First Effective Treatment for Transthyretin Amyloidosis *(continued from page 1)*

hormone and retinol elsewhere in the body. This protein is usually bound in a tetramer form that dissociates into four individual pieces. In some people, these pieces misfold into a square-like shape that agglomerates, leading to amyloid deposits.

Although a subset of patients can be cured with liver transplants, and a drug that could slow the disease somewhat was approved in Europe, there were no truly effective treatments for the majority of patients with this disease in the United States.

"We'd watch patients who rode horses or go square dancing or do needlework lose the ability to do those things," says Johns Hopkins neurology nurse practitioner **Kathleen Burks**. "This disease doesn't cause any cognitive decline, so these patients were just trapped in bodies that were turning on them."

However, several years ago, researchers devised a couple new approaches to this disease. Both centered on knocking down the levels of this protein using either an antisense oligonucleotide or RNA interference (RNAi). Polydefkis says that he, Burks, and their colleagues at Johns Hopkins leaped at the opportunity for Johns Hopkins patients to join these trials. As an aid to track patients' prognoses, Polydefkis' lab developed a protocol to test for amyloid using punch skin biopsies, a method that Polydefkis pioneered years ago to diagnose and follow various forms of neuropathy.

The results from both trials were overwhelmingly positive, says Burks. Although the first part of each trial was double-blind, it was often clear who was taking the oligonucleotide (inotersen) or the RNAi drug (patisiran) and who was taking the placebo: the disease process of those taking either of these drugs stopped progressing. Some of those on the RNAi drug even showed small degrees of improvement.

"To stay the same or improve in this disease is unheard of," Polydefkis says.

Patisiran was recently FDA approved, and inotersen is expected to follow shortly.

"This is a game-changer for a disease we've been completely defenseless against," Polydefkis says. "Now, when I have to deliver this diagnosis, I can be optimistic with patients for the first time." ■

To learn more, call 410-614-1522

"THIS IS A GAME-CHANGER FOR A DISEASE WE'VE BEEN COMPLETELY DEFENSELESS AGAINST."

—MICHAEL POLYDEFKIS

NeuroLogic

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Baltimore, Maryland 21231

This newsletter is published for the Departments of Neurology and Neurosurgery by Johns Hopkins Medicine Marketing and Communications

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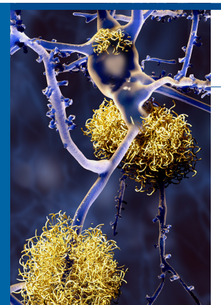
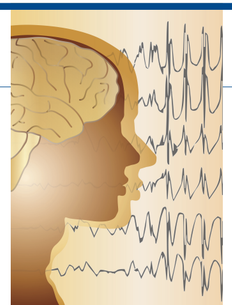
WINTER 2019

