the nanoscale, such as this visualization of beta-tubulin (Pawel Jasnos, 2005).

Indeed, one of the clearest advantages of nanomedicine is in cancer therapy, because of its potential for highly specific, targeted delivery. This potential lives on the back of the so-called enhanced permeability and retention (EPR) effect, the phenomenon in which nano-encapsulated chemotherapeutics preferentially aggregate in tumors. Chemotherapy works by sending as many toxins into malignant sites as possible before they poison the rest of the body. Thus, vectors that

Two of the most successful FDA-approved treatments in cancer nanomedicine, Doxil and Abraxane, utilized exactly this concept—encapsulating previously used chemotherapeutics with liposomes and albumin to reduce their toxicity (Shi et. al, 2016).

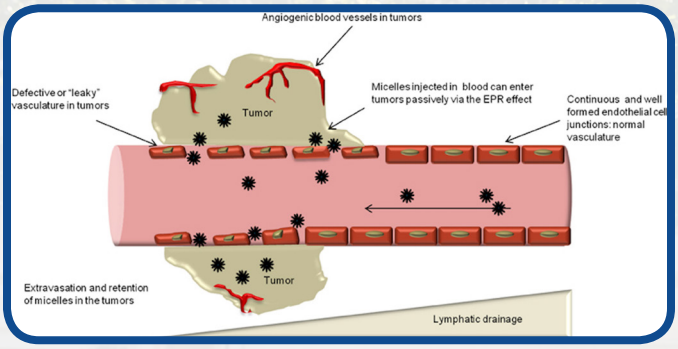
would enable us to deliver more chemotherapeutic agents to malignant areas, with fewer unintended side effects, would dramatically improve our ability to fight cancerous diseases. In fact, two of the most successful FDA-approved treatments in cancer nanomedicine, Doxil and Abraxane, utilized exactly this concept—encapsulating previously used chemotherapeutics with liposomes and albumin to reduce their toxicity. (Shi et. al, 2016). The EPR effect has driven tremendous excitement for early nanomedicine; however, it has also generated significant controversy in recent years.

Though EPR has proven a powerful tool in vitro and even in vivo, we have yet to develop a nanovector that definitively demonstrates an effect of equal magnitude in humans. In 2016, Wilhelm and his team showed that the EPR effect only increased tumor chemotherapeutic uptake by a miniscule 0.7% of the initial dose in humans (Wilhelm et. al., 2016). Since then, many more labs have cast light on the mismatch between nanomedicine's creativity in the lab and its stagnating translation to human patients. This mismatch stems from a supposed lack of evidence showing that nano-encapsulated particles can effectively enhance efficacy and reduce chemotherapeutic toxicity in humans (Lammers et. al., 2016). Experts in the field have proposed several reasons for this scarcity of evidence. Animal models, for example, are believed to be particularly inadequate for testing chemotherapies because of major discrepancies in tumor growth. In mice, tumors often grow to be 10% of their body size (proportionally, this would mean basketball-sized tumors in humans) and rarely possess cells with the capacity to differentiate into lymphatic vasculature. Humans, in contrast, are subject to considerably smaller, highly perfused tumors. Furthermore, even within cancer types, tumors exhibit significant variation in structure and microenvironment from person to person—some patients may respond excellently to nanomedicinal treatment, while others may not at all (Danhier, 2016). Despite nanomedicine's effectiveness in aiding the blights of mice, it seems that significant effort will be needed to enact the same benefits in humans.

And scientists have done just that, doubling down on research efforts to better understand how nanoparticles react inside the human body. In recent years, researchers have utilized imaging agents similar in size and composition to nanoparticle therapeutics as a means of evaluating how nanomedicines circulate throughout the body. If the imaging agent tends to gather in tumors, then it is likely that its companion nanotherapeutic will do so

...many other fields have also begun harnessing nanoscience's potential to improve drug delivery.

as well. Scientists have even combined both imaging agent and therapeutic into one nanoparticle in some applications, kickstarting the growth of the exciting new field of theranostics, the usage of conjugated imaging and therapeutic agents to evaluate drug efficacy in the body. (Kelkar & Reineke, 2011). Other approaches attempt to enhance nanomedicine's ability to respond selectively to the tumor. One such example involves active targeting, where an antibody or other antigen-specific ligand is bound to the nanoparticle, allowing it to seek and destroy cancerous tumor cells. One of the most interesting developments in the last five years involves stimulus-sensitive nanoparticles, which

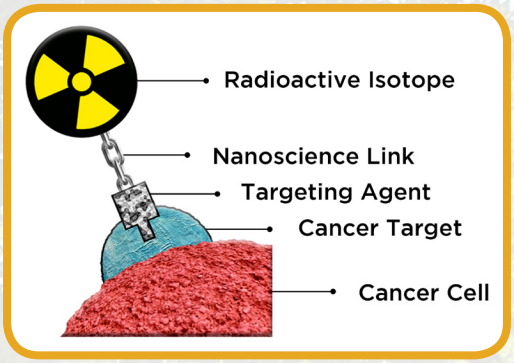


Enhanced permeability and retention effect, a major driver in the ability for nanomedicine's capability for passive targeting, is theorized to work because of tumors' leaky vasculature and poor lymphatic drainage (Jhaveri & Torchilin, 2014).

only release their drug payload upon chemical cues specific to a tumor's microenvironment, such as a change in pH, enzyme concentration, or light intensity (Zhou et. al, 2017). These research fields—theranostics, active targeting, and controlled release drugs—form an exciting front to better understand and to enhance nanovectors for human treatment (Shi et. al., 2016).

