

The Brain Prize 2021

INFORMATION PACK

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The breakthrough in treatment for migraine was 40 years in the making. The pioneering research journey has now led to award of The Brain Prize 2021.

Four decades of careful research have led to new treatments for migraine that are radically improving the lives of sufferers. An international group of four neuroscientists have discovered a key mechanism that causes migraine, a condition that affects more than a billion people and which according to the World Health Organisation is one of the most prevalent and disabling diseases.

Their research paved the way to the development of an entirely new class of migraine-specific drugs called CGRP antagonists which help provide long-term prevention of migraine attacks.

For this, the four neuroscientists are receiving the world's most prestigious prize for brain research - The Brain Prize - which is awarded annually by the Lundbeck Foundation.

This year The Brain Prize worth DKK 10 million (€1.3 million) is awarded to:

**Lars Edvinsson (Sweden) · Peter Goadsby (UK/USA)
Michael Moskowitz (USA) · Jes Olesen (Denmark)**

Professor Richard Morris, Chair of The Brain Prize Selection Committee, explains the reasoning behind the award:

“Migraine is one of the most common and disabling neurological conditions affecting humans. The work of the four recipients contributed to the clinically effective classification of the various types of this disorder, and then to unravelling the key mechanisms that cause it. This understanding led to the development of a novel therapy and has opened windows into future ones. Their work on migraine is a remarkable example of bedside-to-bench-to-bedside research that has yielded tangible clinical benefit.”

What is migraine?

Migraine is much more than a bad headache. It is a serious neurological disease with symptoms that include severe throbbing and recurring head pain, nausea, vomiting, dizziness, extreme sensitivity to sound, light, touch, and smell. Some migraine attacks can last for several days and more than 4 million people suffer at least 15 migraine attacks per month. For many, migraine severely diminishes the quality of life, including the ability to work, and can lead to depression, anxiety, and sleep disturbances. The economic and societal costs associated with migraine are extremely high - in the tens of billions of dollars - worldwide.

Treatments for migraine have been available for some time, but they can have significant side effects and their efficacy is incomplete. There was therefore an urgent need to develop new classes of migraine-specific drugs. The problem was that doctors were at a loss to understand the origin of a migraine attack. Examinations of migraine patients between migraine attacks had not revealed anything out of the ordinary.

Discovering what causes migraine attacks was key to unlocking new ways of treating them.

The breakthrough came when four internationally renowned neuroscientists, **Lars Edvinsson** (Sweden), **Peter Goadsby** (UK/USA), **Michael Moskowitz** (USA) and **Jes Olesen** (Denmark) discovered, over the course of four decades of work, a cause of a migraine attack.

The story begins with **Michael Moskowitz**, an American and a Professor of Neurology at Harvard Medical School at the Massachusetts General Hospital. His work showed that a migraine attack involves an interaction between two key players: the

trigeminal nerve (which is involved in controlling movement of, and sensations in the face) and the meninges and its associated blood vessels (the meninges is a thin membrane that surrounds the brain and is the only structure inside the skull that senses pain). Moskowitz proposed that a migraine attack is triggered when the trigeminal nerve fibres are activated, leading to release of chemical signals that dilate (open up) the blood vessels of the meninges. This results in local inflammation which ultimately results in severe head pain. But what was activating the trigeminal fibres to cause a migraine attack in the first place? Prior to the intense headache, many migraine patients experience auras - unusual sensory experiences such as seeing spots of light, flashes, stars, a brief loss of vision, or tingling sensations in the face or hands. These auras usually last for less than an hour but they often signal the imminent arrival of a migraine attack. Moskowitz provided compelling evidence that the highly unusual pattern of brain activity that results in the auras may also activate the trigeminal nerve fibres.

However, a major piece of the puzzle was still missing. What was the nature of the chemical signals released by the trigeminal nerve fibres which triggered the attack itself? Working together, **Lars Edvinsson** and **Peter Goadsby** showed that a recently discovered peptide (a small protein-like molecule), calcitonin gene-related peptide (CGRP), was released from the trigeminal nerve during a migraine attack and that it was a potent dilator of blood vessels in the meninges. Based on these findings Edvinsson proposed that CGRP may be of crucial importance in migraine, but was the release of CGRP from the trigeminal nerve the cause or a consequence of a migraine attack?

This crucial question was answered by **Jes Olesen**. He showed that when given to migraine patients CGRP could trigger a migraine attack. He then went on to show that drugs which blocked CGRP could help treat migraine. Olesen's work was not only crucial in showing a causal role for CGRP in triggering migraine, but it also demonstrated that CGRP could be an important new target for developing new treatments for migraine.

The work of Michael Moskowitz, Lars Edvinsson, Peter Goadsby and Jes Olesen has led to the development of new drugs called gepants and CGRP monoclonal antibody treatments. The success of these new treatments is remarkable. They are safe and can even reduce the likelihood of future migraine attacks. Patients have remarked that the drugs have "given them their life back".

The human brain is staggeringly complex which means understanding and treating disorders of the brain remains one of science's greatest challenges. We often hear that a major neuroscience discovery "could lead" to improved treatments for patients. The pioneering work of the four Brain Prize winners has actually done so.

Migraine facts

NUMBERS OF PEOPLE AFFECTED

- Migraine affects approximately 1 billion people worldwide.
- Migraine affects 3 times as many women as men.
- Migraine also affects a considerable proportion (approx. 7%) of children.
- According to the Global Burden of Disease Study in 2016, migraine is the 2nd leading cause of disability and accounts for more than all other neurologic disorders combined.

PREVALENCE AND BURDEN

- Migraine is more prevalent than diabetes, epilepsy and asthma combined.
- Migraine sufferers experience recurrent headaches of moderate-to-severe pain lasting 4 to 72 hours.
- Severe migraine attacks are classified by the World Health Organization as among the most disabling illnesses, comparable to dementia, quadriplegia, and psychosis.
- The financial burden of migraine on the UK economy is estimated at £3.42 billion per year. This figure takes into consideration the costs of healthcare, lost productivity through absenteeism and disability.

- Migraine can run in families, with 42% of cases thought to be hereditary. The genetic causes of migraine are not fully understood but it is generally thought to be polygenic, meaning that multiple mutations in different genes may cause the disease.

SYMPTOMS

- The pain is often throbbing, can be on one side of the head, and is aggravated by physical activity.
- Other symptoms include, nausea, vomiting, and sensitivity to light and sound.

