The Journal of the
YNCA
Youth Neuroscience Clubs of America

MONTHLY THEME
NEURODEGENERATIVE DISEASES

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FEATURED ARTICLES

Vitreous Humor:
News Reports
Misinterpret Yet
Another
Neuroscience Study
-- The YNCA Satire Team

Research Methods:
Model Organisms in
Neuroscience
-- Jacob Umans and
Meenu Johnkuty

An Introduction to
Neuroethics: Why
Should We Care?
-- Nicholas
Chrapliwy

Basics of
Neuroscience II: An
Introduction to
Internal Neural
Communication
-- Alexander
Skvortsov, William
Ellsworth, and Jacob
Umans
# Contents

**INTRODUCTION**
- Letter from the Editor  
  pages 2 - 3
- Update from the Chairmen  
  pages 4 - 5

**BASICS OF NEUROSCIENCE**
- Basics of Neuroscience II: An Introduction to Internal Neural Communication  
  pages 6 - 8

**NEUROETHICS**
- An Introduction to Neuroethics: Why should we care?  
  pages 9 - 10

**DISEASE**
- Alzheimer’s Disease  
  pages 11 - 18
- Amyotrophic Lateral Sclerosis: Pathology  
  pages 19 - 22
- Creutzfeldt-Jakob Disease  
  pages 23 - 25
- Lewy Body Dementia  
  pages 26 - 28

**NEUROSCIENCE AND SOCIETY**
- Reagan and Alzheimer’s  
  pages 29 - 31

**NEW TECHNOLOGY**
- Parkinson’s and Deep Brain Stimulation  
  pages 32 - 35

**RESEARCH**
- Research Model Organisms  
  pages 36 - 40
- Research Study: Alzheimer’s  
  pages 41 - 44

**INTERVIEW**
- Parkinson’s Disease Interview  
  pages 45 - 46

**SATIRE**
- Vitreous Humor  
  pages 47 - 49

**CONTRIBUTORS**  
Page 50
Readers,

I hope you enjoy the second issue of the YNCA Journal! We greatly appreciate your continued (or new) readership.

As stated in our inaugural issue, each edition of the journal will center around a core theme. For this issue, we selected neurodegenerative diseases as our theme. A neurodegenerative disease is any disease in which neurons are damaged (and possibly die). Many neurodegenerative diseases are linked to aging, which poses an extraordinary challenge today with the so-called “graying of America”. Common examples of neurodegenerative diseases include Alzheimer’s disease, Parkinson’s disease, and Amyotrophic Lateral Sclerosis.

In the disease section, Jacob Umans and Brendan Mitchell (a new member of the YNCA!) explain the characteristics of Alzheimer’s disease, from macroscopic-level symptoms to microscopic cellular mechanisms; Priya Vijayakumar delves into Creutzfeldt-Jakob disease, a little-known neurodegenerative disease; Christian Gonzalez explains the many facets of Amyotrophic Lateral Sclerosis; Alexander Skvortsov discusses Lewy Body Dementia.

Fortunately, some of the greatest minds across the globe are working on solving these devastating disorders. The research section, featuring articles by Jacob Umans, Meenu Johnkutty, and Kyle Ryan, provides examples of some cutting-edge studies being conducted on Alzheimer’s disease. In the New Technology section, Janvie Naik and Jordan Bartfield explain Deep Brain Stimulation as a treatment for Parkinson’s. I also interview a pair of Parkinson’s researchers at Emory University.

Finally, it is all too easy to become exclusively focused on the minutiae of these disorders--the tiny molecular pathways, the biomarkers, the mouse models. It is important that we take time to remember the effects that these diseases have on individual human beings. My grandmother was one of many afflicted by Alzheimer’s disease. A description of amyloid plaques and neurofibrillary tangles and microglia and the nucleus basalis of meynert can not, and never will be able to, encapsulate her suffering--or that of the millions of others who suffer from neurodegenerative disease. Jack Ross-Pilkington’s article in the Neuroscience and Society section on Ronald Reagan’s battle with Alzheimer’s disease will help illustrate the individual cost of neurodegenerative diseases.
As always, it is critical that we recognize all of our dedicated staff for helping us make this issue the success that it is. You can find all of their names and positions on our Contributors page. If you have any questions, comments, or suggestions for us, please feel free to contact us at YNCA.info@gmail.com. We hope you enjoy our second issue as much as we enjoyed writing it!

Best Regards,

William Ellsworth
Editor-in-Chief, YNCA Journal
Update from the Executive Directors

Readers,

We are glad to release the second issue of the YNCA Journal! Perhaps the most publicized aspect of our organization right now is our journal, but there is much more to the YNCA than just that. Currently, we have a large amount of activity going on within the organization. For this reason, the YNCA Directors would like to describe some of our principal projects.

**Chapter Clubs:** In the acronym YNCA, the word *clubs* shows up. At this point, we already have a few chapter clubs set up, but we are looking to start more clubs for the 2016-2017 academic year. Essentially, YNCA Chapter Clubs will focus on sharing a passion for neuroscience with more students at our schools. This can be done through countless means, including watching videos on the brain, studying neuroscience, or debating the ethics of pressing issues. While clubs will have significant freedom, they will all be linked to the YNCA. Our organization will help in the development of chapter clubs and create a network of like-minded neuroscientists with whom you can work. If you are interested in founding a chapter club at your school, please email ynca.outreach@gmail.com to receive more information on how to do this.

**Membership:** Our national organization currently has over twenty members, and is always looking for new members to help with outreach, journal articles, and web design. Even without being part of a chapter club, it is still possible to participate in the YNCA. The YNCA fosters an environment in which it is easy make connections with other high school students who also are fascinated with neuroscience, allowing your passion for neuroscience to grow. Furthermore, the YNCA hopes to eventually help students develop connections between high-school and college students once more members reach universities, providing substantial benefits for existing members. We have already received an endorsement from Neuroscience News, a prominent group of over one hundred thousand people fascinated with the brain, and are seeking many others. Such connections, both with other members of the YNCA and with larger organizations, could allow members easier access to research opportunities. Please email ynca.outreach@gmail.com to receive more information and join the YNCA.

**Social Activism:** Outside of providing neuroscience education, the YNCA hopes to create positive change within the world. We hope to spread awareness of neurological disorders and the context of neuroscience within the larger framework of society. Through our journal we have strived to do this since the beginning: In our June Issue, we included an article on Migraines during Migraine Awareness Month and in this issue we have established a new segment “Neuroscience and Society” dedicated exclusively to presenting neuroscientific discoveries in a larger, societal context.
Outside of the Journal, YNCA Chapter clubs will be encouraged to participate in volunteer or fundraising events, perhaps even related to the theme of a recent journal topic, connecting different aspects of the club into a larger framework dedicated to effecting positive change.

All the Best,

Jacob Umans
Nicholas Chrapliwy
Alexander Skvortsov

YNCA Executive Directors
Basics of Neuroscience II: An Introduction to Internal Neural Communication

Alexander Skvortsov, William Ellsworth and Jacob Umans

Hello, readers of YNCA Journal, and welcome back to the Basics of Neuroscience course, presented by the YNCA Executive Board. In last month’s lesson, we discussed the basic structure of neurons. We also touched upon basic neural communication, discussing synapses and neurotransmitters. In this edition, we will go further in depth discussing neural communication; specifically, we plan to emphasize electrical forces involved with these functions.

As we discussed in the last edition, the brain is composed of 80 to 100 billion neurons, linked in a contiguous system. These neurons are cells just like any other. However, they also perform the function of transmitting messages throughout the nervous system. They are able to do this due to two branched structures called the dendrite and the axon, which function as input and output systems respectively.

Action Potentials

A neuron firing is usually interpreted as the action potential. An action potential, or a neural output signal, is binary. A neuron either fires, or it doesn’t. This concept is known as all-or-none firing, and it is an extremely important phenomenon in neural signaling.

Action potentials are electrical events. Neurons, like all other cells, have different concentrations of ions (charged particles) inside the cell and outside the cell. This charge difference creates a voltage (also known as electric potential) across the cell membrane (the thin layer separating the inside and outside of the cell).

In an action potential, certain transmembrane proteins, or proteins that have components both inside and outside of the cell membrane, are activated. These proteins are called ion channels, and, when activated, they allow ions to diffuse down their concentration gradients. This movement
changes the voltage across the cell membrane. If the cell is **depolarized** enough, meaning that the charge of the cell relative to the extracellular medium rises to a value close enough to zero, an action potential will be initiated. The **resting potential** of a neuron -70 mV, and if the voltage reaches about -55mV (the **threshold**) an action potential is initiated. At the axon hillock, all inputs into the neurons (discussed later) are integrated; if the charge in this region of the neuron crosses the threshold, an action potential is generated.

The first step in the creation of an action potential is the opening of **voltage-gated sodium channels**, or ion channels that allow sodium ions to enter the neuron, causing a massive increase in the voltage (which can reach up to 30mV). Then, **voltage-gated potassium channels**, which are much slower to respond to changes in voltage, are activated. Potassium ions flow out of the cell, and eventually the voltage drops below -70mV in a process known as **hyperpolarization**. Ultimately, the voltage returns to -70mV, and after a brief period or rest known as the **refractory period**, during which sodium channels are physically unable to reopen, the activated region of the neuron is ready to produce another action potential. During this time, an ion pump known as **Na⁺/K⁺-ATPase** works to restore the concentration of Na⁺ as well as K⁺ to their base levels.