Much effort has been devoted to optimizing nanocarriers for cancer, but many other fields have also begun harnessing nanoscience's potential to improve drug delivery. Researchers around the world have utilized nanomaterials for improving siRNA delivery, gene therapies, and antibiotics (Pattnaik et. al., 2016). Multiple stem cell therapies rely on the correct usage of hydrogels and other biomaterials in order to maximize cell differentiation and survival inside the body. Even

outside traditional medicine, biomedical engineer Zhang and his associates made media rounds in late 2017 for a microneedle patch that turned white fatty tissue into lean brown fat, which utilized



Theranostics, combining therapeutic and imaging agents, holds promise in analyzing patient response to cancer treatment ("What is Theranostics? ").

nanomaterial design (Zhang et. al., 2017). All of these fields have their own risks and challenges, but each holds the potential to transform clinical medicine for the better.

Indeed, the 21st century has witnessed humanity's first systematic expedition into the nanoscale. Because of new and better-understood principles of molecular self-assembly and visualization, we edge ever closer to Feynman's dream of microscopic mastery. These leaps and bounds have faced many challenges, but they have also resulted in new therapies for the clinic, newsworthy devices that alchemize fats to fight obesity, and the understanding of phenomena that will fuel research many years into the future. Nanotechnology dramatically enhances the therapeutic capabilities of almost our entire medicinal arsenal—from chemotherapies to stem cell therapies—and will only evolve into a stronger tool in its maturing years.

Images

Jhaveri & Torchilin. (2014, April). Enhanced permeability and retention (EPR) effect and passive targeting. [Digital Image]. Retrieved February 18, 2018, from https://www.researchgate.net/figure/Enhanced-permeability-and-retention-EPR-effect-and-passive-targeting-Nanocarriers-can_fig2_262055716.

Pawel Jasnos. (2005, March). Tetrachimena Beta Tubulin. [Digital Image]. Retrieved February 18, 2018, from https://en.wikipedia.org/wiki/Confocal_microscopy#/media/File:Tetrachimena_Beta_Tubulin.png.

What is Theranostics? [Digital Image]. (n.d.). Retrieved February 18, 2018, from http://theranostics.com.au/what-is-theranostics/.

References

Danhier, F. (2016). To exploit the tumor microenvironment: Since the EPR effect fails in the clinic, what is the future of nanomedicine? Journal of Controlled Release,244, 108-121. doi:10.1016/j.jconrel.2016.11.015

Frens, G. (1973). Controlled Nucleation for the Regulation of the Particle Size in Monodisperse Gold Suspensions. Nature Physical Science, 241(105), 20-22. doi:10.1038/physci241020a0

Kelkar, S. S., & Reineke, T. M. (2011). Theranostics: Combining Imaging and Therapy. Bioconjugate Chemistry,22(10), 1879-1903. doi:10.1021/bc200151q

Lammers, T., Kiessling, F., Ashford, M., Hennink, W., Crommelin, D., & Strom, G. (2016). Cancer nanomedicine: is targeting our target? Nature Reviews Materials,1(9), 16069. doi:10.1038/natrevmats.2016.69

Patil, Y. P., & Jadhav, S. (2014). Novel methods for liposome preparation. Chemistry and Physics of Lipids,177, 8-18. doi:10.1016/j.chemphyslip.2013.10.011

Pattnaik, S., Swain, K., & Lin, Z. (2016). Graphene and graphene-based nanocomposites: biomedical applications and biosafety. Journal of Materials Chemistry B,4(48), 7813-7831. doi:10.1039/c6tb02086k

Saadat, E., Amini, M., Khoshayand, M. R., Dinarvand, R., & Dorkoosh, F. A. (2014). Synthesis and optimization of a novel polymeric micelle based on hyaluronic acid and phospholipids for delivery of paclitaxel, in vitro and in-vivo evaluation. International Journal of Pharmaceutics,475(1-2), 163-173. doi:10.1016/j.ijpharm.2014.08.030

Shi, J., Kantoff, P. W., Wooster, R., & Farokhzad, O. C. (2016). Cancer nanomedicine: progress, challenges and opportunities. Nature Reviews Cancer,17(1), 20-37. doi:10.1038/nrc.2016.108

TIBBALS, H. F. (2017). MEDICAL NANOTECHNOLOGY AND NANOMEDICINE. S.l.: CRC PRESS.

Wilhelm, S., Tavares, A. J., Dai, Q., Ohta, S., Audet, J., Dvorak, H. F., & Chan, W. C. (2016). Analysis of nanoparticle delivery to tumours. Nature Reviews Materials,1(5), 16014. doi:10.1038/natrevmats.2016.14

Zhang, Y., Liu, Q., Yu, J., Yu, S., Wang, J., Qiang, L., & Gu, Z. (2017). Locally Induced Adipose Tissue Browning by Microneedle Patch for Obesity Treatment. ACS Nano,11(9), 9223-9230. doi:10.1021/acsnano.7b04348

Zhou, M., Wen, K., Bi, Y., Lu, H., Chen, J., Hu, Y., & Chai, Z. (2017). The Application of Stimuli-responsive Nanocarriers for Targeted Drug Delivery. Current Topics in Medicinal Chemistry,17(20). doi:10.2174/1568026617666170224121008

Playtime: The Complicated Link Between Video Games and Mental Health

Authored by: Ameya Gangal
Edited by: Jonathan Regenold
Reviewed by: Dr. Laura Otis

Eyes frozen on plasma screens and the constant rhythm of thumbs tapping over iPhone news are certainly no stranger to the average American. The convenience of new mobile apps and the awe-striking graphics of modern video games represent advances in technology that can potentially impact our cognition (Kirkorian, Wartella, & Anderson, 2008; Shams et al., 2015). While often romanticized for astronomical leaps in memory or chided for ties to violence, video games are particularly fascinating in their role in mental health and cognitive changes.