- Anxiety and depression are significantly more common in people with migraine than in healthy individuals.
- A significant proportion of migraine sufferers experience auras, most commonly visual and, less often, tingling sensations and loss of normal speech.

About The Brain Prize

SCOPE

The Brain Prize, the world's largest brain research prize, is Danish and awarded by the Lundbeck Foundation. Each year, the Foundation awards the prize worth 10 million DKK (approx. €1,3 million) to one or more neuroscientists who have had a ground-breaking impact on brain research. The Brain Prize recognises highly original and influential advances in any area of brain research, from basic neuroscience to applied clinical research, and recipients may be of any nationality and work in any country around the globe. The Brain Prize was first awarded in 2011 and has so far honoured 34 scientists from nine different countries. The Brain Prize is awarded at a ceremony in Copenhagen, presided

over by His Royal Highness, The Crown Prince of Denmark.

PURPOSE

Following the award of The Brain Prize, recipients engage in a series of outreach activities, organised by The Brain Prize team at the Lundbeck Foundation. These activities not only celebrate the achievements of the recipients but also serve to establish and strengthen collaboration within the Danish and international neuroscience community. The Brain Prize is also used to engage with and educate the public about the importance, challenges, and breakthroughs in brain research. The Brain Prize is at the heart of the Lundbeck Foundation's strategic priority of making Denmark a

world leading neuroscience research nation, and of raising public awareness of the brain, brain disorders and the importance of brain research.

NOMINATION AND SELECTION OF THE BRAIN PRIZE WINNERS

Only candidates who are nominated by others will be considered for The Brain Prize. The rewarded research must - from an international perspective - be outstanding. It is the task of The Brain Prize selection committee to decide in each individual case, what characterises the research as outstanding and therefore deserves the prize. The current selection committee consists of nine eminent neuroscientists from five countries who are global leaders in their respective fields.

About the Lundbeck Foundation

The Lundbeck Foundation's history goes back over 65 years. The Foundation was established in 1954 by Grete Lundbeck, a visionary businesswoman and widow of the founder of H. Lundbeck A/S, Hans Lundbeck. When she died in 1965, the Foundation was sole heir to her assets.

The Lundbeck Foundation is one of Denmark's largest commercial foundations, worth over DKK 65 billion. The Foundation awards research grants of more than DKK 500 million each year to Danish-based, biomedical sciences research - primarily in the field of brain research.

As the largest private financial contributor to Danish public brain research, it is the Foundation's ambition for Denmark to be the world's leading brain research nation. At the same time, it has a strong focus on raising public awareness of the brain and brain disorders.

The aim of the Lundbeck Foundation is to promote the careers of the most promising scientists and help fund a strong pipeline of biomedical science researchers, regardless of their field of research.

The Lundbeck Foundation's commercial activities encompass three large subsidiaries, an international portfolio of 18 venture capital companies, a portfolio of small biotech companies based on Danish university research and in-house administration of assets of around DKK 19 billion.

At the heart of the Lundbeck Foundation's activities is their purpose: "To create powerful ripple effects that bring discoveries to lives through investing actively in business and science at the frontiers of their fields."

History and evolution of the migraine field

Marie-Germaine Bousser,
Emeritus Professor of Neurology at Paris University

Reported in Mesopotamian poems around as early as 3000 BC, migraine has always been and still is one of the most frequent diseases in the world. It often runs in families and affects about 10% of children and 15% of adults, with a female preponderance of 3 to 1. Among non-lethal diseases migraine is the first cause of disability in young adults.

Migraine is characterised by recurrent attacks of severe, pulsating, often unilateral headache lasting a few hours to 2-3 days. Headache is usually associated with nausea, vomiting, and enhanced sensitivity to light, sound,

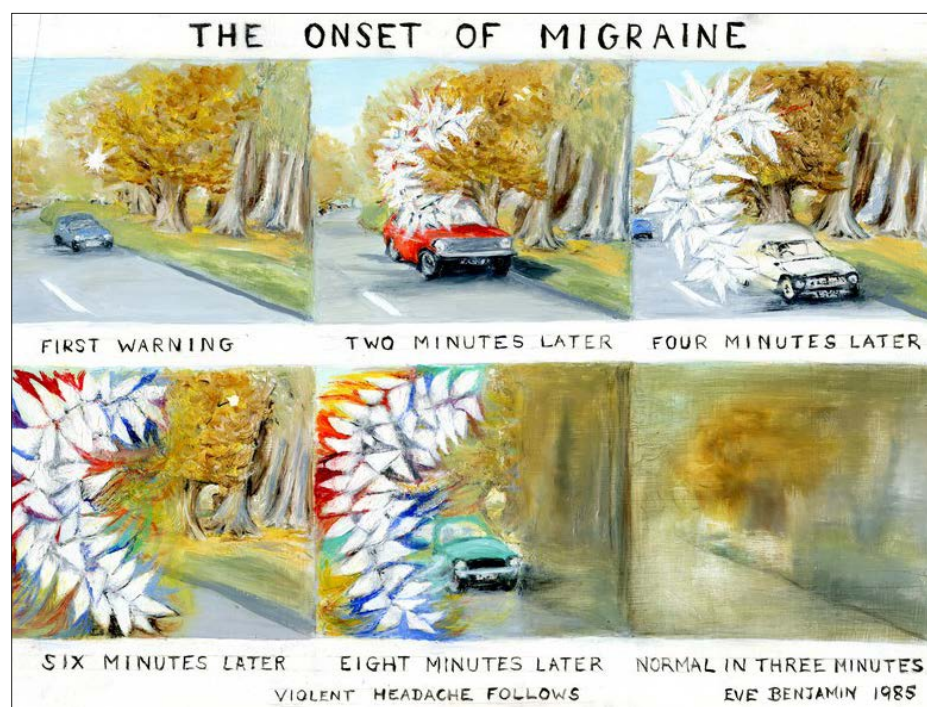
touch, and smell. Headache is sometimes preceded by short lasting neurological symptoms, mostly visual, referred to as « the aura ». « *He seemed to see something shining before him like a light, ... after a moment, a violent pain supervened in the right temple, then in all the head,.... vomiting, when it became possible, was able to divert the pain and render it more moderate* » wrote Hippocrates around 400 BC.

The frequency of attacks is highly variable, with a median of 1.5 per month. In women, attacks usually disappear during pregnancy but recur during

post-partum. Attacks usually start in children or in young adults and decrease in frequency and severity with aging. Numerous factors have been reported to trigger attacks including menstruation, stress, various food products, skipping meals, changes in weather, bright or flickering lights, and changes in sleep patterns.