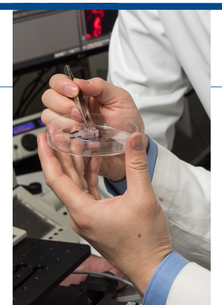
NEWS FROM THE JOHNS HOPKINS DEPARTMENTS OF NEUROLOGY AND NEUROSURGERY

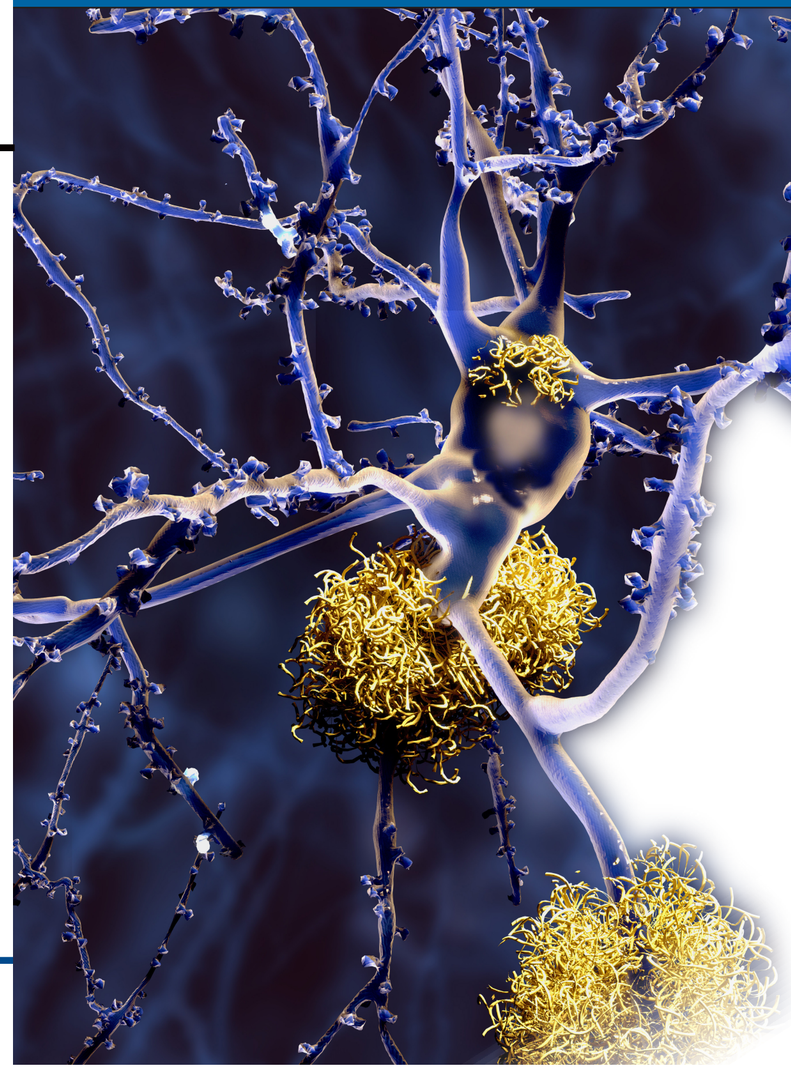
JOHNS HOPKINS MEDICINE

Inside









Although a subset of patients can be cured with liver transplants, and a drug that could slow the disease somewhat was approved in Europe, there were no truly effective treatments for the majority of patients with this disease in the United States. Image shows 3D representation of abnormal amyloid buildup in nerves.

First Effective Treatment for Transthyretin Amyloidosis

Johns Hopkins research into rare disease leads to approval of the first drug that can halt its progression.

Over the past two decades, Johns Hopkins neurologist **Michael Polydefkis** has cared for hundreds of patients with transthyretin (TTR) amyloidosis. This inherited disease, affecting an estimated one in 100,000 people in the U.S., causes the abnormal proteinacious deposits known as amyloid to accumulate in the nerves, heart and other locations—leading to neuropathy, heart failure and eventually death.

"It was a disease that I dreaded diagnosing in patients because I knew what they had in store," Polydefkis says.

Now, research conducted in Polydefkis' lab and elsewhere is providing new hope for patients, paving the way for drugs that have the potential to reverse this disease's progression for the first time.

Polydefkis explains that this disease stems from TTR, a protein produced mainly in the liver that ferries thyroid

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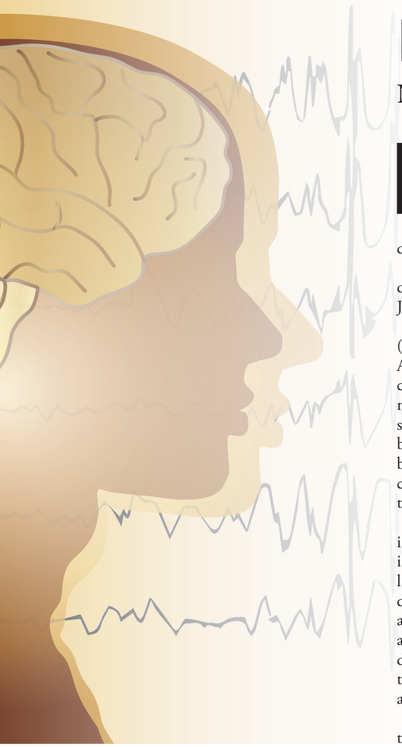


Epilepsy Late in Life

New study highlights risk factors for seizures after age 60

Epilepsy is often thought of as a disease that only arises in childhood. But that's a common misconception, says Johns Hopkins neurologist **Emily Johnson**.

Epilepsy has the highest incidence in old age, with each decade after 60 bringing even more new cases," she says.

While some of these diagnoses can be attributed to brain damage caused by stroke and neurodegenerative disease, Johnson explains, up to half of cases have no known cause.