**Action Potentials** travel through the axon using a process known as **saltatory conduction**. We already discussed that axons are coated with a lipid layer known as myelin in order to insulate the electrical signal, with gaps in between called **Nodes of Ranvier**. During saltatory conduction, ions entering sodium channels at one Node of Ranvier diffuse past the myelinated region to depolarize the next region to continue propagating the action potential. Overall, this allows the action potential to skip from one Node of Ranvier to the next, thus greatly increasing speed of conduction. One interesting feature about saltatory conduction is that the signal can only move in one direction, unlike most other transmission processes where the signal spreads out wherever possible. This phenomenon is caused by the inability of sodium channels to propagate signals during its refractory period—once the refractory period is over, the charge in the cell is unable to cause another action potential.

**Postsynaptic Potentials**

After the action potential fires, the signal is transferred to the dendrite of the receiving neuron through a process called synaptic transmission, but more on that in the next edition. Basically, chemicals called neurotransmitters are released upon firing which then react with the receiving neuron, triggering a signal called the Postsynaptic Potential. Unlike the action potential,
the voltage of the Postsynaptic Potential can vary. This depends on the number of neurotransmitters released.

Another major difference is the existence of both Excitatory Postsynaptic Potentials (EPSPs) alongside Inhibitory Postsynaptic Potentials (IPSPs). As discussed previously, whether or not an action potential is released is determined by changes in the voltage across the cell membrane. The membrane voltage change is primarily set by the sum of all incoming Postsynaptic Potentials. Charges from all EPSPs and IPSPs from different parts of the postsynaptic dendrite are added together to produce the total membrane voltage. This is known as **spatial summation**. Now, the purpose of IPSPs becomes clear. IPSPs allow for inhibition of an action potential. This can be crucial at the right time. For example, let’s consider a basic muscle movement. An alpha motor neuron fires, which triggers contraction of a muscle fiber. Now, without inhibition control, the antagonist muscles would remain in their relative states, whether that be contracted or relaxed. This would result in muscle tearing. However, the antagonist muscle receives an inhibitory charge, which allows muscle movement without damage (Byrne, J. H. and Dafny, N. (eds.), 1997).

Similarly to spatial summation, there is a process called **temporal summation**. This is when a high occurrence of Postsynaptic Potentials build upon each other, allowing the charge to reach the threshold for activation more easily.

One final basic principle to consider in terms of Postsynaptic Potentials is signal deterioration. When a PSP is released on the dendrites, the charge dissipates as it travels along the dendrite towards the soma. As a result, the signal that factors into spatial summation will be much weaker than they were upon first affecting the neuron. Because of this, inputs from several neurons are necessary to pass the threshold voltage and initiate an action potential. This allows for many thousands of neurons to contribute to calculations of a single neuron without completely frying it. Using this process, individual neurons act in a manner similar to microprocessors, working together to evaluate data and perform operations with it.

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An Introduction to Neuroethics: Why Should We Care?

Nicholas Chrapliwy

If you’ve ever thought about the possibility of taking a drug that enhances your ability to remember or perform well on a test, you’ve thought about neuroethics. If you’ve ever watched a film or read a story in which a truth serum or mind-controlling drug was used, you’ve thought about neuroethics. And if you’ve ever thought that you might learn much better if your teacher taught his or her class in a different way, you’ve thought about neuroethics. The International Neuroethics Society defines neuroethics as, “…a field that studies the implications of neuroscience for human self-understanding, ethics, and policy” (International Neuroethics Society, 2003). As an organization that wants to connect young neuroscientists to the people and institutions that will grant them the most opportunity to serve the field, the YNCA will be dedicated to fostering an ethical awareness among its members. Monthly articles that discuss and debate one of the facets of neuroethics will be featured in each issue of the YNCA Journal, as well as programmed discussions in the forums of the YNCA website.

By doing this, we hope not only to make our members more sensitive to the moral issues surrounding the field they are all passionate about, but also to incorporate young neuroscientists who love the idea of an ethics debate, but might not be as skilled as others in remembering all the details of neuroanatomy. Issues such as brain privacy, drug enhancement, courtroom justice, and even how education should be accomplished will be thoroughly perused and often debated. So if you find yourself a little confused after reading a detailed description of Alzheimer’s disease, there will always be an article in the YNCA journal about a current ethical issue in neuroscience that will provoke your moral reasoning and hopefully interest you enough to respond and take action.

The YNCA will also provide a few additional paths to expressing interest in neuroethics besides forum debates and neuroethics articles. The option to serve your community in a way
relevant to your interest in neuroscience will be one of the ways a YNCA Club Charter can fulfill its membership requirements. Anything from volunteering to help Alzheimer’s or Parkinson’s patients at your local hospital to raising money to donate to a foundation that funds the study of cures for those diseases will be considered for YNCA community service credits. (These hours may additionally apply to credits required for national honor societies like the Beta Club). Connecting to people during service will also be its own reward. The YNCA wants to include neuroethics for several reasons, but ultimately in order to accomplish our vision of being a group of young neuroscientists who intentionally work together to achieve excellence in the study and collaborative progress of neuroscience.

For more information about starting your school’s YNCA club, or to learn more about how you can become involved in current conversations about neuroethics, visit our website at www.youthneuro.org.

References

Alzheimer’s Disease

Jacob Umans and Brendan Mitchell

Alzheimer’s disease, the most common form of dementia, is a neurodegenerative disorder that leads to memory loss. As of 2016, Alzheimer’s disease affects 5.4 million Americans and is the sixth leading cause of death in the United States (Alzheimer’s Association, 2016). There are two principal forms of the disease. Familial Alzheimer’s disease, a form of Alzheimer’s disease that is hereditary, accounts for an estimated 200,000 Alzheimer’s disease cases in the United States alone. The remainder of Alzheimer’s disease cases is classified as sporadic Alzheimer’s disease. The key difference between early onset familial Alzheimer’s disease is that it is the consequence of the malfunctioning mutated genes, whereas late-onset is more likely due to the gradual accumulation of age-related malfunctions (Strobel, n.d.). The prevalence of Alzheimer’s disease varies among a myriad of factors such as age, gender, genetics, comorbidities (another disease manifesting itself at the same time—for example, heart disease, which may alter cerebral blood flow, increasing one’s susceptibility to Alzheimer’s), and environment. With our current technology, Alzheimer’s disease can only be definitively diagnosed after death through an examination of the brain tissue in an autopsy (National Institute on Aging, n.d.). Although there is no cure for Alzheimer’s, current research shows promise.

Symptoms and Progression

The symptoms of Alzheimer’s disease progress over a time period of about 8 to 10 years. There are three main phases of the disease’s progression, each with its own challenges and symptoms. By recognizing the current stage of the disease, physicians can then predict expected symptoms and respond with the respective treatments.

The early stage, or mild stage, of Alzheimer’s disease is in many cases the stage during which the disease is first diagnosed. This stage typically persists for 2 to 4 years in which friends and family members start to notice a decline in the patient’s cognitive abilities. Hallmark symptoms of this stage include the following: an inability to recall recent events and information, difficulty with solving
problems or making decisions, changes in personality usually resulting in irritability and isolation, difficulty in expressing thoughts, and getting lost or misplacing belongings (Mayo Clinic Staff, 2015).

In the middle stage, or moderate stage, of Alzheimer’s disease cognitive sharpness continues to decline and the symptoms experienced in the mild stage are intensified. This stage usually lasts 2 to 10 years, making it the longest stage of the disease. Patients often experience increased difficulty with memory and may need assistance to complete daily activities. Key symptoms of this stage include the following: increasingly poor judgement and confusion, difficulty completing complex tasks, greater memory loss, and stark personality changes such as social withdrawal and suspicion of caregivers (Mayo Clinic Staff, 2015).

In the late stage, or severe stage, of Alzheimer’s disease cognitive capacity continues to dwindle and physical ability is gravely impacted. This final stage often lasts 1 to 3 years. In this stage, families often face difficulties in properly caring for the patient which results in nursing home or other long term care facility placement. Core symptoms appearing in this stage include the following: loss in the ability to communicate coherently; reliance on others for personal care such as eating, dressing, and toileting; and inability to function physically including being unable to walk, swallow, and control bladder and bowel movement (Mayo Clinic Staff, 2015).

Etiology

AD has a strong genetic basis. Perhaps the most well-known mutation implicated in its onset is Apolipoprotein E Epsilon 4 (ApoE-e4). In one study on the link between ApoE-e4 and Alzheimer’s disease, the p-value was under 0.000001, meaning that there is almost certainly a link between that gene and Alzheimer’s (Blacker et al., 1997, p.139).

Familial Alzheimer’s disease is linked to Presenilin 1 and 2 genes (PSEN1 and PSEN2, respectively). It produces the catalytic domain of Gamma Secretase, which is involved in cleaving proteins (including Amyloid Precursor Protein, a protein known to be extensively involved in the pathology of Alzheimer’s). Mutants in this gene are loss-of-function mutations, meaning that mutations prevent PSEN1 from completing its normal function. Research indicates that Presenilin proteins play a key role in memory preservation, and their loss can cause symptoms resembling Alzheimer’s disease. In particular, the L435F mutation causes impaired hippocampal long term potentiation; this change is linked to a decreased ability to complete memory-based tasks (Xia et al., 2015).