Although known and fully described since ages migraine has long been, despite its frequency and its burden, one of the most mysterious conditions affecting human beings and the field of migraine long remained more artistic than scientific. Many famous writers such as Victor Hugo, Lewis Carroll or Sigmund Freud fully described their migraine attacks while others, from Hildegard of Bingen around 1150 to Giorgio de Chirico, painted pictures inspired by their visual aura.

Physicians were deeply puzzled by migraine and at a loss to understand its origin. Clinical examinations of patients between attacks were normal and all investigations they could think of were also normal. There was no specific treatment either to abort or to prevent the attacks which were mostly treated by folk remedies, bed rest and later, when they appeared, by ergot derivatives and analgesics. Furthermore, there was no satisfactory animal model. They started to think – as many patients do – that the triggers of the attacks could explain the origin of the disease and this led to a host of theories about migraine, thought to be hormonal, allergic, psychosomatic, or gastrointestinal in origin, only to mention some of the hypotheses. Even the revolution of neuroimaging did not help either to confirm the diagnosis of migraine or to find the cause of the disease.



Migraine Action Art Collection: Image 337, Eve Benjamin, The onset of migraine (1985). Available at <http://www.migraineart.org.uk/artwork/the-onset-of-migraine/>

It was not until the second half of the twentieth century that migraine was recognised as a disorder of the brain, as suggested by many migraine specialists, such as HG Wolff, JMS Pearce, OW Sacks and JW Lance. There was an agreement that migraine was a complex neurovascular disorder involving the brain and its vessels, but there was still a debate whether the origin of attacks was primarily neuronal, as suggested by the aura, or vascular as suggested by the pulsatile character of the headache. The work of these pioneers paved the way for a more scientific approach to migraine, to which the 4 winners of the Brain Prize 2021 were major contributors.

A crucial step for a scientific approach to migraine was to differentiate migraine from other varieties of headache. In the absence of a biomarker for migraine, this was not an easy task, particularly since, for many patients, migraine and headache were synonymous. The credit goes to Professor Jes Olesen from Denmark for having achieved this goal. In 1985 he gathered many headache specialists in order to discuss and propose operational criteria to define each variety of headache. This led to the first International Headache Society (IHS) classification of headaches published in 1988. It was a crucial step in headache research, particularly for primary headaches such as migraine, because for the first time, it was possible for researchers to speak the same language. Since then, Professor Olesen has chaired all the following editions of the IHS headache classification. Besides this major achievement, Olesen has had over the last 40 years played a key role in the field of migraine research. He was one of the first to show the spreading depression during a migrainous aura by studying cerebral blood flow with xenon and to show that focal cerebral ischemia could trigger migraine attacks with aura. He particularly studied substances able to trigger attacks such as NO, CGRP, glyceryl trinitrate and PGE₂. Overall, he has performed research on almost every aspect of migraine including epidemiology, genetics, imaging, and animal models.

Most of the research performed by the three other Prize winners, Lars Edvinsson from Sweden, Michael A Moskowitz from USA, and Peter J Goadsby from Australia, was experimental and orientated towards elucidating the relationships between the brain and the vessels and their implication in migraine. Moskowitz and colleagues



The Head Ache, February 12, 1819. After Captain Frederick Marryat. Artist, George Cruikshank. (Heritage Images via Getty Images)

introduced the trigeminovascular hypothesis of migraine headache, pointing to a key role for the trigeminal nerve (one on each side of the head) and its vasoactive axonal projections to the meningeal blood vessels. The theory focussed on discharging trigeminal nerve fibres, release of vasoactive neuropeptides (of unknown identity then) into the meninges and ensuing headaches as one explanation for unilateral migraine pain. He later coined the term « trigeminovascular system » to designate the relationships between the trigeminal nerve, the meningeal vessels, and the central nervous system. The Moskowitz hypothesis of the involvement of the trigeminovascular system during migraine attacks, plus the emerging age of vasoactive neuropeptide transmitters, initiated a new era in migraine research. Edvinsson was a pioneer, detecting in 1976 by immunohistochemistry, the presence of a first neuropeptide in the intracranial vasculature, the vasoactive intestinal polypeptide (VIP), a potent vasodilator representing a new class of molecule.

Over the next 10 years, a large number of neuropeptides were identified in the cerebrovascular innervation. Among those, CGRP (calcitonin gene-related peptide), discovered by MG Rosenfeld, proved the most interesting. Edvinsson set up the methodology to study its role in the trigeminovascular

system. He showed in 1985 that over half of the neurons in the trigeminal ganglion contain CGRP and that lesioning the ganglion led to the elimination of CGRP fibres in intracranial arteries. Functional studies showed that CGRP was a potent dilator of cerebral arteries and played a key role in the trigeminovascular reflex whereby, in response to a local vasoconstriction, there is a release of CGRP by trigeminal nerves causing vasodilation. These experimental findings led Edvinsson to suggest the involvement of CGRP in the pathophysiology of migraine attacks. This was confirmed a few years later when he started a fruitful collaboration with Goadsby. In the years 1990-94 they found that CGRP was selectively released from the trigeminal ganglion during a migraine attack and that this release was prevented by Sumatriptan, the serotonin agonist discovered in 1988 by the british pharmacologist Patrick Humphrey and shown to be the first specific and effective treatment of migraine attacks. This work on a serotonin agonist and neuropeptide release supported research by Moskowitz's lab (1988-1994) showing that serotonin receptors are expressed by trigeminal sensory fibers and agonists like Sumatriptan and ergots inhibit neuropeptide release. Sumatriptan became the leader of a new class of acute antimigraine drugs called the triptans which have changed the life of many migraine sufferers.

The scene was set for building up the clinical background for CGRP in migraine. This was a remarkable achievement of Edvinsson, Goadsby and their teams. It took them more than 10 years to develop the first CGRP antagonist drug effective in the acute treatment of migraine attacks, as shown in a large trial involving Olesen and his team in 1984. This drug was a small molecule called olcegepant which became the leader of a new class of antimigraine drugs, the gepants. Two other gepants have been approved for the acute treatment of migraine attacks and others are in evaluation in phase 3 trials in both the acute and prophylactic treatment of migraine attacks. The idea of blocking the CGRP pathway took another direction with the development of monoclonal antibodies (MABs) towards CGRP or its receptor as prophylactic treatment of migraine attacks. At the moment there are 4 MABs that have been shown, when administered subcutaneously or intravenously once a month or once every 3 months, to reduce by half compared to placebo the number of migraine days, with a response rate of roughly 50% of migraineurs. Two of these MABs have been approved and are already on the market. The long story of the development of CGRP antagonist drugs has opened a new era in migraine research and therapy. Although they do not cure

migraine, they markedly improve the quality of life of many migraineurs. They are also the first drugs to have a duality of mechanism, being active in both the acute treatment and the prophylaxis of attacks and they have paved the way for the study of other potential targets.