Video games have a striking impact on the mental health and behavior of users, often resulting from increases in the amount of playtime (Hastings et al., 2009). Some estimates of video game usage among adolescents average from about six to eight hours a week, with some teens playing up to three hours a day (Jones, Scholes, Johnson, Katsikitis, & Carras, 2014). This extended amount of time that gamers spend accessing scenes or events that are often not a part of their daily lives brings about a profound question about how these scenes may influence their mental health. While many studies fail to find causal connections between video game use and impacts on mental health, some studies have found links between self-reported measures of aggressive behaviors and violent video games (Lemmens, Valkenburg, & Peter, 2011). Similarly, violent video game usage is linked to depression in pre-adolescent youth (Tortolero et al., 2014). Excessive video game use has also been linked to an increase in self-reported indicators of sadness and suicidal ideation (Messias, Castro, Saini, Usman, & Peeples, 2011). Although these findings may suggest that excessive video game usage may be detrimental to mental health, separate studies provide further evidence that these possible links between video games and mental health detriments may be due to confounding negative social relations for those who choose to play video games for an extended period of time (Chak & Leung, 2004). These findings blur the causality between mental health conditions and playing time. With the current evidence, it may be more likely that the relation between mental health conditions and excessive playing time is bidirectional—a cycle that may promote both playing time and worsening mental health.

Video games have recently been implicated in violent behaviors (Turrell, 2013).

Although video games have been shown to have negative impacts on mental health, they have also been linked to positive changes, such as empathy and prosocial behavior. One caveat to linking these two different effects on behavior to video game use is simply the large variance in video game content and game objectives. First-person shooter games wholly differ from role-playing games, which further differ from puzzle games. Within the context of prosocial video games, playtime has been linked to greater interpersonal empathy and reduced pleasure in another player's misfortune (Greitemeyer, Osswald, & Brauer, 2010). This study shows that video games can similarly impart positively socializing influences on gamers.

For example, morality of characters within a game can influence the reasoning and aggression of players (Gao, Weng, Zhou, & Yu, 2017). This shift in morality based on character development

> Perhaps even more interestingly, character changes within a single video game can modify a player's attitude both inside and outside of the game setting.

and decisions within a game exemplifies how video games may be able to exert subtle impacts on users beyond only the graphic or visual experience.

Examining these experimental results holistically suggests that video game use and mental health have

Video games have an integral link to mental health that cannot be overlooked (Bailey, 2016).

a far more complex relationship than previously thought. Video games vary greatly in their psychological and emotional impacts on players and the variance in game content further confounds any large conclusions that can be made between video game playtime and mental health. While it remains difficult to quantify or causally link video game usage and mental health, the relationship between the two is increasingly relevant as technology continues to occupy a central role in our lives.

Images

Bailey R. (2016, May 24). Video Gaming is Entirely Beneficial for Cognitive Functioning. [Digital Image]. Retrieved from http://reason.com/blog/2016/03/24/video-gaming-is-entirely-beneficial-for.

Turrell, J. (2013, February 11). Shooting in the Dark. [Digital Image]. Retrieved from http://www.nytimes.com/2013/02/12/science/studying-the-effects-of-playing-violent-video-games.html?pagewanted=all

References

Chak, K., & Leung, L. (2004). Shyness and locus of control as predictors of internet addiction and internet use. Cyberpsychology & Behavior: The Impact of the Internet, Multimedia and Virtual Reality on Behavior and Society, 7(5), 559–570. https://doi.org/10.1089/cpb.2004.7.559

Gao, X., Weng, L., Zhou, Y., & Yu, H. (2017). The Influence of Empathy and Morality of Violent Video Game Characters on Gamers' Aggression. Frontiers in Psychology, 8, 1863. https://doi.org/10.3389/fpsyg.2017.01863

Greitemeyer, T., Osswald, S., & Brauer, M. (2010). Playing prosocial video games increases empathy and decreases schadenfreude. Emotion (Washington, D.C.), 10(6), 796–802. https://doi.org/10.1037/a0020194

Hastings, E. C., Karas, T. L., Winsler, A., Way, E., Madigan, A., & Tyler, S. (2009). Young Children's Video/Computer Game Use: Relations with School Performance and Behavior. Issues in Mental Health Nursing, 30(10), 638–649. https://doi.org/10.1080/01612840903050410

Jones, C. M., Scholes, L., Johnson, D., Katsikitis, M., & Carras, M. C. (2014). Gaming well: links between videogames and flourishing mental health. Frontiers in Psychology, 5. https://doi.org/10.3389/fpsyg.2014.00260

Kirkorian, H. L., Wartella, E. A., & Anderson, D. R. (2008). Media and young children's learning. The Future of Children, 18(1), 39–61.