Though one’s genetics makes a contribution to the onset of Alzheimer’s disease, it is not the only factor responsible. Scientists have found links between Alzheimer’s, stress, and exercise. It has
been proposed that through certain pathways stress exacerbates the disease while exercise ameliorates it. Such pathways are either categorized as direct or indirect. One example of a direct pathway is that these processes may alter in cerebral blood flow. Possible indirect pathways include altering the risk of diabetes and hypertension, and through these affecting the brain (Nation et al., 2011, p. 847).

Diet has also been identified as a contributor to the onset, or lack of, Alzheimer’s disease. See the research section for more.

It is clear that there is no single, clear-cut cause of Alzheimer’s disease as there often is in many other disorders. Both genetic and environmental factors play a key role, and researchers are still working to elucidate the connection between these two influences.

Pathology

Related to the causes described above are the actual mechanisms by which Alzheimer’s disease attacks the nervous system. Mutant genes produce proteins that cannot complete their normal function, and environmental influences create conditions favorable to the onset and development of the disease.

The insidious progression of the symptoms of Alzheimer’s disease is exacerbated by the accumulation of two distinct deformities in the brain, neurofibrillary tangles (created by the abnormal accumulation of Tau) and senile plaques (created by the abnormal accumulation of Aβ). The neurofibrillary tangles are found in the cytoplasm of neurons in the entorhinal cortex. The protein Tau, which creates these plaques, particularly in its phosphorylated form (which causes abnormalities in transport and axon function), also makes a key contribution to the damage caused by Alzheimer’s disease (Humpel, 2011). There are two different types of plaques, neuritic and diffuse, that are found in the neocortex of the brain. Neuritic plaques are spherical structures that contain neurites that are surrounded by amyloid—an abnormal protein. The Aβ concentration in the bloodstream is an indicator of the severity of Alzheimer’s disease (McLean et al., 2001, p. 860), indicating its importance in the pathophysiology of the condition. Diffuse plaques lack neurites and have an amorphous appearance (Serrano-Pozo et al., 2011). As the concentration of these deformities increase, healthy neurons begin to become ineffective. As neuronal injury and death proliferate throughout the brain, connections between networks of neurons disintegrate and consequently die, affected regions begin to shrink in a process known as brain atrophy. Neuron death, particularly in the hippocampus, inhibits the patient’s ability to form new memories, thus contributing to the symptoms of the disease.
One specific process these molecules alter is **Long-Term Potentiation (LTP)**, or the molecular mechanism by which memories are formed. **Oligomers**, or short polymers which contain fewer Aβ monomers than plaques, of Aβ have been shown to inhibit hippocampal LTP in vivo (Walsh et al., 2002, p. 535). While plaques were given significant attention in the past, researchers have recently begun to focus more closely on oligomers. As forgetfulness of new information is a key symptom in early Alzheimer’s disease, and the hippocampus is linked to the consolidation of memories, this study suggests that alterations of normal LTP is a key part of Alzheimer’s pathophysiology. Another, more recent study on human patients made similar discoveries: they found that LTP is abnormal in the cortex of Alzheimer’s patients (Di Lorenzo et al., 2016).

In addition to Aβ and Tau tangles, abnormal Acetylcholine neurotransmission is thought to play a key role in Alzheimer’s disease. One characteristic pathological feature of Alzheimer’s disease is the loss of neurons in the **Nucleus Basalis of Meynert**. As this nucleus is a key center for cholinergic neurons (neurons producing and transmitting Acetylcholine), this damage represents a key feature in the pathology of Alzheimer’s disease. Furthermore, the loss of neurons producing Acetylcholine is linked to cognitive impairment in Alzheimer’s, but not necessarily its cause. It may be the case that Acetylcholine abnormalities and cognitive deficits are caused by another factor, or that the mechanism by which Acetylcholine is linked to the progression of Alzheimer’s disease is indirect. Because of this link between Acetylcholine and Alzheimer’s disease, **Cholinesterase inhibitors** (inhibitors of the enzyme Acetylcholinesterase, which removes Acetylcholine from the synapse) are one class of medications used to treat Alzheimer’s disease (Francis, Palmer, Snape, & Wilcock, 1999).

Metals are also thought to play a role in the pathology of Alzheimer’s disease. Specifically, zinc and copper have been implicated in causing abnormalities in the activity of NMDA Glutamate receptors, known to play a critical role in Long-Term Potentiation, and thus memory as well. Furthermore, heightened iron content in certain tissues is also seen in the brains of Alzheimer’s patients (Barnham & Bush, 2011, p. 222).

**Treatment**

While there is no current cure for Alzheimer’s disease, there are multiple drugs that have proven to slow disease progression and ameliorate symptoms. In order for specific symptoms to be treated, physicians categorize the symptoms into either “**cognitive**” or “**behavioral and psychiatric**.” Cognitive symptoms disrupt memory, language, judgment, and thought processes. Behavioral symptoms affect a patient’s actions and emotions (Alzheimer’s Association, n.d.).
Treatment for cognitive symptoms requires the alteration of chemical messengers in the brain. The U.S. Food and Drug Administration (FDA) has approved two types of medications to treat the cognitive symptoms of Alzheimer’s disease: cholinesterase inhibitors and memantine (Alzheimer’s Association, n.d.). The first type, currently approved for treating the symptoms of Alzheimer’s disease in the early to moderate stages, blocks the enzyme responsible for the breakdown of Acetylcholine (ACh) in the brain. ACh is a salient neurotransmitter for learning and memory. Normal aging triggers a slight fall in the concentrations of ACh, causing periodic forgetfulness. However, in Alzheimer’s disease, the concentration of ACh is starkly diminished by about 90%, resulting in significant cognitive decline. The function of these drugs is to bolster communication among neurons by keeping ACh concentrations high. There are three cholinesterase inhibitors commonly prescribed for treating the cognitive symptoms of Alzheimer’s disease: Donepezil (approved to treat all stages), Rivastigmine (approved to treat mild to moderate stage patients), and Galantamine (approved to treat mild to moderate stage patients).

In addition to cholinesterase inhibitors, memantine is a drug approved by the FDA for treating the cognitive symptoms of Alzheimer’s disease but for remedying the moderate to severe symptoms of Alzheimer’s disease. Memantine regulates the activity of the brain’s most abundant excitatory neurotransmitter, glutamate which is involved in learning and memory, by acting as a N-methyl-D-aspartate (NMDA) receptor antagonist. When glutamate binds to NMDA receptors to facilitate the flow of calcium in cells, glutamate can cause depolarization and increased intracellular Ca\(^{2+}\) ion concentration. A rising Ca\(^{2+}\) ion concentration in the cytoplasm prompts Ca\(^{2+}\) influx into mitochondria, in which mitochondrial Ca\(^{2+}\) accelerates and disrupts normal metabolism causing cell death (Gennady Ermak & Kelvin J.A Davies, 2002). Malfunctions in the action of the glutamate-glutamine cycle can spawn a “self-perpetuating neuronal death cascade” which may be the cause of the neurodegeneration seen in Alzheimer’s disease. Brain cells are over-excited to death by the pathophysiological action of glutamate in a process known as excitotoxicity (Heather Scott Walton & Peter R. Dodd, 2006). Memantine is a drug that aims to protect the nerves from the overstimulation of glutamate by blocking the NMDA receptors.

In addition to cognitive decline, Alzheimer’s disease can cause grave behavioral and psychiatric symptoms. These symptoms include sleeplessness, agitation, hallucinations, and delusions (National Institute on Aging, 2015). There are two possible methods of treating the behavioral symptoms of Alzheimer’s disease: non-drug intervention and medication. Non-drug intervention approaches aim to alter the environment to eliminate obstacles and increase security. Another possibility is to investigate any potential conflicts or interactions between the patient’s
medications that could cause adverse effects to behavior or psychiatric health. If these interventions fail to ameliorate the symptoms, introducing medication may help. Although the FDA has not specifically approved drugs to treat the behavioral and psychiatric symptoms of Alzheimer’s disease, physicians may consider practicing off label use of medications, that is, prescribing medications for a different purpose than what is it is approved. There are a multitude of medications that could be chosen depending on the symptoms. If the patient is experiencing depression, an antidepressant such as Prozac or Zoloft can be prescribed. Antipsychotics and anxiolytics may be prescribed to reduce hallucinations and anxiety, respectively (Alzheimer’s Association, n.d.).