The CGRP story was crucial for the understanding of the migrainous headache but it did not shed light on one of the most unique features of migraine attacks, the neurological aura which precedes the headache in about 20% of patients. The study of the neurological aura was one of the main themes of research of Moskowitz. In 2001, using fMRI, he showed for the first time that during a migrainous aura there are bold signal changes which share many characteristics with the cortical spreading depression (or depolarization), CSD. The changes developed in the extrastriate cortex, progressed continuously and slowly over the occipital cortex while the patients had the typical visual symptoms of the migrainous aura. The CSD phenomenon, described by Leao in 1940, had long been suspected to underlie the migrainous aura but this was the first demonstration in humans. A year later Moskowitz showed that the CSD activates the trigeminovascular system and induces a series of cortical, meningeal

and brain stem events consistent with the development of headache. This was the first experimental evidence of the link between aura and headache during migraine attacks. He also showed that cerebral ischemia could induce the CSD in accordance with Olesen's previous clinical observation. He further explored the link between aura and headache and showed in 2010 that CSD leads to a long-lasting activation of nociceptors that innervates the meninges. Recently, he showed that acute sleep deprivation, a possible trigger of migraine attacks, enhances CSD.

The four recipients of the Brain prize 2021 have completely modified the migraine world in bringing science, both clinical and basic, in this previously mostly artistic field. The IHS classification of headaches, the identification of the trigeminovascular system, the CGRP story leading to MABs, the elucidation of the link between the aura and the headache during attacks have all been major achievements to better understand migraine and improve the quality of life of migraineurs. Furthermore, these four migraine experts have inspired many young people all over the world, clinicians as well as basic scientists, to become interested in migraine.

The Brain Prize winners, 2021

Short Biographies

LARS EDVINSSON

Lars Edvinsson is Swedish and a Professor of Internal Medicine at Lund University. He is also president of The International Headache Society and Professor in Clinical Pharmacology at Copenhagen University. He trained at Lund University Medical Faculty and graduated as MD with PhD in 1980. He became a full professor at Lund University and senior consultant at the University Hospital in Lund in 2002. He is also the founder of the Glostrup Research Park and has been its leader for the last 15 years.

He is a leading expert in the field of cerebral circulation and migraine. He has been a major contributor to what is known about the roles of the cerebral vasculature in health and in stroke and primary headaches. Working with Peter Goadsby, he identified calcitonin gene-related peptide (CGRP) as a key transmitter in the trigeminal pain



Lars Edvinsson

pathway and which is selectively released during a migraine attack. Based on his findings he proposed that CGRP may be of central importance in cerebral blood flow and migraine. Professor Edvinsson and his group have contributed numerous basic research and clinical insights that have enabled the successful translation of CGRP drugs from bench to clinic. He is currently studying the female bias in migraine. Recently he showed that the trigeminal CGRP-containing neurons are equipped with receptors for estrogen and oxytocin, and they may hence be regulated by the dynamic changes in levels of these hormones in females. Typically, both hormones drop just prior to menstruation and this may be a trigger for migraine attacks. The molecular understanding is still not solved so more research in this area is on the horizon.

PETER GOADSBY

Peter Goadsby is Professor of Neurology, University of California, Los Angeles. He is Director, NIHR-Wellcome Trust King's Clinical Research Facility, King's College London and Honorary Consultant Neurologist, King's College Hospital. He is an Honorary Consultant Neurologist at the Hospital for Sick Children, Great Ormond St, London, UK.

He obtained his medical degree and training at the University of New South Wales (UNSW), Australia. His PhD in neural mechanisms involved in headache disorders and his Neurology training was with James W. Lance. His clinical neurophysiology training was with David Burke. After post-doctoral work in New York with Don Reis at Cornell, Jacques Seylaz at Universite VII, Paris, and post-graduate neurology training at Queen Square, London with C David Marsden, Andrew Lees, Anita Harding and W Ian McDonald, he returned to UNSW, and the Prince of Wales

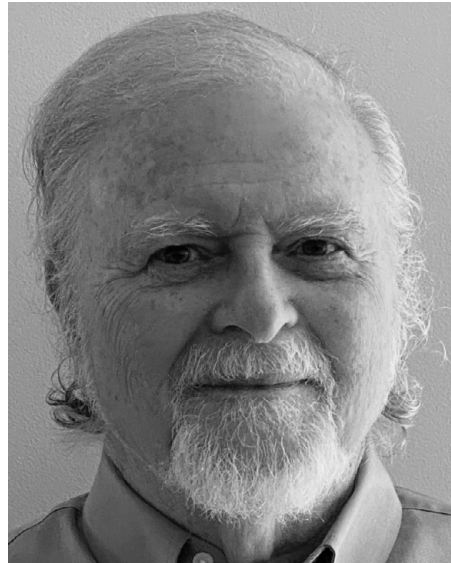


Peter Goadsby

Hospital, Sydney as a consultant neurologist and became an Associate Professor of Neurology. He was appointed a Wellcome Senior Research Fellow at the Institute of Neurology, University College London and was Professor of Clinical Neurology and Honorary Consultant Neurologist at the National Hospital for Neurology and Neurosurgery, Queen Square, London until 2007. He was Professor of Neurology, at University of California, San Francisco, 2007-2013.

He has studied headache disorders from bench to bedside, collaborating with Lars Edvinsson to be the first to show the involvement of CGRP in migraine and cluster headache, which led directly to the development of gepants and CGRP monoclonal antibody treatments for migraine. He has explored migraine and cluster headache mechanisms with laboratory models, human experimental medicine, functional brain imaging and clinical trials, while maintaining an active clinical practice that focuses his efforts on real translational benefits for patients with headache disorders.