Lemmens, J. S., Valkenburg, P. M., & Peter, J. (2011). The Effects of Pathological Gaming on Aggressive Behavior. Journal of Youth and Adolescence, 40(1), 38–47. https://doi.org/10.1007/s10964-010-9558-x

Messias, E., Castro, J., Saini, A., Usman, M., & Peeples, D. (2011). Sadness, suicide, and their association with video game and internet overuse among teens: results from the youth risk behavior survey 2007 and 2009. Suicide & Life-Threatening Behavior, 41(3), 307–315. https://doi.org/10.1111/j.1943-278X.2011.00030.x

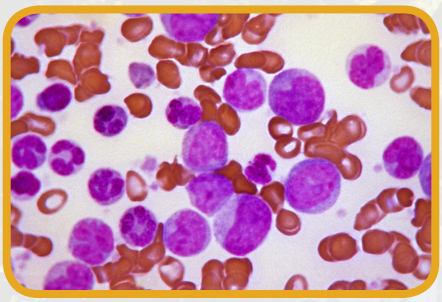
Shams, T. A., Foussias, G., Zawadzki, J. A., Marshe, V. S., Siddiqui, I., Müller, D. J., & Wong, A. H. C. (2015). The Effects of Video Games on Cognition and Brain Structure: Potential Implications for Neuropsychiatric Disorders. Current Psychiatry Reports, 17(9), 71. https://doi.org/10.1007/s11920-015-0609-6

Tortolero, S. R., Peskin, M. F., Baumler, E. R., Cuccaro, P. M., Elliott, M. N., Davies, S. L., … Schuster, M. A. (2014). Daily Violent Video Game Playing and Depression in Preadolescent Youth. Cyberpsychology, Behavior and Social Networking, 17(9), 609–615. https://doi.org/10.1089/cyber.2014.0091

Kymriah: A New Era for Gene Therapy

Authored by: Deanna Altomara
Edited by: Christopher Keyes **Reviewed by: Dr. Gregg Orloff**

Emily Whitehead was five years old when physicians diagnosed her with acute lymphoblastic leukemia (ALL), a dangerous form of cancer with a U.S. 5-year survival rate of 68.2% (Cancer Stat Facts). The bubbly little girl was quickly mired in an endless parade of grueling therapies. When these treatments failed to secure a relapse-free recovery, the physicians told her parents to expect the worst, and advised them to put their kindergartener into hospice care.



A microscopic view of ALL cells V. (2007, January 15).

The Whiteheads were distraught, but they refused to listen to the doctors who had forecasted Emily's quickly approaching death. Instead of planning their daughter's final days and funeral, they went to the Children's Hospital of Philadelphia for help. There, Emily was enrolled in a clinical trial involving a new technology called CAR-T cell therapy. This gene therapy, the first of its kind, carried significant risks, but Emily didn't have any other options. Prospects looked gloomy when Emily's condition plummeted in the two weeks following her treatment with CAR-T cell therapy. But the following week, her treatment team was astonished.

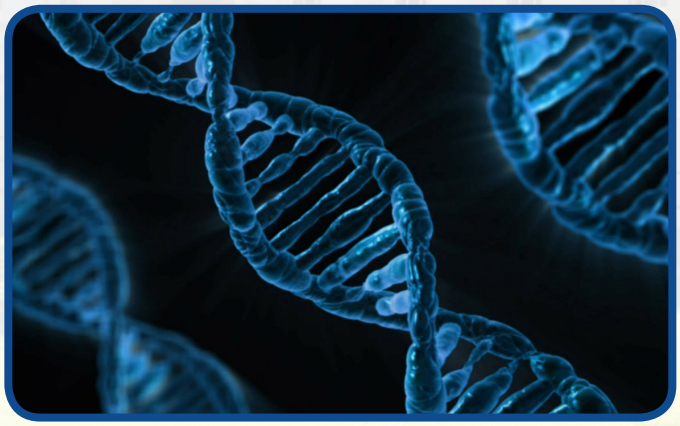
Her biopsy came back with no evidence of cancer.

> ...each one-time dose will cost $475,000 (Grady, 2017).

CAR-T cell therapy has since developed into KymriahTM (tisagenlecleucel), the first gene therapy to be approved by the FDA. Called a "living drug" by pediatric oncologist Dr. Kevin J. Curran, the life-saving treatment was developed through a partnership between the University of Pennsylvania and Novartis. Dr. Carl June, who helped create the treatment, is still stunned. "Now, I have to keep pinching myself to see that this happened," he said (Grady, 2017).

Kymriah works by harnessing the natural power of the body's immune soldiers: T-cells. White blood cells, including the aforementioned T-cells, help to regulate and carry out the immune response to any foreign objects or dangerous conditions within the body. In an optimal case, these T-cells would be able to identify cancer cells and destroy them before they are able to do much damage. However, T-cells often cannot recognize cancer cells as something dangerous.

In this form of therapy, T-cells are removed from the patient's blood and sent to the Novartis lab in Morris Plains, NJ (Grady, 2017). There, researchers use harmless viruses to deliver new genes to the awaiting T-cells. The new genes encode the instructions for how to create Chimeric Antigen Receptors, a surface feature that is then developed on the T-cells. These specialized receptors help the immune cells to identify cancer. Once the T-cells are genetically modified to become CAR T-cells, they are allowed time to multiply and then are shipped back to the medical center serving the patient. The T-cells are funneled back into the patient's bloodstream, where they can begin the work of



DNA holds the instructions for all of life's processes ("DNA", n.d.).