To help shed light on what may lead to late-onset epilepsy (LOE), Johnson recently led a study using data from the Atherosclerosis Risk in Communities study, a prospective cohort study started in 1987 that's followed nearly 16,000 men and women recruited form one of four study centers scattered across the country when these volunteers were between 45 to 64 years old. Patients in this study have been examined in-person six times over the years and are contacted yearly by telephone to answer questions about their health.

Johnson and her colleagues collected the baseline health information from 10,420 of these individuals, which included both demographic factors such as age and race; lifestyle factors such as whether participants were exercisers, drinkers or smokers; and pre-existing health factors such as whether they had hypertension, diabetes, or carried the apolipoprotein E4 gene variant, a risk factor for Alzheimer's disease. They then used claims data to determine which of these individuals was eventually diagnosed with epilepsy after age 60 by December 2013.

Their findings show that a variety of factors appear to increase the risk of LOE, including having baseline hypertension, diabetes, stroke or dementia, or being a smoker. Having the apolipoprotein E4 gene variant also boosted LOE risk, even in patients who didn't have dementia.

Other factors seemed protective, such as higher levels of physical activity and moderate alcohol intake.

Although these findings don't point to a "smoking gun" for LOE's cause, she says, they suggest that it may be possible to modify some risk factors for this condition. Future studies might focus on whether making changes later in life, such as increasing physical activity, might ward off this disease—or even whether modifying risk factors in patients who are already diagnosed might affect seizure frequency.

Regardless of age, she adds, all adults who visit a neurologist for new seizures should receive a comprehensive workup with neuroimaging and an electroencephalogram to look for structural reasons and identify possible foci. This knowledge can help guide treatment decisions, such as choosing anticonvulsant medications. Older patients often have a higher risk for medication interactions simply because medication use rises with age. Doctors should also pay close attention to preventing falls, either from the epilepsy itself or from instability induced by medication, since they can be more consequential in older age.

"Our ultimate goal is to improve seizure control," Johnson says, "so patients can live their best life no matter old they are." ■

To refer a patient, call 410-955-9441

2 New Faculty Members Join the Department of Neurosurgery

Cameron McDougall, M.D.

Director of Endovascular Neurosurgery

Cameron McDougall has focused his entire career on the treatment of stroke and cerebrovascular disease and was one of the first neurosurgeons in the country to receive fellowship training in endovascular techniques.

He has been extensively involved in research to improve endovascular techniques, including being the principal investigator on large, randomized, international studies. He is a past president of the Society of NeuroInterventional Surgery and has published more than 200 papers in peer-reviewed journals, and his publications have been cited more than 14,000 times. He is certified in neurological surgery by the Royal College of Physicians and Surgeons as well as the American Board of Neurological Surgery.

To refer a patient, call 410-955-2438

Debraj Mukherjee, M.D., M.P.H.

Neurosurgeon

Debraj "Raj" Mukherjee's clinical focus is the treatment of patients with primary and metastatic brain lesions. His clinical work and research emphasize the development of individual treatment plans that optimize survival and quality of life in all patients.

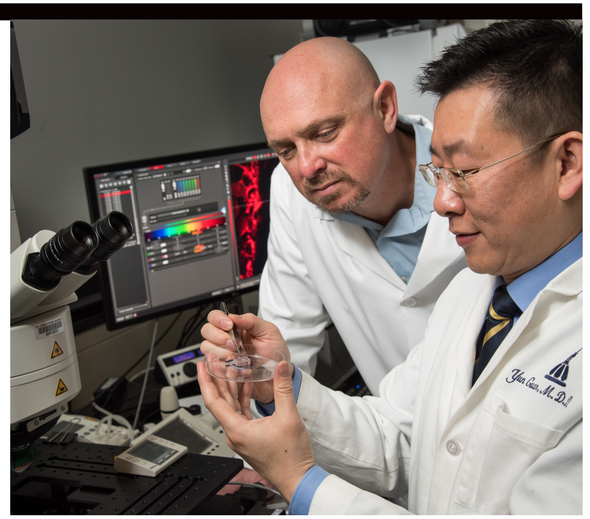
After receiving his medical degree from Dartmouth Medical School, he was recruited to Johns Hopkins, where he studied epidemiology, biostatistics and clinical design at the Johns Hopkins Bloomberg School of Public Health and served as co-director of the Neuro-Oncology Surgical Outcomes Laboratory in the Department of Neurosurgery.