The Brain Prize winners, 2021 Short Biographies



Michael A. Moskowitz

MICHAEL A. MOSKOWITZ

Michael A. Moskowitz is professor of neurology at Harvard Medical School. His laboratory has been in the departments of Radiology, Neurosurgery and Neurology at the Massachusetts General Hospital where he spent most of his career following 8 years as a postdoctoral fellow and faculty member at the Massachusetts Institute of Technology. His research focuses on translational mechanisms underlying migraine and stroke and is credited with foundational discoveries that ushered in modern day migraine therapeutics.

Professor Moskowitz was born in Brooklyn, New York. He received his undergraduate and medical degrees from Johns Hopkins University and Tufts University School of Medicine. He became intrigued by migraine after 6 years of clinical training in internal medicine and neurology at Yale and Harvard Hospitals. He was the first to hypothesize that vasoactive neuropeptides contained within trigeminal meningeal nerve fibers participate in migraine pathophysiology and to suggest new strategies for prophylaxis and treatment. After discovering the sensory nerves to the circle of Willis within the meninges, penning the name

trigeminovascular system and identifying the first neuropeptide in this pathway, he proposed a migraine road map that implicated trigeminal neuropeptides and their receptors as therapeutic targets. His laboratory showed that classical antimigraine drugs (ergots, triptans) inhibited neuropeptide release, thereby inspiring use of drugs and biologicals that block release and inhibit a meningeal inflammatory response.

Building on this scheme, his laboratory looked for upstream endogenous triggers and identified spreading depression (underlying migraine aura) as the first candidate that activated the trigeminovascular system and as a target of preventative antimigraine drugs. Identifying other upstream triggers, whether from brain or blood vessels, will greatly facilitate our understanding of migraine going forward.

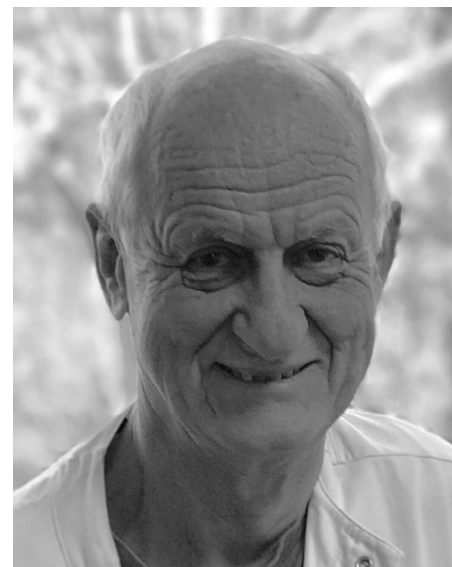
Based on his formulation and research plus the pioneering research of his co-honorees, more than 20 new drugs and biologicals are now in the clinic that impact the trigeminovascular system and its upstream and downstream targets.

JES OLESEN

Jes Olesen is a professor of neurology at the University of Copenhagen and a chief physician at the Danish Headache Center, Rigshospitalet Glostrup, Copenhagen, Denmark. He is the father of the International Headache Classification and has identified several signaling mechanisms in migraine leading to new drug targets and registered drugs.

Jes Olesen was born in Denmark, studied at the University at Copenhagen and defended his doctoral thesis on human brain blood flow there. His neurological education included a residency at Cornell Medical School, New York, and a volunteer period at the National Hospital Queen Square, London. He founded and for many years led the Danish Headache Center where he is still an attending physician.

In his thesis he showed for the first time in humans that physical activity increased blood flow in the relevant brain area. The relation between brain function and brain blood flow has subsequently developed to an avenue of science but Jes Olesen did not pursue that path. Instead, he first showed that cortical spreading depression is the likely physiologic mechanism of the migraine aura. Next, he developed a human provocation model and showed the crucial importance of nitric oxide, calcitonin-gene related peptide and pituitary adenylate cyclase activating peptide in migraine mechanisms. Likewise, an increase in second messengers cyclic guanylyl monophosphate and cyclic adenylyl monophosphate activated migraine mechanisms. More recently he continues his work in animal models of migraine and in the exploration of migraine genetics. Along with his scientific work he has also initiated and chaired the International Classification of Headache Disorders and has been the prime mover organizing the European Federation of Neurological Society and the European Brain Council.



Jes Olesen

Autobiographies of the winners

Lars Edvinsson

I trained at Lund University Medical Faculty and graduated as MD 1980 and did my PhD in 1975 during my MD studies. I became specialist in Clinical Pharmacology 1985 and specialist in Internal Medicine 1988. I chose Internal Medicine and became associate professor (docent in internal medicine) 1988 and full professor in 2002 at Lund University and senior consultant at the University Hospital in Lund.

In parallel with my clinical duties, currently as a senior consultant in ICU, I started my own research group where numerous PhD students and post-docs were educated throughout the years at Lund University. My students consider me as a very appreciated supervisor and teacher.

I consider myself an expert in the interpretation of the sensory nervous system and am recognized as a leading expert in the field of vascular innervation and receptor regulation. My extensive research has been a major contributor to understanding roles of autonomic and sensory mechanisms in regulation of the cerebral circulation in health and diseases such as stroke and primary headaches. I have written many well-recognized educating books. My research has led to the discovery, understanding and development of novel drugs for the treatment of neurovascular diseases, such as the successful treatments of migraine.

I consider the following recognitions, honors and awards as highlights of my career:

- 2018 *Forska Sverige prize; awarded to the best scientist in all disciplines in Sweden.*
- 2014-2019 *Elected Trustee, Director and President, International Headache Society*
- 2013- *Member, Steering Board, European Headache Federation*
- 2013 *Honorary Doctorate, Xián University, China.*

- 2012 *Lifetime Achievement Reward by American headache leaders (Boston).*
- 2012 *Honorary Doctorate, University of Szeged, Hungary.*
- 2008- *Bland Lane International Distinguished Professor Award, FAMRI, USA.*
- 2002- *Honorary Fellow, British Pharmacology Society.*
- 1985- *Honorary Fellow, Stroke Council, American Heart Association*

- 2004-2020 *Adjunct Professor, Basic and Translational Research Institute, Xian University, Xian, China*
- 1990-2020 *Adjunct Professor in Pharmacology, Southern Illinois University, Illinois, USA*
- 1990-1995 *Professor II in Neuroscience, Trondheim University, Norway*

I started my research at the second semester of my medical studies in Lund. For 5 years I was devoted to the study of innervation, vascular receptors, and the role of autonomic nerves on cerebral circulation. These were great years for a young researcher, it was there I got input and collaborated with laboratories in Paris University (Seylaz), and Glasgow University (Harper, MacKenzie, McCulloch). I spent much time there and was educated in new methods and scientific teachings at the highest level. It was extreme freedom in the scientific arena. When I returned to finish my MD it was hard work because in principle I continued research and MD studies simultaneously while building my own research group at the Lund University.