In a Phase II drug trial, 83% of the patients—all of whom were severely ill children or young adults—were in remission within three months ("Novartis receives").

defeating the cancer ("Chimeric"). The process takes about 22 days to complete and is given in a single dose.

Unfortunately, the arrival of the genetically-enhanced T-cells can sometimes shock the body into overproduction of cytokines, a type of signaling molecule that regulates the immune system. When this happens, it is called a "cytokine storm," or Cytokine Release Syndrome (CRS), and this

A researcher pipettes a sample. Laboratory. (2017, March 23).

is exactly what caused Emily's initial and rapid decline before the treatment eventually succeeded. CRS can cause a sudden fever, low blood pressure, and neurological problems, among other issues. While most reactions are mild, some can be fatal. To prevent fatalities, Novartis requires that all facilities using Kymriah must be specially trained and equipped to administer proper CRS treatment. Novartis is certifying only the medical centers that it feels are prepared to safely dispense the drug (Grady, 2017).

Despite the side effects, Kymriah has performed magnificently thus far. In a Phase II drug trial, 83% of the patients—all of whom were severely ill children or young adults—were in remission within three months ("Novartis receives"). Hoping that Kymriah would be able to treat other types of cancer besides ALL, Novartis also ran a trial on adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) that had not succeeded in autologous stem cell transplants. Out of the participants, 30% completely recovered six months into the trial, and 58% experienced some degree of CRS ("Primary Analysis"). In January, the FDA granted Kymriah priority review for this subset of patients. Meanwhile, the European Medicines Agency also granted Kymriah an accelerated assessment process for both young ALL patients and adult DLBCL patients who are ineligible for stem cell treatment ("Novartis granted"). These steps are meant to bring the drug to market more quickly.

Yet the market is precisely what is giving Novartis the most difficult time with Kymriah. Since each treatment must be individually crafted for the patient, each one-time dose will cost $475,000 (Grady, 2017). This is not only a frightening prospect for insurance agencies—who simply may push the brunt of the cost burden on the customer—but also for uninsured patients. Novartis has responded to the outrage by claiming that it carefully reflected upon matters of cost before deciding on the price tag. According to CEO Joseph Jimenez, Novartis "considered many factors including its clinical benefits, the outcomes it provides to patients, and the value it offers to health systems." In fact, he argues, Kymriah is a bargain, as one assessment "determined a cost-effective price would be $600,000 to $750,000" (Jimenez). After all, the company has already invested and will continue to invest in the time, labor, and research required to develop this drug. All of those investments must inevitably add to the cost. Despite this, Kymriah is still less expensive than the more conventional bone marrow transplant (Grady, 2017). However, Novartis acknowledges that this price will still be impossible for many families to pay. In order to make this treatment accessible to all patients,

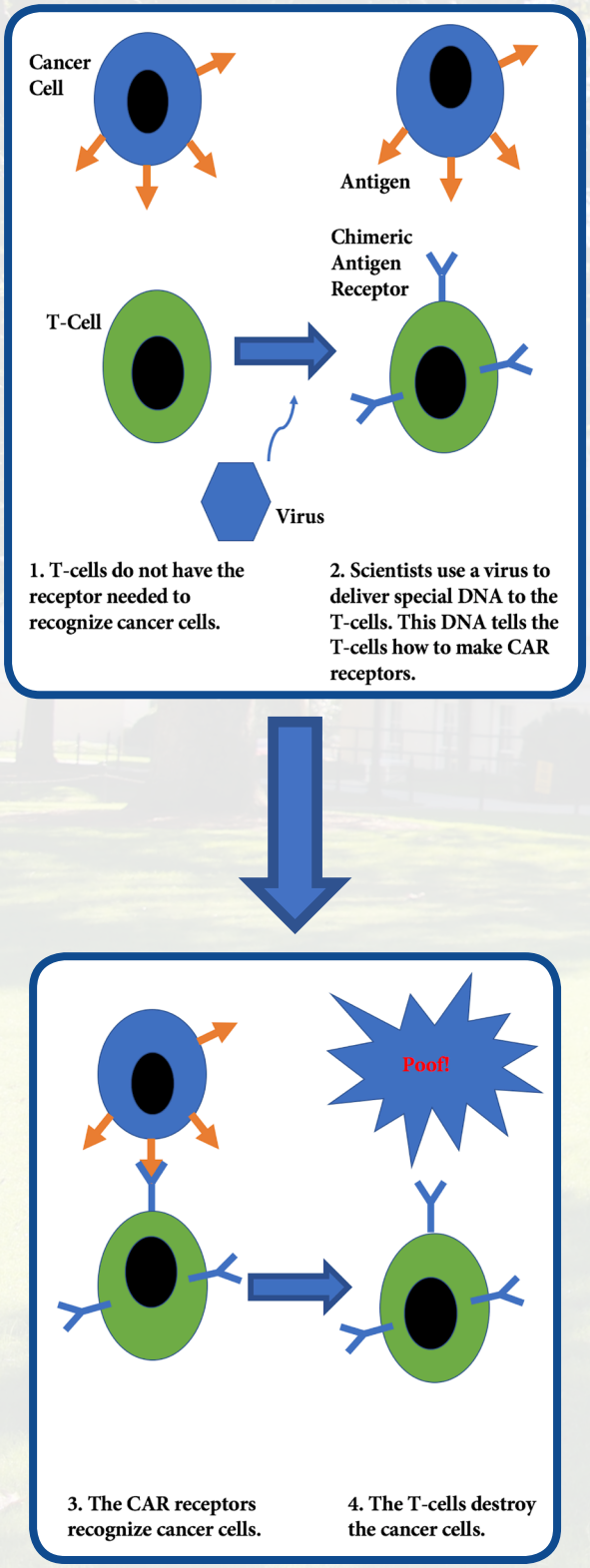
Kymriah works by harnessing the natural power of the body's immune soldiers: T-cells.

regardless of socioeconomic status, it has partnered with the Centers for Medicare and Medicaid Services. This partnership aims to bill patients and insurance agencies with "outcome-based pricing": if an ALL patient does not respond to treatment within the first month, payment is waived completely ("Novartis receives").