Mukherjee completed an open and endoscopic skull base fellowship at the Center for Skull Base Surgery at University of Pittsburgh Medical Center. During this time, he continued his patient-centered research pursuits, developing a national registry for patients with brain tumors and creating a disease-specific quality of life instrument for patients with skull base meningiomas. His work was supported by the American Medical Association and National Cancer Institute.

To refer a patient, call 410-955-6406

Understanding Neuromodulation

New gift will help researchers study basic and applied science behind this pain-relieving approach.



Gene Fridman and Yun Guan recently showed that application of direct electrical current can block the activity of pain-promoting neurons.

For centuries, people have been applying stimuli aimed at nerves that don't ferry pain signals to affect the function of those that do, an effect known as neuromodulation. It's the concept behind transcutaneous electrical nerve stimulation (TENS) units or implanted spinal cord stimulators. And while many patients report that these interventions provide substantial relief, exactly how they work has been a mystery.

"Although there are a lot of educated guesses about how these devices work, the truth is that no one really knows," says **Michael Caterina**, director of the Neurosurgery Pain Research Institute at Johns Hopkins. "The science behind neuromodulation is limited."

A recent $3.5 million gift from the Theodore N. Lerner Family Foundation, establishing the Lerner Family Fund for Pain Research, will help researchers delve into the mechanisms behind this phenomenon—potentially leading to new ways to effectively apply this strategy to more patients. This endowed fund will be split between the Neurosurgery Pain Research Institute at Johns Hopkins and the laboratory of **Thomas Smith**, a specialist in palliative care at the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center.

The institute is using much of its part of the gift to fund basic research in the lab of **Yun Guan**, a researcher in Johns Hopkins' Departments of Anesthesiology and Critical Care Medicine and Neurosurgery and the institute's Director of Pain Neuromodulation Research. Guan's is working on developing animal models to study the fundamental mechanisms of neuromodulation at the cellular and molecular level. Developing an essential understanding of neuromodulation at the most basic level, explains Caterina, can help researchers make these pain-fighting modalities work better and longer for a broader swath of patients.

This work is already paying dividends, he adds. In a recently published study, Guan, along with **Gene Fridman** in Johns Hopkins' Departments of Biomedical Engineering and Electrical and Computer Engineering and their colleagues, showed that using direct current—rather than the alternating current of most neuromodulatory devices—disproportionately blocks the activity of neurons that promote pain, compared to those that quiet pain transmission. These findings could help researchers develop devices that target a range of different types of neurons or are tailored to specific types of pain.

"ALTHOUGH THERE ARE A LOT OF EDUCATED GUESSES ABOUT HOW THESE DEVICES WORK, THE TRUTH IS THAT NO ONE REALLY KNOWS."

—MICHAEL CATERINA

Guan and his colleagues are also using this gift to collaborate with Smith, much of whose work focuses on a patented approach called Scrambler or Calmare Therapy. This form of neuromodulation involves several electrodes being placed on different areas of the body with electrical signals running concurrently between them for a set time period—for example, 30-45 minutes a day for two weeks. The two labs are working together to better understand the basic mechanisms behind why this therapy is so successful for some patients when other interventions have failed.

A subset of the gift will fund a fellow who will not only make contributions toward fundamental neuromodulation work in Guan's lab, but also use this research to launch her or his own scientific career—an expansive use of these funds that will continue this important work in future generations of scientists, Caterina says.

"Traditional funding sources tend to focus on additive research based on previously established research concepts. But truly novel exploratory ideas, like understanding neuromodulation for cancer-related pain, are less likely to receive funding," says **Henry Brem**, director of Johns Hopkins' Department of Neurosurgery.

"These types of high-risk, high-yield programs benefit enormously from philanthropy. It's our hope that with these nontraditional funding methods, we will make discoveries that are not just evolutionary, but revolutionary." ■

Introducing the Johns Hopkins Doctor Referral App

This new app provides a simple way for health care providers to connect with and refer patients to physicians across Johns Hopkins Medicine in the departments of orthopaedics, surgery, neurosurgery and urology. Registration required.

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Correction

Johns Hopkins Departments of Neurology and Neurosurgery apologize for not recognizing the contributions made by Boston Children's Hospital in the article "An Innovation in Neurosurgical Simulation" which appeared in the winter 2018 issue of NeuroLogic. We regret this error.