Domestically, I met my beloved and supportive companion Marie-Louise, we were married in 1979 and were blessed by two wonderful boys.

In 1976 I was at the right position, in time and location, since people had developed antibodies towards different neuropeptides, and it benefitted the vivid scientific environment in Lund.

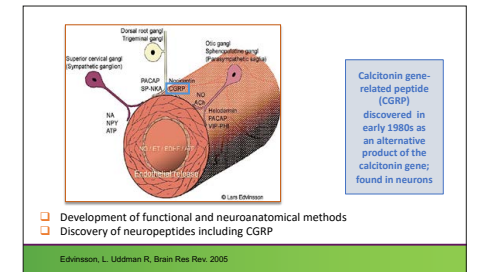


Fig 1. The Prepared Mind: 1970s-1990s Era of characterizing the Innervation and Neural Regulation of Cerebral Blood Vessels

The law of Canon stated; one nerve one signal molecule, but new data challenged this dogma. We were the first to show VIP in perivascular nerves in brain vessels. This was a starting point, and many neuropeptides were identified in the cerebral vessels, for me with perivascular nerves, both in autonomic and in sensory fibers (Figure 1). I was invited to The Migraine Trust and to Brain conferences to discuss our findings in relation to clinical contexts. This educated me and pointed my research in the direction towards finding the roles of all these newly discovered neuronal signaling molecules. In Glasgow we discovered the trigeminovascular reflex 1986 (Figure 2).

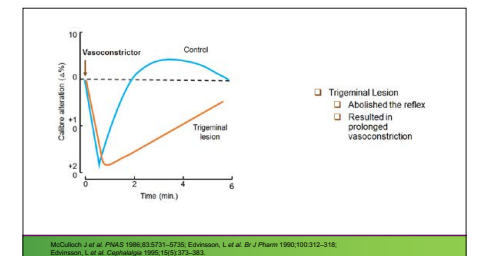


Fig 2. The Trigeminovascular Reflex

In the following years, I developed excellent collaborations and life-long friendship with colleagues in Paris, Glasgow, Copenhagen, Szeged, Sydney and Los Angeles. We were young and shared a deep interest in advanced science. We realized that by joining forces and sharing technologies we could all get closer to understanding our scientific quests. I was appointed adjunct professor and honorary doctor at many

Universities throughout the world. In Lund I became professor of Internal Medicine and had a very productive team at the University. In Copenhagen I was given the opportunity early to set up a unit and later to build the Glostrup Research Park and be its leader now for nearly 15 years. I was honored to be appointed to the position of professor in Clinical Pharmacology at Copenhagen University.

The new molecular insights on perivascular nerves in the cranial circulation went two ways; into headache disorders and towards stroke. As the number of neuropeptides increased in these nerves it was difficult to identify their individual roles. The first clinical studies in primary headaches revealed that the sensory neuropeptide, calcitonin gene-related peptide (CGRP), was the only neuronal messenger reliably released in migraine (Figure 3). This clearly pointed towards migraine and this is what we celebrate today with effective medications to treat millions of

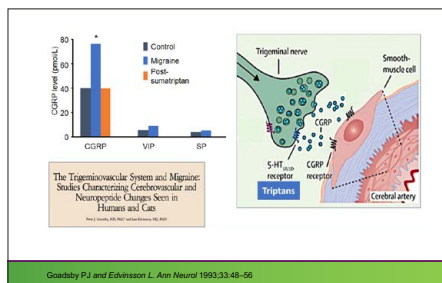


Fig 3. Mechanism of Triptans: Suppression of CGRP Release from Trigeminal Nerves via Presynaptic 5-HT_{1B/D} Receptors

sufferers. We have focused much attention towards explaining the site of their action, as shown in Figure 4 (action of CGRP receptors in the trigeminovascular pathway) and at the nodes of Ranvier where CGRP in C-fiber boutons is released into the nodes where we find CGRP receptors.

Currently we are examining the important question why females dominate in migraine. This year we showed that the trigeminal neurons are

equipped with receptors for estrogen and oxytocin, and they may hence be regulated by the dynamic changes in levels of these hormones in females. Typically, both hormones drop just prior to menstruation and this may be a trigger for migraine attacks in females. The molecular understanding is still not solved so more research is on the horizon.

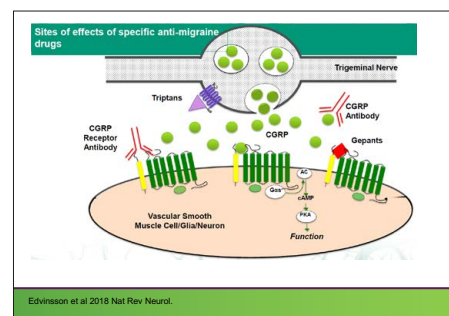


Fig 4. Sites of effects of novel specific anti-migraine drugs

Peter Goadsby

I grew up in the Western suburbs of Sydney, a town called Blacktown. Dad worked hard in a factory job that I am sure he hated, and mum was at home until my youngest sister went to school, when, as a mathematics teacher, she went back to work. My childhood memories are of my brother and I playing together; they were happy days. High School memories are mixed. I blossomed academically in high school and did well in everything I liked: maths, science, languages, particularly Latin, history and in later years economics. I was not a fan of music and art, resenting what I saw as wasted time. I found considerable inspiration in my Latin teacher who encouraged me to be excellent at serious subjects. Likewise, my mother was never content with anything less than perfection. She recognized that 100% was the only acceptable score in maths! She taught me self-discipline and rigour; frankly, it is the only reason I have been at all successful. I found school socially isolating for many years. I became interested in rugby league refereeing and to this day recall the excitement of the match.

I liked to read about what I considered factual subjects. I would spend many happy hours reading randomly in an encyclopaedia or browsing the local library reference reading room. I recall vividly proving the maths teacher wrong about an obscure point of set theory when I was thirteen years old. I spent weeks in the local library reading about the subject. We were not allowed to use the school library for schoolwork since our teachers, who were Patrician Brothers, thought we should be outside – it was healthier by their byzantine world view. I presented the work to the teacher who gave me a caning for being impudent. I presented it to my mother, a maths teacher, who agreed it was correct, and asked the teacher who said: “a teacher should never admit being wrong to a student”. This was a useful lesson as a supervisor of students over the years in how not to behave. The fact that I was correct satisfied me immensely. I’ve always loved the precision and beauty of numbers. I spent most of my adolescent years saddened and unhappy by uncurious and unimaginative teachers. I would sit in my room at home and wonder what life would be like in such a world that I did not want to be part of. My junior high school years until year 11 were the most miserable years of my life, yet the

most formative in terms of self-reliance and self-discipline.