The era of gene therapy has arrived, with all the celebrations and pitfalls that it may harbor. Humans have unlocked the first few puzzles out of thousands involving the genetic code and how it shapes us.

Will gene therapy be the panacea it promises to be? Will it lead to a medical revolution of the likes of which have not been seen since penicillin? Are the side effects and ethical arguments worth it, and are there more that we are as yet unaware of? While there is much to be learned, at this point one thing is certain: we have crossed a milestone.

There is no going back.



Images

[DNA]. (n.d.). Retrieved from https://pixabay.com/en/dna-biology-medicine-gene-163466/

[Laboratory]. (2017, March 23). Retrieved January 26, 2018, from https://pixnio.com/science/medical-science/doctor-laboratorymedical-medicine-chemistry-test-tube-science

V. (2007, January 15). Acute Leukemia-ALL. [Digital Image]. Retrieved from https://commons.wikimedia.org/wiki/File:Acute_leukemia-ALL.jpg

References

Cancer Stat Facts: Leukemia - Acute Lymphocytic Leukemia (ALL). (n.d.). Retrieved January 26, 2018, from https://seer.cancer.gov/statfacts/html/alyl.html

Chimeric Antigen Receptor (CAR) T-Cell Therapy. (2015, September 10). Retrieved February 11, 2018, from http://www.lls.org/treatment/types-of-treatment/immunotherapy/chimeric-antigen-receptor-car-t-cell-therapy

Grady, D. (2017, August 30). F.D.A. Approves First Gene-Altering Leukemia Treatment,
Costing $475,000. The New York Times. Retrieved January 24, 2018, from https://www.nytimes.com/2017/08/30/health/gene-therapy-cancer.html

Jimenez, J. (2017, September 1). Novartis CEO: Here's How We Handled A Milestone In Pediatric Cancer. Forbes. Retrieved January 25, 2018, from https://www.forbes.com/sites/sciencebiz/2017/09/01/novartis-ceo-heres-how-i-handled-a-milestone-in-pediatric-cancer/#6f2e317c37f9

Novartis. (2017, August 30). Novartis receives first ever FDA approval for a CAR-T cell therapy,
Kymriah™ (tisagenlecleucel, CTL019), for children and young adults with B-cell ALL
that is refractory or has relapsed at least twice [Press release]. Retrieved January 25,
2018, from https://novartis.gcs-web.com/novartis-receives-fda-approval-for-KymriahTM

Novartis. (2017, December 10). Primary analysis results from Novartis pivotal JULIET trial show Kymriah™ (tisagenlecleucel) sustained complete responses at six months in adults
with r/r DLBCL, a difficult-to-treat cancer [Press release]. Retrieved January 25, 2018, from https://novartis.gcs-web.com/Primary-analysis-results-from-Novartis-pivotal-JULIET-trial-show-Kymriah-tisagenlecleucel-sustained-complete-responses-at-six-months-in-adults-with-r-r-DLBCL-a-difficult-to-treat-cancer

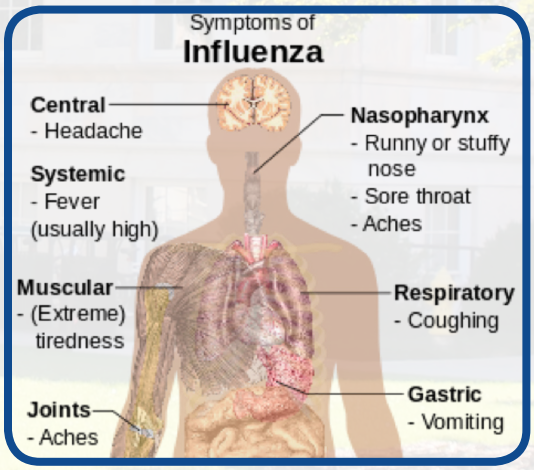
Novartis. (2018, January 17). Novartis granted US FDA Priority Review for Kymriah(TM) (tisagenlecleucel), formerly CTL019, for adults with r/r DLBCL [Press release]. Retrieved January 25, 2018, from https://www.novartis.com/news/media-releases/novartis-granted-us-fda-priority-review-k
ymriahtm-tisagenlecleucel-formerly-ctl019-adults-rr-dlbcl

The Urgent Need for a Universal Influenza Vaccine

Authored by: Anirudh Pidugu
Reviewed by: Nivedita Potapragada **Edited by: Dr. Kim Tran**

Influenza, commonly known as the flu, is a year-round disease that affects millions of people worldwide. In the northern hemisphere, the flu's peak season usually starts around October and lasts till March. The most common symptoms include high fever, sore throat, and muscle pain. The influenza virus spreads through the air via particles generated during coughing, sneezing, or even talking. There are approximately 3 to 5 million severe cases resulting in about 500,000 deaths (CDC, 2018). This year's flu season is on track to be the worst in a decade. The current hospitalization rate is at 31.5 people per 100,000 residents in the United States. Unfortunately, the flu vaccine has had only about a 10% effectiveness this year (CDC, 2018). So why is the vaccine not working?