Key Terms

Familial Alzheimer’s Disease- A form of Alzheimer’s disease linked to genetics
Sporadic Alzheimer’s Disease- A form of Alzheimer’s disease without a known genetic cause
Neurofibrillary Tangles- Pathological feature of Alzheimer’s disease caused by abnormal accumulation of Tau proteins, also known as Tau Tangles
Senile Plaques- Also called Amyloid-Beta (Aβ) Plaques, key pathological feature of Alzheimer’s disease
Neuritic Plaques- One subtype of senile plaques characterized by the presence of neurites and their spherical shape
Diffuse Plaques- Another subtype of senile plaques characterized by the absence of neurites and an amorphous shape
Long-Term Potentiation - The cellular process by which Glutamate neurotransmission alters synapses through the AMPA and NMDA glutamate receptors, and a subsequent signaling cascade
Oligomer- A short polymer
In vivo- In living organisms, contrast with in vitro (in test tubes, labs, etc.)
Nucleus Basalis of Meynert- A brain region highly implicated in Acetylcholine production and neurotransmission
Cholinesterase Inhibitors- A class of medications that target acetylcholinesterase (an enzyme that removes Acetylcholine from the synaptic cleft after signaling). Common types used to treat Alzheimer’s disease include Donepezil, Rivastigmine, and Galantamine
N-methyl-D-aspartate (NMDA) Receptor- A receptor for the neurotransmitter Glutamate that is implicated in learning through supporting Long-Term Potentiation
Non-drug intervention- A treatment of behavioral and psychiatric symptoms of Alzheimer’s disease involving altering the environment in which the patient lives
Cognitive Symptoms- Symptoms of Alzheimer’s disease involving cognitive functions, including memory, language, judgment, and thought processes

Behavioral and Psychotic Symptoms- Symptoms of Alzheimer’s disease affecting a patient’s emotions and actions

Memantine- A regulator of Glutamate used to treat moderate to severe symptoms of Alzheimer’s disease
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The Pathology of Amyotrophic Lateral Sclerosis

Christian Gonzalez

Introduction

In 2014 an explosive internet trend was started that raised approximately $115 million for scientific research focused on curing a disease. Millions of people viewed celebrities such as Bill Gates and Mark Zuckerberg dumping numbingly cold buckets of water on their head and the reactions that followed. Through this simple act, public awareness of ALS surged and a great deal of vital funding for research was raised. Unfortunately, it is reasonably inferable that many who enjoyed the challenge watched without ever learning what ALS actually is. Moreover, although the ALS Ice Bucket Challenge reached such a vast crowd across the globe, it was likely not enough to spur a significant amount of progress toward ending one of the least understood of neurological conditions (Song, 2014).

ALS is a rare neurodegenerative disease affecting about 450,000 people worldwide. The disease begins either spontaneously or occurs in a patient genetically, being passed on from an earlier generation. It is invariably fatal and progresses rapidly; every 90 minutes a patient will receive a diagnosis of ALS and most patients die just 2.5 years after the onset of their symptoms (with only 10% of patients surviving for 10 years). Currently, there is no cure for the disease, and the cause remains unknown in 90-95% of patients (“ALS Frequently Asked Questions,” n.d.).

The course of ALS is the result of neurodegeneration of two different types of motor neurons called upper motor neurons and lower motor neurons. Accordingly, ALS is also referred to as motor neuron disease in several countries (“Amyotrophic Lateral Sclerosis Fact Sheet,” n.d.). When damage occurs, the regular functionality of these nerve cells gets disrupted, which makes it difficult and eventually impossible for ALS patients to move most or all of their voluntary muscles. Typically, involuntary muscles remain healthy for much longer during ALS, which is why normal body functions such as breathing and digestion are less affected. Unfortunately, even involuntary movement eventually becomes greatly impaired and thus the most common cause of death in ALS is respiratory failure. Often times, when the disease progresses, the neurotransmitter glutamate is found at elevated levels within the brain and is believed to cause the excitotoxicity associated with certain types of further damage (Shaw & Ince, 1997).

Symptoms and Traits
The symptoms of ALS vary widely and are dependent upon the stage of progression in which a patient is in. Moreover, symptoms are extremely dynamic within stages and vary from patient to patient. During the beginning of the disease, some of the most common symptoms include difficulty walking, clumsiness, weakness, fasciculations, and muscle cramps. As the disease progresses, breathing becomes difficult due to weakened muscles, and eventually patients will lose the ability to walk on their own and perform simple tasks. Speech becomes difficult to perform, and communication between patient and caretaker can sometimes be very tedious. Throughout the progression of ALS, patients typically experience muscle spasms and cramps, extreme fatigue, constipation, spasticity, depression, and excessive salivation. Shortness of breath and dysphagia (difficulty swallowing) are also commonly experienced before the eventual paralysis that results from the death of a large number of motor neurons over time (“ALS, Amyotrophic Lateral Sclerosis, Lou Gehrig’s disease,” n.d.).

Precursory Indicators
With over 90% of all cases diagnosed without a known cause, the molecular origins of ALS are poorly understood. Only 5% patients have identifiable genetic histories with relatives affected by ALS. Although nine out of every ten patients suffer from sporadic ALS, there is currently no evidential correlation between a patient’s lifestyle and their probability of developing the disease. Factors that can often influence other diseases like Alzheimer’s, multiple sclerosis, and diabetes such as weight, geographic location or diet have not been linked to the onset or progression of the disease (“ALS, Amyotrophic Lateral Sclerosis, Lou Gehrig’s disease,” n.d.).

Genetic Factors
There are many different genes involved in the development of familial ALS. Specifically, approximately 30-40% of familial ALS cases are the result of mutations in the gene C9orf72. Other genes such as FUS and TARDB account for one out of every twenty cases of ALS, and about one out of every five patients with familial ALS have mutations in the SOD1 gene. Gene mutations in ALS can result in the inability to break down toxic substances, which contributes to a buildup of toxins in neurons. As these toxins accumulate, motor neurons can be killed off, resulting in the array of symptoms in ALS. Alternatively, gene mutations directly disrupt axonal development, which can impair the functional transmission of muscle nerve impulses and cause atrophy (“Amyotrophic lateral sclerosis,” n.d.).

Diagnosis
ALS is typically diagnosed with a variety of methods that are collectively referred to as the El Escorial criteria. The four identifying factors that this criteria looks for are degeneration of upper motor neurons, degeneration of lower motor neurons, absence of other explanations for symptoms, and progressive worsening of physical signs (“Criteria For the Diagnosis of ALS,” n.d.). Typically, the first step in reaching an accurate diagnosis involves a complete examination of family medical history. This is often done to rule out whether or not a patient might have familial ALS. Neurologists conduct simple evaluations of muscle and nerve health initially as well. MRI scans can also be used to diagnose patients based on changes in biomarkers. In order to differentiate ALS from other similar diseases in its earliest stages, tests such as electromyography (EMG) and nerve
conduction studies can assess muscle health and peripheral nerve damage, which can also aid in the
diagnosis of the disease. Even with these tests though, the main component in a diagnosis is
symptoms (“Amyotrophic Lateral Sclerosis Fact Sheet,” n.d.).

Treatment
While there is no cure available today, there are several drugs that can aid in slowing the
progression of ALS and lessening the severity of the symptoms that many patients experience. The
most common drug is riluzole. This drug can slow disease progression in certain patients by
inhibiting the neurotransmitter glutamate. Additionally, the drug gabapentin can be used to lessen
pain, and the drugs diazepam and baclofen are prescribed to control spasticity, or muscle stiffness
(“ALS Treatment,” n.d.).

Advocacy and Awareness
To get involved in the fight against ALS and assist in efforts that aim to develop novel
treatments and eventually find cures for the disease, please contact the ALS Association and find
out how you can help. If you want to help improve public awareness, sign up an Advocate today at

ALS Association- http://www.alsa.org/

KEY TERMS
Neurodegeneration- The progressive destruction of the function and structure of neurons
Upper Motor Neurons- Nerve cells in the motor cortex involved in voluntary movement
Lower Motor Neurons- Motor neurons located in the brainstem and spinal nerve roots that play an
important role in voluntary movement
Motor Neuron Diseases- Group of neurodegenerative diseases that destroy motor neurons
Glutamate- Main excitatory neurotransmitter in the human nervous system
Excitotoxicity- Process of neuron death by overstimulation of glutamate receptors
Fasciculations- Brief and spontaneous muscle contractions under skin visible by the human eye
Spasticity- Muscle stiffness
Dysphagia- Difficulty swallowing
C9orf72- Most common gene mutation associated with familial ALS
FUS- Gene mutated in 5% of familial ALS patients
TARDB- Gene mutated in 5% of familial ALS patients
SOD1- Gene mutated in 20% of familial ALS patients
El Escorial criteria- Method for diagnosing ALS based on four main factors
Electromyography- Diagnostic method that assesses muscle health based on electrical activity
Riluzole- Glutamate blocker used to treat ALS
Gabapentin- ALS medication used to treat nerve pain
Diazepam- Benzodiazepine drug used to treat muscle spasms in ALS
Baclofen- Muscle relaxant used to treat muscle spasms in ALS
References


Creutzfeldt-Jakob Disease

By Priya Vijayakumar

Discovered in the 1920s by German scientists Hans Gerhard Creutzfeldt and Alphons Maria Jakob, Creutzfeldt-Jakob disease (CJD), or Spongiform Encephalopathy, is a neurodegenerative disorder that causes physical changes in the brain’s spongiform tissue (BSE Info, 2016). With the annual incidence of one in a million, CJD is a rare disorder that exists in three broad forms: sporadic, familial, and acquired. Sporadic CJD affects patients, on average, at the age of 65 and is triggered by unknown factors. (Creutzfeldt-Jakob Disease n.d.; The Creutzfeldt-Jakob Disease Foundation n.d.).

The sporadic type accounts for 85% of all CJD cases and is suggested to involve infectious prion proteins that interrupt normal brain protein function and neuronal connections (BSE Info 2016; Creutzfeldt-Jakob Disease n.d.; Creutzfeldt-Jakob Disease 2016). Familial CJD occurs when a mutated prion protein gene is inherited. In the United States, approximately five to fifteen percent of CJD cases are familial. Acquired CJD is obtained from environmental factors such as the consumption of infected meat from a cow with Bovine Spongiform Encephalopathy, more commonly recognized as Mad Cow Disease, or contamination during medical procedures such as blood transfusions or general surgeries (BSE Info 2016).

Diagnosis and Notable Features

CJD is clinically identified through motor system examinations, blood tests, CT scans and MRIs of the brain, EEGs, and spinal taps. Noting abnormal lapses in cognitive behavior can also serve to identify the presence of CJD (UCSF Memory and Aging Center n.d.).