I had no interest in medicine or even biology when I was in school. I thought biology imprecise, largely driven, I suspect, by the teaching. I did chemistry and liked it greatly. I loved maths and more so economics. I first thought about being a teacher, but it seemed a default not a real choice. I recall being forced to stop Latin in high school; I objected and was told it was a subject for “doctors and lawyers” and that when I was working in a factory later in life I would have no need for it. The school with its totally anti-intellectual environment really motivated me to be better; not be sucked into a world of mediocrity that many of the teachers had created for themselves.

By the end of high school, I had decided I wanted to be Treasurer of Australia. I liked quantitative economics. I subscribed to the Reserve Bank statistical bulletin, memorized the quantitative data and thought the then treasurer of Australia was rather subpar: untrained and not thoughtful, or apparently knowledgeable about economic theory. I subscribed to Federal Parliament Hansard, the record of oral activity, and spent many happy hours

reading it. I considered the debates poorly constructed and ill-considered. I felt I could easily do better. I planned to do economics and law and join a political party. Our school library had no information about university courses. One day I had a blazing argument with my mother and at the last moment I changed by preferences for university to do medicine to prove a point. I was truly dismayed when I got in. Years later I understood politics was not about knowledge but presentation; I am glad I did not get into law.

Prior to starting I had an interview by the head of community medicine and a few others. At the time university places were decided by the outcome of the Higher School Certificate, best mark, most choice. There was no interview. The university decided to do interviews to see how their predications would develop and design an interview system to complement the marks in the high school examinations. My interview was a disaster. I understood I had nothing in common with the questioners, and knew the interview meant nothing since I was already in. I had to take a day off work, I had started a job to pay for my medical books and so on. My commute was two hours, bus-train-bus each way, a routine I was to become accustomed to but never enjoy for several years. I did not know where the university was and had never been there; the first trip was certainly an unpleasant shock. I turned up in shorts, flip-flops and with attitude in spades. It was concluded by one of the heads of department saying I was exactly the type of person an interview process would try to identify and keep out of medicine.

So, the first week was weird; I remember thinking I was out of place. I had a long commute. One of my classmates told me they did not travel that far on summer holidays. I soon discovered the Students Union, thinking I could engage in debate for fun. I found it full of entitled, lazy-thinking individuals with no life experiences. I certainly thought my class had many rather sheltered members. I thought I’d made the wrong decision and wondered how to change. I understood my cultural references were very different to everyone around me, so it took many months to find friends, one of whom I am still in contact with to this day.

There was no formal research component unless one elected to do it. My life was transformed by a lecture Jim Lance

gave when I was in year two. He talked about non-dominant parietal lobe syndromes - including autotopagnosia - it struck me that medicine had interesting aspects, and he had a way of enticing you to think about the mechanisms (1). As these things happen, we saw a case in our clinical studies tutorial some weeks later and I knew I wanted to be a neurologist. I read about the relevant physiology from Vernon Mountcastle (2), and felt energised. It was one of those moments in life that completely alter the path. It sounds crazy, but I wanted to be an academic neurologist doing research and clinical work after this combination of the paper, Lance’s lecture and seeing the case. I did not do research until after the penultimate year of the course because of financial constraints but I was completely clear about my direction.

I published my first paper in 1982 (3). Jim Lance was a patient mentor and editor, Geoff Lambert an excellent teacher in the lab and John Duckworth, who was on many subsequent papers, a very detailed and patient educator. They each, in their way, drew my attention to my breathtakingly poor writing. I still have - Why not say it clearly? Echoing my mind from time to time. Laboratory members introduced me to PC technology in 1981. Ross Hand showed me the C Programming language book, and Unix operating system triggering a technical love-affair that has persisted to this day.

I went on the following year to stay in the laboratory and transitioned from a Bachelor of Medical Science to a PhD. I had found the joy of discovery. Jim Lance advised me to start a PhD and delay finishing medicine. It was a leap that I enjoyed. In the following two years I worked reasonably hard and wrote a two volume, 965-page thesis, which was submitted two years to the day after enrolling. It had a sad element in that my medical school class moved on and graduated and I was working away; but it was incredibly exciting to do research. I went back to do the last year of medicine, which was awful. It seemed simply to delay becoming an academic neurologist. At the end of the year I combined various elective terms and the first part of internship and went to Cornell in New York for a post-doc in the laboratory of Don Reis, where I was fortunate to work with Steve Arneric, Mark Underwood and Costantino Ladecola. At the end I was offered a position in that laboratory by Don Reis, but Jim Lance said, no, come back and get your medical training. I took his advice.

It must sound like a theme; the earlier clinical years were awful. I recall finding internship tedious. When I came back from the US, I was able to establish a physiology laboratory and began to use the quantitative cerebral blood flow and metabolism methods I had learned. Jim Lance found funds for the equipment, and I began to do experiments on weekends or any days off I had.

I had observed that US doctors had an MD, and I was MB BS PhD. I thought it might be nice to get an MD. I had begun doing laboratory work, so I thought enrolling part-time would be simple. I had to meet the then Professor of Medicine, John M Dwyer, to sign off the form. He had not long before coming back from Yale to take up the post and was an immunologist. We met. He advised me not to do an MD, giving me a little talk about burn-out and work-life balance. At the end of his talk I thanked him and asked him to sign the form since I was going to do the work anyway. He was less than pleased as he signed the form. More than 30 years later I must be still burning out.

The laboratory work proceeded well. I was incredible lucky to hear a lecture by Lars Edvinsson at a meeting in Lund in June 1985. He was doing remarkable work on the trigeminal effects on the cranial circulation and novel neuropeptides, particularly CGRP. He was very gracious to listen to my pitch over coffee and we set up the collaboration that resulted in the CGRP work. The goal we had was to do translational work as we went along rather than do years of laboratory work and then take it to humans. We showed we could cause release in humans and experimental animals of CGRP. At the same time I was studying for the FRACP examination – the Australian specialist board qualification. The combination made me not terribly accessible socially, and it did not work well at some level. I decided to study for the US ECFMG while a resident, thinking about returning there. I recall being called into the ICU Director’s office to be asked why I sat away from everyone reading; the nursing staff had complained I was anti-social. I explained I was studying and preferred reading; this explanation did not seem comprehensible, and the Director’s attitude that social interactions were more important than studying perplexed me. Professor Dwyer called me to his office to say he was concerned that I did not get on with the nursing staff, describing that I was considered a robot

who would do rounds, write very clear notes, carefully chart medicines and not leave any room for error. He complained I left no room for “normal social interaction”. I asked him if he was asking me to make errors for conversations sake; this was not a discussion I would recommend having with the head of medicine.