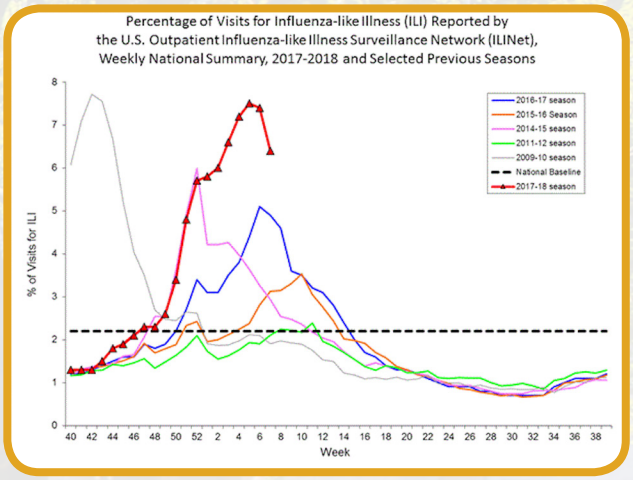
The current flu problems have existed for a large part of the past two decades. Over ten of the past



The serious symptoms of Influenza. (Häggström, 2014)

thirteen years, the flu vaccine has had below 50% effectiveness. That number becomes even lower in people older than fifty years old. However, unlike most years, everyone at all ages has been affected and older people are in real danger of being affected by the flu (CDC, 2018).

Antibodies develop inside the body about two weeks after vaccination. The antibodies protect against the viral strains of flu that are within the vaccine. The traditional seasonal flu vaccine protects against particular viruses that various research outlets predict will be most common during the annual flu season. This year's vaccine was created to guard against three key viruses, including the influenza A (H1N1), influenza A (H3N2), and influenza B strains (Murray, 2015). Other vaccines have been created to protect against four different flu viral strains known as quadrivalent viruses. Currently, these vaccines target two major proteins



The current rate of influenza cases over the current flu season. It is much higher than any of the nine flu seasons and the national baseline (Centers for Disease Control and Prevention, 2018)

on the periphery of the virus. These two proteins are known as hemagglutinin (H) and neuraminidase (N), which make up any particular strain (Houser & Subbarao, 2015). There are 18 known H subtypes and 11 N subtypes.

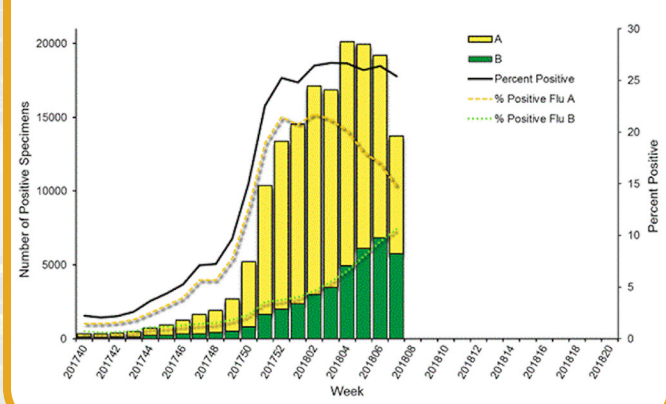
Since the virus tries to battle against the vaccine, it continuously evolves and changes shapes. Hemagglutinin and neuraminidase are formed in many shapes like spanners or wrenches. The existing vaccines produce antibodies to latch onto a specific shape that is linked to a specific strain (Frew et al., 2012). However, once the virus evolves, the shapes and sizes change significantly, which tricks cells of the immune system into thinking that the virus is harmless, rendering previous priming by the vaccine ineffective. This evolution of the virus has caused the spike in flu cases during this year's flu season. The H3N2 virus, the most common virus this season, has evolved many times and at a quick

rate (Paules et al., 2018). As a result of this frequent evolution, the vaccine has not been that effective against H3 viruses, in general.

A potential solution that many researchers have called for is the development of a universal vaccine. Currently, there are numerous types of vaccines

A potential solution that many researchers have called for is the development of a universal vaccine.

specifically used to treat a specific type of strain but not one that is targeted at several strains (Osterholm et al., 2012). A universal vaccine not only targets surface proteins, but also interior proteins that are common in all influenza A and B viruses. H1N1 and H3N2 are the two most common virus strains and this is what the universal vaccine should be equipped to battle—a combination instead of each



High rates of Influenza A compared to Influenza B. Primarily out of all Influenza A viruses, H3N2 is the strain that is currently affecting a high amount of people this flu season. (Centers for Disease Control and Prevention, 2018)

strain separately.

There are currently other methods being tested to battle the current epidemic of influenza. The current mission at Emory University School of Medicine is to find an effective vaccine for seasonal influenza, as well as other diseases such as mycobacterium tuberculosis, norovirus, and HIV. Researchers at University of California Los Angeles have also been examining the genome of the Influenza A strains to understand the genetic weapons it uses to get beyond the body's immune defense.

There should be optimism in these current approaches and their potential to generate a successful response to the seasonal flu this season and the future. The World Health Organization has estimated a record number of deaths this year. Understanding the properties of the influenza virus will be key to lowering the record high rate of the seasonal flu this year.