Because of its lengthy incubation period, CJD can remain in patients for a long time without being recognized. After initially contracting CJD, patients may experience cold-like symptoms. The severe effects of CJD do not become apparent until many years, even a decade, after initial contraction. Personality changes such as the development of anxiety, depression or amnesia occur earlier on in the disease process and progress into severe dementia in the long-term (UCSF Memory...
and Aging Center n.d.). Eventually, patients have difficulty with higher-level cognitive functions such as thinking, organizing, and planning. Patients may also struggle to walk due to the loss of coordination and balance as well as muscle stiffness, twitching, or jerkiness (Creutzfeldt-Jakob Disease 2016; UCSF Memory and Aging Center n.d.). On top of the shared characteristics listed above, the features of CJD vary based on the form of the neurodegenerative disorder. For example, later stages of sporadic CJD are accompanied by hallucinations, blindness, muscle rigidity, slurred speech, difficulties in swallowing, and Akinetic Mutism, a disorder in which the patient can no longer speak or move (BSE Info 2016). After initial detection of CJD due to apparent cognitive and physical declines, patients face an average life expectancy of a mere 12 months and often fall into a coma before dying (UCSF Memory and Aging Center n.d.).

**Treatment Options**

Currently, there is no cure for CJD, but there are still therapeutic treatments that help patients ease their symptoms. Selective Serotonin Reuptake Inhibitors (SSRIs), including citalopram and escitalopram, are effective in treating depression resulting from CJD. For cases of severe muscle jerkiness and seizures, clonazepam and anti-epileptic drugs such as valproic acid respectively have also proven to be useful. **Atypical antipsychotic medication** is also recommended for CJD patients who experience visual hallucinations. Although sufficient treatment does not exist to stop the progression of CJD, ongoing research holds hope in understanding the neuropathology behind CJD and thereby developing more effective therapies (UCSF Memory and Aging Center n.d.). Aside from medication, family counseling can also play a pivotal role in treating the behavioral symptoms of CJD and the toll it has on the patient and his or her family.

**Prevention and Control**

As the triggers of sporadic CJD are unknown, many preventative measures do not exist. Although there are no proven cases of the transmission of CJD through airborne means or casual contact, blood transmission devices and other vital surgical utensils should be adequately sterilized to prevent the accidental transmission of CJD. For familial CJD, if the gene causing the development of prions is identified through genetic testing, therapeutic abortions can prevent the inheritance of CJD (BSE Info 2016; The Creutzfeldt-Jakob Disease Foundation n.d.).
Terms
Atypical antipsychotic medication: A group of antipsychotic medication that treats psychiatric conditions such as schizophrenia, bipolar disorder, and various types of psychoses.

References
Lewy Body Dementia
By Alexander Skvortsov

Robin Williams was a well-known actor, comedian, and philanthropist. Starring in movies such as *Dead Poet's Society* and *Good Will Hunting*, as well as numerous shows and standup comedy productions, Robin was widely considered one of the best comedians of the late 20th century, and embodied the very heart and soul of comedy.

Robin Williams committed suicide in 2014. For several months before his death, his widow and colleagues reported him as exhibiting unusual conditions, in particular depression and paranoia. However, Robin wasn't just feeling down. An autopsy after his death revealed that he was likely suffering from Lewy Body Dementia. ("Robin Williams and Lewy Body Dementia", 2014).

Many people are familiar with Alzheimer's, but few know that Lewy Body Dementia, or LBS, is the second leading cause of dementia in the world. Approximately 1.4 million Americans suffer from Lewy Body Dementia every year, second only to Alzheimer’s in terms of neurodegenerative diseases. It is also one of the most misdiagnosed neurological diseases in America ("What is LBD?", n.d.). Lewy Body Dementia is a blanket term for two specific dementias: Parkinson’s Disease Dementia and Dementia with Lewy Bodies (DLB). Both Lewy Body Dementias are caused by abnormal buildup of proteins called Lewy Bodies: aggregates of proteins inside neurons. Lewy Bodies were discovered in the early 1910s by Frederic Lewy while researching Parkinson’s, and were later named in his honor by Russian neuropathologist Konstantin Trétiakoff (Lewy Body Dementia: Information for Patients, Families, and Professionals, 2015).

Cause and Types

While we do not know specific causes of LBD, there are many features associated with it, such as Lewy Bodies. Lewy Bodies are abnormal buildups of the protein alpha-synuclein. Alpha-synuclein is usually abundant throughout the brain, found at presynaptic terminals. While scientists do not know its exact function, we do know that alpha-synuclein plays a role in neural communication (Lewy Body Dementia: Information for Patients, Families, and Professionals, 2015). Alpha synuclein buildups impede the function of, and later kill, the affected neuron- generally cholinergic...
or dopaminergic. Acetylcholine is important for memory and learning, and dopamine is heavily tied to mood, movement, sleep, cognition, and behavior. The primary brain region affected by Lewy Bodies is the substantia nigra in the midbrain, although other brain regions are affected, especially the cortex, limbic system, hippocampus, and brainstem (Lewy Body Dementia: Information for Patients, Families, and Professionals, 2015).

As aforementioned, there are two classifications of Lewy Body Syndrome: Dementia with Lewy Bodies, and Parkinson’s Disease Dementia. DLB starts off almost identical to Alzheimer’s, with patients experiencing declines in thinking and memory problems. However, over time, various symptoms arise which differentiate Dementia with Lewy Bodies from Alzheimer’s Disease. The primary difference is parkinsonism, or movement conditions similar to those experiences with Parkinson’s.

The other type of LBD is Parkinson’s Disease Dementia. Parkinson’s Disease Dementia is an aspect of Parkinson’s that develops as a dementia, alongside the usual movement disabilities. Not all Parkinson’s patients will develop Parkinson’s Disease Dementia, but it is considered that getting Parkinson’s later in life increases your chances of contracting PDD as well.

**Symptoms**

Lewy Body Dementia primarily affects cognitive function. LBD is classified as a dementia, and so patients exhibit dementia-like symptoms. A dementia is classified as “a decline in mental ability severe enough to interfere with daily life” (“What is Dementia?,” Alzheimer’s Association). Dementia can result in confusion as well as problems with multitasking, reasoning, performing basic tasks, spatial abilities, coordination. Memory loss generally arises later in LBD, while in Alzheimer’s memory loss is present in early stages (Lewy Body Dementia: Information for Patients, Families, and Professionals, 2015).

As stated above, parkinsonian movement disorders are also prevalent among LBD patients, especially amongst Parkinson’s Disease Dementia patients. These include difficulty of movement, tremors, and rigidity. Other differentiating symptoms can be REM sleep disorders, and hallucinations. Patients of Dementia with Lewy Bodies can also acquire parkinsonian symptoms later in life, albeit less often than PDD patients (Lewy Body Dementia: Information for Patients, Families, and Professionals, 2015).

In addition to cognitive and movement impediments, there are several other major symptoms of Lewy Body Dementias. Sleep disorders are prevalent among LBD sufferers, primarily
REM disorders, but also insomnia or excessive sleepiness. Most of these sleep symptoms set in early, before LBD diagnosis (Lewy Body Dementia: Information for Patients, Families, and Professionals, 2015).

Mood symptoms can also be common among LBD patients. Depression and paranoia, both of which afflicted Robin Williams, are common, as well as anxiety, agitations, or delusions. Hallucinations are also rare, but present (Lewy Body Dementia: Information for Patients, Families, and Professionals, 2015).

Lewy Body Dementia is a harsh, brutal neurodegenerative disease that affects millions of people. While we do not currently have ways of curing LBD, scientists will continue into the future to seek better treatment options, and, ultimately, total prevention and eradication procedures for LBD, as well as for other neurodegenerative disorders.

References


Ronald Reagan and Alzheimer’s Disease

Jack Ross-Pilkington

Introduction

The study of society and the study of the brain are two deeply interesting and complementary fields. Both are diverse and exciting, and both intersect with everyday life. Just as the human brain influences human society, society can influence the brain. Therefore, in order to understand them both, it is important to understand where they connect. In this column, we will investigate the intersections of neuroscience and politics, history, and even pop culture. In addition, this column will ideally make the sometimes dense and abstract field of neuroscience more relatable.

Taking office at almost 70 years old, Ronald Wilson Reagan was the oldest president in US history (Ronald Reagan, 1). He had won a landslide election: 44 states voted for him (History.com Staff, 1); a record-level win that would soon be surpassed in his re-election campaign, when he won every state but Minnesota (History.com Staff, 1). He campaigned on the idea that he would restore “the great, confident roar of American progress and growth and optimism.” (Ronald Reagan, 1). Branding himself as a fierce conservative, one of his most famous quotes was “The most terrifying words in the English language are: I’m from the government and I’m here to help.” (White House, 1). He was a former actor and governor of California, and came to office during a very trying time in the nation’s history (History.com Staff, 1). The economy was stagnating, and the country was in the midst of the final days of the Cold War (Ronald Reagan, 1). In order to solve these problems, Reagan cut taxes and social programs, and increased the military budget (Ronald Reagan, 1). While his critics say that this led to an increase in the budget deficit and favored wealthier Americans, Reagan’s policies arguably led to economic prosperity and the collapse of the Soviet Union (History.com Staff, 1). In addition, Reagan survived an assassination attempt, which increased his popularity (History.com Staff, 1). All in all, Reagan’s presidency was a very important and memorable one.

However, a few years after Reagan left office, he released a letter that shocked the world. He announced publicly that he had Alzheimer’s disease (Stem Cell Pioneer, 1). The
letter was very emotional and eloquently worded. Most of the focus was not on him, but on his wife, Nancy. As he said in the letter:

“Unfortunately, as Alzheimer’s disease progresses, the family often bears a heavy burden. I only wish there was some way I could spare Nancy from this painful experience. When the time comes, I am confident that with your help she will face it with faith and courage.” (Stem Cell Pioneer, i). Sadly, the disease did indeed progress—on June 5, 2004, Reagan died in Bel-Air, California (History.com Staff, i).

Reagan’s struggle with the disease comes with a hint of controversy. Even though he was diagnosed with Alzheimer’s many years after he left office, some say that Reagan began showing symptoms during his presidency (Altman, i). In fact, even before he took office, some of his critics accused him of being too old to serve (Altman, i). In response, Reagan said he would resign if he believed he was suffering from dementia (Altman, i). While he never did resign, researchers at Arizona State University have since analyzed his speeches and detected subtle changes in his speaking patterns that are tied to Alzheimer’s (Altman, i). For example, Reagan’s use of repetitive words, and substituting general words like “thing” for specific nouns increased toward the end of his presidency, compared with its start. This does not prove that Reagan was unfit to lead. Instead, these findings could possibly be used to detect the onset of Alzheimer’s earlier, which in turn could lead to more effective treatment (Altman, i).

Reagan’s death was a tragic occasion, but it led to an increase in advocacy for Alzheimer’s research. Perhaps the staunchest advocate for research was his wife, Nancy (Stem Cell Pioneer, i). According to Dr. Hans Keirstead, an Alzheimer’s researcher who specializes in the use of stem cells,

“Nancy Reagan took private conversations and threw them out into the public sphere, and in so doing created a tremendous awareness for Alzheimer’s disease that she then leveraged politically...Nancy Reagan was really the first that stepped forward and put clarity to that, and brought the attention of the president of the United States and all the communication that surrounds that position to bear on Alzheimer’s awareness.” (NPR, i).

In addition to raising awareness of the disease, she also supported embryonic stem cell research, which was generally unpopular among conservatives (Gallup, i).

Reagan’s suffering and death was important because it showed how humbling Alzheimer’s disease can be. It strikes all different types of people. It doesn’t matter how wealthy you are, or your accomplishments in life. Whether you are the president or an ordinary citizen, you still have a chance of getting Alzheimer’s, and losing who you are, and those you love through it. Ultimately, that is why it is so imperative to research a cure. A disease that reduces the mind to a shadow of what it once was should be treated as the ultimate enemy.
References


Deep brain stimulation, more commonly referred to by its acronym DBS, is a beacon of hope for patients suffering from Parkinson’s disease. Only approved by the FDA in 2002, this new technology utilizes electrical signals to regulate abnormal neuronal firing, helping alleviate motor symptoms of Parkinson’s.

**Developments Leading to DBS**

(A history of deep brain stimulation: Technological innovation and the role of clinical assessment tools, 2013)
**Procedure**

The surgeon places the patient in a specialized frame used to keep the patient still during the procedure, also known as a halo. MRI and CT scans are used to locate the target brain structure, in reference to the placement of the halo, and form an internal map, allowing the surgeon to make accurate and precise incisions (“Deep Brain Stimulation: Medline Plus Medical Encyclopedia, 2015). The patient is given an IV sedative and the surgical field is numbed with local anesthetic. The surgeon drills holes on each side of skull in order to mount an apparatus that will guide the electrodes (“Deep Brain Stimulation for Parkinson’s Disease Information Page”, 2013). The patient is then allowed to wake fully before the microelectrodes are advanced to the planned target in the brain. During this time neurological activity is transformed into a chirping sound, which allows the surgical team to monitor different regions of the brain. The patient is asked to move, talk, and report symptoms to ensure that damage does not occur during this time. After the target is located, the DBS electrode is inserted and tested. Later on, while the patient is under general anesthesia, a pulse generator is implanted in the collarbone. This is connected to the leads, coiled wire insulated in polyurethane with four platinum iridium electrodes, and is placed in one or two different nuclei of the brain, by a thin wire which is placed under the skin and threaded along the neck, behind the ears. The final step is to turn on and program the DBS (“Deep Brain Stimulation for Parkinson’s Disease Information Page”, 2013).

**How Does It Work?**

Parkinson’s disease results from the death of neurons in the substantia nigra, which is a center for dopaminergic neurons. Due to diminished amounts of dopamine, the activity of basal ganglia neurons become abnormal, resulting in the symptoms characteristic of Parkinson’s disease (“Parkinsonism,” 2015). DBS works by using electricity to regulate neuronal firing, thereby alleviating symptoms. The specific process of how DBS regulates neuronal firing is not completely known, but some reputable theories exist. One postulates that the electric signals from DBS activate inhibitory interneurons, resulting in a suppression of hyperactive neuronal activity in the area the device is implanted. For Parkinson’s disease, the device is usually implanted in thalamus, subthalamic nucleus, or the globus pallidus (“NINDS Deep Brain Stimulation for Parkinson’s Disease Information Page,” 2015). Some scientists theorize that DBS interferes with the depolarization of certain neurons, which is an essential step in the process of action potentials (Okun et al., 2016)--more information on this in our Basics of Neuroscience 2 article. Despite the uncertainty surrounding the mechanisms of DBS, it is apparent that DBS is an effective treatment option for patients with Parkinson’s disease.

**Post-Surgery and Lasting Effects**

After surgery, the doctor performs either a CT or MRI scan to confirm that the electrodes are in the correct location and to check for intracranial bleeding. Patients typically only stay in the hospital for one or two nights following surgery. They stay in the hospital until postoperative pain can be managed using oral medications, and they can eat, drink, and walk. Even when patients are sent home, they are still in the recovery process and should take certain precautions. Medical professionals advise the patient to have someone at home to assist them with daily activities. Patients should not touch the wound or get it wet before it has healed. Roughly a month after
surgery, an appointment is made to turn the device on, beginning DBS. In the months following surgery, patients have frequent appointments in order to adjust DBS intensity and find an effective balance between DBS and medication (“What is the recovery period like after DBS surgery?,” 2016).

The effects of DBS are generally positive. DBS has been shown to be effective in reducing the motor symptoms of Parkinson’s disease; however, it may exacerbate cognitive symptoms such as dementia. Levodopa, a common medication used in treating Parkinson’s, can result in a side effect known as dyskinesia, which is characterized by involuntary movements. DBS may be useful in suppressing this side effect (“NINDS Deep Brain Stimulation for Parkinson’s Disease Information Page,” 2015).

Other Uses
Deep Brain Stimulation may also be used in the treatment of the following:


- Tourettes syndrome, with surgery focusing on the internal Globus pallidus (GP) and the centromedian-parafasicular nuclei of the thalamus (“Deep Brain Stimulation for Tourette’s syndrome”, 2015).


- Severe Obesity, surgery focusing on the lateral hypothalamus, the ventromedial hypothalamus, and the nucleus accumbens (“Obesity and Deep Brain Stimulation, 2015).


References


Research Methods: Model Organisms in Neuroscience

Jacob Umans and Meenu Johnkutty

In the previous issue of the YNCA Journal, we discussed how neuroscientists have studied human patients to learn about the brain. Despite the progress that can be made in human studies, such studies are very limited in scope due to the moral issues involved in human experimentation. Due to these ethical barriers, scientists often turn to animals to perform research. In all fields of biology, animals commonly used in research, or “model organisms”, are critical to experimentation. For this reason, the research team decided to place an emphasis on understanding the importance of model organisms in neuroscience in this edition of the YNCA Journal.

Caenorhabditis Elegans

*Caenorhabditis Elegans*, more commonly known by the abbreviated name *C. Elegans*, is perhaps the simplest model organism in neuroscience. Since Dr. Sydney Brenner proposed its use as a model organism in 1963, *C. Elegans* has vastly aided scientific progress. It is a one millimeter long nematode that can feed on bacteria such as *E. Coli* in laboratory settings.

There are many advantages to using *C. Elegans* as a model organism. First, *C. Elegans* has a relatively short life cycle (about 2-3 weeks). Owing to this, researchers can analyze several generations of *C. Elegans* in a relatively short period of time. Furthermore, its relative simplicity (with hermaphrodites—which make up the majority of *C. Elegans*—having only 302 neurons) has allowed scientists to make a complete map of its nervous system, allowing for incredibly precise studies of its anatomy ("A short history," n.d.). Though its nervous system is small, *C. Elegans* does exhibit complex behaviors, such as locomotion and chemotaxis, which can be analyzed in depth by researchers. Furthermore, analyzing neural circuits is simple in *C. Elegans* models (when compared to studying circuits in other organisms), as individual neurons can be experimentally ablated with lasers.
The same simplicity that makes *C. Elegans* such a good model organism is also its primary limitation. As it lacks a brain, *C. Elegans* cannot be used in many studies analyzing complex cognitive phenomena.