Images

Centers for Disease Control and Prevention. (2018). Influenza Positive Tests Reported to CDC by U.S. Clinical Laboratories, National Summary, 2017-2018 Season [Digital image]. Retrieved from https://www.cdc.gov/flu/weekly/index.htm

Centers for Disease Control and Prevention. (2018). Percentage of Visits for Influenza-like Illness ILI) Reported by the U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet), Weekly National Summary, 2017-2018 and Selected Previous Seasons [Digital image]. Retrieved from https://www.cdc.gov/flu/weekly/index.htm

Häggström, M. (2014). Symptoms of Influenza [Digital image]. Retrieved from https://en.wikiversity.org/wiki/WikiJournal_of_Medicine/Medical_gallery_of_Mikael_Häggström_2014

References

Centers for Disease Control and Prevention. (2017). Retrieved February 22, 2018, from https://www.cdc.gov/flu/protect/keyfacts.htm

Centers for Disease Control and Prevention. (2018). Retrieved February 22, 2018, from https://www.cdc.gov/flu/weekly/index.htm

Frew, P. M., Painter, J. E., Hixson, B., Kulb, C., Moore, K., Rio, C. D., . . . Omer, S. B. (2012). Factors mediating seasonal and influenza A (H1N1) vaccine acceptance among ethnically diverse populations in the urban south. Vaccine,30(28), 4200-4208. doi:10.1016/j.vaccine.2012.04.053

Houser, K., & Subbarao, K. (2015). Influenza Vaccines: Challenges and Solutions. Cell Host & Microbe,17(3), 295-300. doi:10.1016/j.chom.2015.02.012

Murray, T. (2015). Repeated flu shots may blunt effectiveness. Canadian Medical Association Journal,187(6). doi:10.1503/cmaj.109-5000

Osterholm, M. T., Kelley, N. S., Sommer, A., & Belongia, E. A. (2012). Efficacy and effectiveness of influenza vaccines: A systematic review and meta-analysis. The Lancet Infectious Diseases,12(1), 36-44. doi:10.1016/s1473-3099(11)70295-x

Paules, C. I., Sullivan, S. G., Subbarao, K., & Fauci, A. S. (2018). Chasing Seasonal Influenza — The Need for a Universal Influenza Vaccine. New England Journal of Medicine,378(1), 7-9. doi:10.1056/nejmp1714916

Young Physicians Initiative: Cultivating Future Doctors in Immigrant Communities

Authored by: Sharon Hsieh
Reviewed by: Anna Farrell

What can 15 minutes do to a person's life? For Dr. Heval Kelli, a cardiology fellow at Emory University School of Medicine, 15 minutes can change a high school student's life perspective of despair and uncertainty. In 2016, Dr. Kelli was contacted by his alma mater, Clarkston High School, to deliver a talk about defying challenges as a Syrian refugee and paving his own road to becoming a physician. "I didn't quite know what to say, so I made a presentation about what it takes to become a doctor," Dr. Kelli said. "I left my email address at the end of the presentation. When I went home, my inbox was inundated with emails. One of them stuck with me. It was from an Vietnamese immigrant student. She had to work after school every day to support her parents. She felt hopeless about her future. Yet, upon hearing my talk, she believed she could also achieve her dream of pursuing higher education."

Years later, Dr. Kelli could still recite the email dialogue that galvanized him to launch Young Physicians Initiative (YPI), a pre-medical after school program dedicated to expose disadvantaged high school students to rigorous college preparation and medical experiences. Students meet once per month after school for an hour over the span of 10 months. The interdisciplinary interactive sessions are led by medical students from Emory School of Medicine and they cover medical school application workshops, Emergency Cases simulation, and panel discussions featuring physicians. The program first piloted at the Academy of Oaks in January, 2016. The practical framework of the program helped foster a positive learning environment and made the program at Academy of Oaks an unprecedented success. A few months later, YPI launched its second program at Clarkston High School.

Dr. Heval Kelli giving a Medical Case presentation to the high school students at Clarkston High School. (http://www.ypiprogram.com/)

Extending the program to Clarkston High School was a cause near and dear to Dr. Kelli's heart. "I felt the urge to invest in my local community. Treating an individual is something I deal with everyday; but changing a community is grand. My role as a physician extends beyond patient care. I wanted to lead by example and serve students like me—refugees, minorities, and people without education," Dr. Kelli shared. Instead of bringing the students out of the community, YPI makes role models— medical students and physicians—available to the students in the community. "The three essential things to instill purpose into a student are to be present in their lives; introduce them to the essence of medicine; and expose them to the pathway," Dr. Kelli said.

Dr. Heval Kelli, founder of YPI; Hannah Williams, Medical Student Director; and YPI fellow students. (http://www.ypiprogram.com/)

Amidst a period that is rife with tumult and cultural division, the classroom environment of YPI serves as a stark contrast. "The teacher is Caucasian and the children are immigrants and refugee students of different races. But there is no divide in the classroom. Everyone works collaboratively with a smile on their faces. It teaches us about tolerance and compassion," Hannah Williams, the Medical Student Director of YPI, shared. Indeed, YPI affords both the medical student instructors and the high school students an unique opportunity to acquire culturally articulate leadership by forging deep relationships with people from culturally diverse backgrounds. Looking forward, Dr. Kelli strongly encouraged people to follow his lead of investing back in local, underprivileged communities. He suggested that Young Engineer Initiative or Young Lawyer Initiative can be established and applied nationwide to different industries.