*Drosophila Melanogaster*

The fruit fly *Drosophila Melanogaster* is another very well-known model organism in the sciences. Its genetic amenability, or its conduciveness to testing, has made it a valuable model for Alzheimer’s Disease and Parkinson’s - two genetically-linked neurodegenerative disorders. Alongside its use for gene research, studies investigating proteopathies (diseases resulting from the misfolding of proteins) such as Alzheimer’s Disease and Parkinson’s show *Drosophila Melanogaster*’s invaluability in the investigation of chemical compounds which can prevent or ameliorate disease. Furthermore, its relatively short lifespan allows for relatively fast analysis of many generations. *Drosophila* is also cheap and easy to maintain in the laboratory. Its offspring is genetically identical and its sophisticated brain and associated behaviors make the *Drosophila* a rather commendable research model (Hirth, 2010).

Thomas Hunt Morgan popularized the use of the fruit fly after having early successes with his research and experiments with chromosomes and heredity. After teaching at Bryn Mawr for over 13 years, he established his famous “Fly Room” at Columbia University. Morgan’s early chromosomal experiments with the fruit fly confirmed the chromosomal theory of inheritance, which states that a) genes are located on chromosomes and b) some genes are linked. The ease at which his genetic experiments were conducted make them classics for undergraduate genetics education even today. In his honor, the map unit (a unit measuring genetic distance) was given an alternate name: the centimorgan (“Thomas Hunt Morgan: The Fruit Fly Scientist,” n.d.).

The contributions of *Drosophila Melanogaster* to the field of genetics and neuroscience are great and many. From its use in the investigation of proteopathies, such as Alzheimer’s and Parkinson’s, to its predominance in Morgan’s early genetic experiments, the fruit fly has established itself as a crucial ally in neuroscience research.

*Aplysia Californica*

With just 20,000 neurons—compared to the billions of neurons within the average human—the sea slug *Aplysia Californica*’s simple nervous system allows it be a prime animal model for the study of learning and memory. Its rather large neurons range from 0.1 mm to 1 mm in diameter (*The Broad Institute*). The *Aplysia Californica* is also commonly used in the study of defense mechanisms.
Similar to withdrawing one’s hand from a hot stove, the sea slug withdraws its sensitive appendages, the siphon and the gill, when touched. *Aplysia* also exhibit a form of learning known as **habituation**. Similar to a goldfish becoming desensitized to a child tapping on its fishbowl, the Aplysia shows a reduced response to repeated stimuli of the same degree (“The Machinery of Memory”).

A neuroscientist known for his research with the *Aplysia Californica* is Eric Kandel. Some of his most famous work focuses on Long Term Potentiation (LTP), or the cellular mechanism by which memories form. Kandel chose to focus on the hippocampus, a structure in the brain responsible for the storage of memories, and he needed a simpler organism with which he could study at the cellular level. Since the *Aplysia* contained the simplified nervous system and rather large neurons, Kandel, much to the surprise of his colleagues who preferred to use vertebrates, chose the sea slug as his model for study. Today, Kandel continues to research the molecular mechanisms behind different types of memory with the aid of the *Aplysia*. One recent discovery of his is that one isoform of the protein cytoplasmic polyadenylation element–binding protein (CPEB) “regulates this synaptic protein synthesis in an activity-dependent manner” (Cell and Molecular Biological Studies of Memory Storage, n.d., Para. 3). In other words, CPEB is a molecule critical to synaptic changes in response to neuronal activity (The machinery of memory, 2010).

**Danio Rerio**

Native to Southeast Asia, the *Danio Rerio*, or zebrafish, is a popular model organism in biomedical research. Like *Drosophila Melanogaster*, *Danio Rerio* is genetically amenable and cheap. The zebrafish responds to behaviors tested in the lab quite well, such as aggression, novelty exploration, and anxiety responses. But what makes Danio Rerio quite exceptional is the transparency of its larva (Stewart, Braubach, Spitbergen, Gerlai & Kalueff, 2014, p. 264).

Joseph Fetcho, a neurobiologist at Cornell University, pioneered the use of brain-circuit research in fish with the aid of the *Danio Rerio*. After getting frustrated with goldfish brains, Fetcho made the switch to zebrafish after noticing the ease at which its embryonic cells divided over a short period of time to form organs and limbs. Fetcho, in his first paper, used a green calcium-sensitive dye to track the activity of motor neurons during a predator-escape reflex. Using another approach with the *Danio Rerio*, Florian Engert and his postdoctoral students utilized a two photon microscope and virtual environments in order to study the circuitry of the zebrafish. Compared to the use of rodents or flies, during which the scientists must cut through animals’ heads to expose the parts of the brain they desire, the zebrafish can be manipulated in a virtual environment in which its movements can...
be tracked using a computer. In addition, its neurons can be analyzed using a two-photon microscope.

Though many researchers are still hesitant to use the zebrafish in their studies due to its complex behaviors and lack of communication, its contributions to the fields of developmental and circuitry research cannot be discounted (Hughes, 2013).

Mus Musculus

Mus Musculus, or the house mouse, is another common organism used in neuroscience. Analysis of congenic mice, or strains that differ at only one genetic locus, is especially valuable to research—this allows researchers to focus on individual genes when studying animals. As it is a mammal, this organism shares many more traits with humans than the other organisms on this list; thus, it is a very useful model in studying the pathophysiology of disease because “evolutionary conservation of large linkage groups within the mouse and human genomes with respect to the nature of the encoded genes and their linear order along chromosomes has been a great asset in the identification of potentially corresponding homologous mutations and disease genes” (Nguyen & Xu, 2008, p. 56). In other words, mouse and human genetics are similar enough that researchers can extrapolate their discoveries on the mouse model to human research. Obtaining mouse embryonic stem cells and transforming them with specific mutations allows researchers to conduct functional research on these genes and elucidate both normal brain function and the effects of these mutations on the pathology of disease, among other things. Alternatively, transposons can be used to create and analyze mutations.

Mus Musculus serves as a key model organism in Parkinson’s disease: the use of the MPTP neurotoxin allows researchers to simulate and study the disease outside of human patients. MPTP causes damage to dopaminergic neurons in the substantia nigra; in doing so, it imitates the normal neurodegenerative effect of Parkinson’s disease. Even the topographic characteristics of the neurodegeneration, both in the striatum (caudate nucleus, putamen) and midbrain mimics the decline in humans. One weakness to this specific model is that Parkinson’s is normally progressive, whereas MPTP application does not replicate this (Meredith & Rademacher, 2012).

Questions to Consider:
What makes one model organism better than another in a particular study?
How can researchers find a balance between similarity to humans and ease of manipulation?
YNCA Researchers

These members of the YNCA are conducting research with the model organisms described in this article. In parenthesis are the topics they are studying. Feel free to email ynca.info@gmail.com or comment on our forum to ask them questions about their research.

C. Elegans: Jacob Umans (relationship between chemosensation and lifespan)
D. Melanogaster: Kyle Ryan (Genomic drug targets found through new pain and chronic pain pathways.)

References


Research Summary: Amyloid-β peptide protects against microbial infection in mouse and worm models of Alzheimer’s disease

Jacob Umans and Meenu Johnkutty

As discussed in the disease section of the YNCA Journal, the peptide Amyloid Beta (Aβ) is highly linked to the pathophysiology of Alzheimer’s disease. Plaques form when Aβ clumps together in the synapses of neurons, blocking cell-to-cell communication. Though always viewed in a rather unfavorable light, the study featured in this issue of the YNCA Journal adds new insight into the role of this peptide in Alzheimer’s disease. The research conducted by this Harvard-based team suggests that Aβ, rather than being purely destructive, also acts as an antimicrobial peptide (AMP). Furthermore, the team suggests that “infectious or sterile inflammatory stimuli may drive amyloidosis” (Kumar et al., 2016, p. 1). In other words, the research team posits that infections (by bacteria or fungi, for example) may contribute to the pathology of Alzheimer’s disease.

When conducting this study, the research team analyzed data from experiments on mice, C. Elegans and in vitro studies of cell cultures. The team analyzed the transgenic (meaning that some genes came from another organism—humans in this case) mouse model of Alzheimer’s disease, 5XFAD, in its resistance to infection by S. Typhimurium bacteria. After injecting S. Typhimurium into the brains of both wild-type and 5XFAD mice (and injecting controls with heat-killed bacteria), the team found that “Survival of Aβ-expressing 5XFAD mice was significantly increased compared to that of nontransgenic littermates (P = 0.009)” (Kumar et al., p. 2, 2016). These results suggest that Aβ provides mice with increased resistance to infection. The graph on the left also demonstrates a statistically different concentration of bacteria in the brains of mice with or without the transgene after a day of exposure to the bacteria. The bacteria were injected into the
right hemisphere, explaining the difference in brain bacterial load between the different hemispheres.

Continuing to analyze the specific effect of Amyloid-β on pathogens, the research team also studied the response of *C. Elegans* to infection by *Candida Albicans* fungi. The team used transgenic strains, one of which expressed one isoform of the human Aβ peptide (Aβ42) and green fluorescent protein (GFP). The only transgene expressed in the control strain was GFP. In this portion of the experiment, the researchers found significantly reduced mortality in *C. Elegans* expressing the transgenic Aβ.

In this study, the researchers also analyzed both human brain neuroglioma (H4) and Chinese hamster ovary (CHO) cell cultures. They found that 28 hours after infection, cells overexpressing Aβ showed significantly higher survival rates than those not doing so. Furthermore, in analyzing these cells, the researchers found that the concentrations of Aβ within the culture media were approximately one hundred times lower than the minimal inhibitory concentration for Aβ to express fungicidal properties; this finding is consistent with analysis of other AMPs, such as LL-37, which show activity below this threshold. Analysis of agglutination of *Candida* cells (or the aggregation of cells as a result of AMP activity), which gives LL-37 its antimicrobial properties, showed a statistically significant difference between Aβ-overexpressing cell cultures and control cultures (see graph on left). Aβ acts in a manner similar to LL-37, suggesting that the two proteins may also share a common antimicrobial function. According to the figure cultures of both H4 cells (expressing two different isoforms of the Aβ peptide) and CHO cells which overexpress the Aβ peptide (CHO-CAB) revealed *Candida* agglutination levels significantly higher than control cultures. In this analysis, the researchers also found that oligomers (short polymers of the Aβ peptide, of approximately 2-30 monomeric units) were found to have a key role in the antimicrobial properties of Aβ. A central role for oligomers in Aβ protective antimicrobial activities is important because in prevailing amyloidosis models these species are viewed as intrinsically abnormal and the cause of neurodegeneration in AD.

In addition to this, the researchers characterized the specific aspect of the Aβ peptide implicated in its antimicrobial properties. Both LL-37 and Aβ share a heparin binding domain, which according to the study allows the Aβ peptide to bind carbohydrates attached to the cell wall of
pathogens. As shown in the graphs on the left, treatment with glucan and mannan (two sugars that bind to the heparin domain of Aβ, inhibiting its antimicrobial activity) both increase the percentage of yeast adhesion and decrease yeast agglutination. From these results, the researchers found more evidence supporting the idea that Aβ uses a heparin-binding domain to target microbes. Further research into the mechanisms of action of Aβ suggest that fibrils of Aβ mediate the agglutination observed in cell cultures and animal models.

Aβ’s antimicrobial properties are consistent with a potential role it can play in vivo. Expression of Aβ in cell culture, nematode, and mouse models was linked to increased host survival. On the other hand, low expression of Aβ resulted in a greater mortality rate among these models. However, the same properties exhibited by Aβ are also related to its pathophysiology, or its physiological processes associated with the formation of disease. For example, LL-37 is necessary for normal immune function and low levels lead to lethal infection. Conversely, higher levels of LL-37 is cytotoxic to host cells. Thus, if AMPS are not regulated, disease can result.

The key to making advances in the study of Alzheimer’s Disease lies in further investigation of the properties of Aβ. This study sheds a new perspective on the characteristics of this protein and the alternate forms it can take, both as an antimicrobial peptide and a component of amyloid plaques in Alzheimer’s patients. Uncovering other characteristics of Aβ will allow for a better understanding of the correlation between the antimicrobial properties of the peptide and the pathology of Alzheimer’s disease. Hopefully, with further research, the properties of Aβ can be elucidated in order to open up avenues for future therapeutic intervention in Alzheimer’s disease patients.
References

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INTERVIEW

Parkinson’s Disease: An Interview

William Ellsworth

Rachel Cliburn and Carlie Hoffman are Neuroscience PhD students at Emory University. Rachel and Carlie study Parkinson’s disease, specifically focusing on the role of vesicular proteins. I interviewed Rachel and Carlie, asking about their research, the life of a PhD student, and Parkinson’s Disease.

William: What aspect of Parkinson's are you studying?

Rachel: I study vesicle dynamics...how dopamine and other similar neurotransmitters are packaged into packets so that they’re ready for release.

Carlie: My research focuses on some of the molecular underpinnings of Parkinson’s disease, specifically the role of vesicle loading and release on the risk of getting Parkinson’s disease.

William: Describe a typical day of your research.

Rachel: Ha! My days vary widely based on what project I’m working on. For a while, I would go and do behavioral experiments alone in the mouse facility all day, every day. I went through a lot of books on tape during those months! During a time when I was trying to collect more neurochemical data, I spent every day using a specially made recording device to measure dopamine release from brain slices. That was a lot more fun, but I spent half the time troubleshooting the equipment! Lately I’ve been getting writing done while also doing more basic immunochemical methods. Writing is mentally exhausting (for me), so it pairs perfectly with the banal, repetitive work of immunochemistry.

Carlie: A lot of my work is in cells, so a typical day involves a lot of time in the cell culture hood. I perform experiments in the hood (usually treating cells with chemicals and seeing how they affect vesicle loading or altering protein expression in the cells and seeing how that affects vesicle loading) and working on cell maintenance (splitting cells- moving them from one plate to another, and feeding the cells with fresh media).

W: What aspects of Parkinson's research show the most promise for future developments?

R: I may be biased towards our lab’s area of research, but I truly think the most promising future of health, including Parkinson's, is in prevention. Understanding how and why people develop disease is a powerful tool for preventing it from ever happening. Early
biomarkers of Parkinson’s are an interesting avenue for being able to stave off the progress of the disease before it becomes a major burden.

C: I am not familiar with the entire scope of Parkinson’s research, but I think trying to determine the causes of Parkinson’s has the most promise for future developments. If we can figure out what is going wrong, then that will give us new targets for treatment.

W: How do you think that your work can translate into tangible gains for human Parkinson’s patients?

R: Working with model systems, such as mice, allow us as researchers to gain incomparably more understanding of the biological mechanisms underlying human disease. We owe a huge amount of our current medical knowledge to lab animals. In mice, we can directly test hypothesis...impossible to achieve in humans.

C: I do not work too much with mouse models, but a lot of my cell work is with human cell lines, which translates directly into human Parkinson’s patients. The proteins that I am studying are in people and mice alike, so figuring out how these proteins work (using both mice and cell lines) will also help us figure out how the proteins work in humans.

W: What are some common misconceptions about Parkinson’s?

R: That it’s a purely motor disease. Parkinson’s disease also affects sleep, digestion, mood, and, eventually, cognition.

C: I think a common misconception about Parkinson’s is that by the time a patient shows symptoms, the person has already had extensive and irreversible brain damage. So our treatments will not be able to cure Parkinson’s, just help make the symptoms more manageable.

W: What is an interesting fact about Parkinson’s that few people know?

R: Most people develop Parkinson’s from a combination of environmental and genetic factors. However, it is possible to develop full-blown Parkinson’s disease following an injection of a particular neurotoxin, MPTP. This was discovered in the 80’s after a group of young opioid addicts in southern California injected themselves with a batch of drug contaminated with MPTP. They were soon hospitalized with severe symptoms of advanced Parkinson’s disease. What has been a sad story for these “frozen addicts”, as they came to be called, was a boon for research: MPTP is now used to model Parkinson’s disease and has pushed forward the field of PD research by leaps and bounds.

C: There are a lot of side effects other than tremors and difficulty walking, such as sleep problems and gastrointestinal problems.
A new neuroscience study entitled “A Novel Protein Target for Aging-Associated Neuronal Degeneration” led to a flurry of reports in the news. These reports had such titles as “Are Proteins Involved in Neuronal Degeneration? IDK, I didn’t read the study,” “Can Books in Department Stores Revolutionize Science? Target Novel Shows Promising Results,” and “New Study Implies that all Diseases will be Eradicated by End of 2016.”

The media has a long history of misunderstandings in the realm of science, including a recent incident in which a new mouse model led to a plethora of headlines regarding animal cruelty at the Victoria’s Secret fashion show. Another model organism noted in the article to have been seen at the show, the fruit fly *Drosophila Melanogaster*, weighed in at less than a gram, leading the media to criticize unrealistic beauty standards in the modeling industry.

Other examples of the media’s misinterpretations of science include:

- “A New DNA Mutation in the Domesticated Chicken Provides for More Sustainable Meat Production” was reported as “Is there DNA in Your Meat? The Shocking Truth that Food Corporations Don’t Want you to Know”
- “The Potential of Gene Therapy in Medicine” was reported as “New Study Finds that Wearing Denim Pants Can Cure Disease”
- “New PET Scan Analysis Algorithm shows Potential in Diagnosing Psychiatric Disorders” was reported as ”Putting your Dog in Brain Scanners could Reveal Mental Illnesses”
A recent survey of scientists found that with regards to the issue of media miscommunication of scientific topics, 41% “sees this as a problem”, 2% “sees this as a non-issue”, and 57% “would like to go get cupcakes.” From this survey, the media reported that over 99% of scientists do not believe media misinterpretation of research to be a “significant problem”.

Media corporations say that in response to this growing problem, significant action must be taken. They believe that a “fair and just solution” to this “minor issue” is a “large CEO pay raise.”

***Disclaimer: This article is intended purely as satire. As such, any resemblance to existing persons living or dead, events, or locations, is purely coincidental. Any references to well-known celebrities, locations, events, or corporate entities is intended purely as fiction, and all statements made in this article are intended to be interpreted as such; no statement made should be interpreted as fact. The YNCA Journal holds high standards of quality and respect. Thus, should any entity want us to change the names used in our article, the YNCA editing staff will promptly rectify this problem. Please contact YNCA.info@gmail.com with any queries regarding the aforementioned service. Furthermore, we at the YNCA realize that neurodegenerative disorders are far from a laughing matter and do not in any way intend to treat them as such--our sole aim in this article is to make light of the poor relationship between certain media reports and scientific truth. We understand that many news outlets focus on accurate reporting in the sciences, and do not mean to criticize all outlets but instead call attention to the problems arising from when reports come out inaccurate. The YNCA extends a sincere and heartfelt apology to anyone who may find this article offensive. The YNCA does not intend to give any medical advice, and no statement in this article should be interpreted as such.

*The Rabies vaccines currently available are, to the best of our knowledge at the YNCA, effective. Rabies can be prevented after exposure to infected animals with a vaccine, but it is important to contact a licensed doctor if exposed.
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