I finished ECMFG and started studying for the FRACP. Professor Dwyer felt I was ill-suited to be a physician. He wrote an assessment that said I had below average inter-personal skills. I retain a PDF copy as a reminder of that one can always do better. I was not appointed to the medical training scheme that was designed to facilitate examination study. Jim Lance had to insist I was appointed as a medical resident and vouch that I would keep out of trouble; without his intervention I would not have had a job. The situation turned out to be a boon; unencumbered by the scheme I could work in a self-directed way, and I had time to get the initial CGRP work done. The then senior medical registrar was delegated to tell me that I could take the examination, a form needed to be signed, as long as I agreed that if I passed, I would not pursue a clinical career but rather a laboratory career. I agreed to the deal, regarding any agreement as a reasonable ploy for the greater good.

I have seldom been totally lost for words. On the first medical Grand Rounds after the FRACP clinical examination at which I passed, Professor Dwyer greeted me with enthusiasm and hugged me. I have never had a more disingenuous interaction to this day.

Completing the FRACP let me focus on neurology and my laboratory work. My collaboration with Lars Edvinsson blossomed and culminated in the study of neuropeptides in acute migraine (4), which cemented for us the CGRP hypothesis of migraine. We collaborated on cerebrovascular physiology studies of novel neuropeptides and I could focus during the day on neurology training and learning particularly about migraine. I completed six full publications for the MD and submitted it in the months before I went to London for further training. Jim Lance told me I should go and get polished a little; as with all his advice, it was excellent, and admittedly needed. Queen Square was arguably at its peak. David Marsden, Anita Harding and Andy Lees in movement disorders, Ian McDonald in MS, Ralph Ross-Russell in vascular neurology, John

Morgan-Hughes in muscle, PK Thomas in peripheral nerve, Martin Rossor in dementia, Simon Shorvon in epilepsy, John Scadding in pain and Roman Kocen, ever disciplined, in general neurology. I met colleagues for life; spent many weekends in Paris doing cerebrovascular physiology to learn some more laboratory skills and was bitten by the excitement of being in the midst of the action.

I applied for Wellcome Trust funding to return to Australia and was successful. Returning in 1991, I set up a physiology laboratory for myself drawing on what I had left, and with great generosity and collaboration of Sandrino Zagami and Geoff Lambert. I continued the collaboration with Lars Edvinsson when we tested the effect of the recently developed sumatriptan on CGRP levels in migraine, showing them to be normalised (5). We showed shortly after that CGRP was involved in a truly horrible problem: cluster headache (6). These studies really cemented the CGRP target in migraine and cluster headache that has proven now to be so useful. I went back to London after four years in Australia and have never lived in Australia since.

I have been almost indescribably fortunate to be able to have seen the CGRP story through the last translational mile in recent clinical trials (7);(8). I have always wanted to make the world a better place for people with disabling headache disorders and have been fortunate to work with patient groups, such as the Migraine Trust and the Organisation for Understanding Cluster Headache (UK), who have taken me in and treated me as one of their own. I understood this best when the late Michael Pollock, who was chair of the cluster headache group and a long term patient, told me on his death bed that he was more scared of his next cluster attack than dying; and by the way would I speak at his funeral. I have spoken in front of large audiences and on television and radio, and not to diminish these, yet the sense of trust and responsibility I felt the day I spoke at Mike's funeral still gives me both pause and purpose today.

More personally, I have three children James, an obstetrics/gynaecology trainee, David, a recruitment consultant, and Georgia, a student of political science and influencer video producer. What I lack in intelligence, charm, savvy, and goodness, all resides in them with a measure that makes me prouder than

anything else in this narrative. I can say I have no hobbies and I do not like reading books, well fiction books. I like browsing Wikipedia on mathematics and computer security. I consciously chose in 1994 when I decided to move to the UK to stop having hobbies and focus on work. I do not regret that decision at all. I like mindless action movies. I like travelling to places I have not been, meeting colleagues and, of course, touching base with Australia from time to time.

There are two components to success in combining research and clinical work. The first, and most important, is your mentor and colleagues. A good mentor will nudge you when off course and opens doors that are otherwise inaccessible. Good colleagues make the difficult doable. I have been blessed by both. Jim Lance taught me the job of training others; certainly, who we train and how we motivate them is one of the exceptional opportunities that academia offers.

The second thing is totally personal. The degree of success you will have is in proportion to how hard you work. It is not magic. The more success you want, the more you have to be prepared to sacrifice. Work-life balance is a myth in the sense that it can be achieved at all levels of success; in my experience it cannot. There is nothing wrong with being unbalanced, if that is what you enjoy. Rule two: do what you enjoy in proportion to its enjoyment.

My greatest fear in life is retirement; I cannot think of a more painful experience than not being able to work. I feel privileged to work in medicine with headache disorders, to make some small differences and help the incredibly brave patients I see do just a little better.

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Michael Moskowitz

The first major breakthrough in treating migraine happened by accident more than 150 years ago, when an Italian doctor treated a patient for postpartum hemorrhage with an extract containing ergot alkaloids, powerful smooth muscle constrictors, and discovered it also stopped a migraine attack.

The modern era of migraine therapeutics, and my part in it, began more than four decades ago in a much more scientific way—with the generation of a hypothesis based on knowledge of the tissues within the cranium that sense pain, the proximity of pain fibers to blood vessels, and emerging evidence of neuromediators released from pain fibers. This hypothesis ultimately led to the discovery of many therapeutically-relevant drugs and biologicals that have brought lasting relief to tens of millions of migraine sufferers who once had few options other than lying in a darkened room.



Surrounded by maternal grandparents

My own journey to these discoveries started, like so many Americans, with my European forebearers escaping religious persecution to find opportunity in the teeming streets of New York City. Both of my Jewish grandfathers endured tremendous hardships before fleeing to the west. My maternal grandfather was born in Kiev and learned to play a

musical instrument so that he could travel to border towns with the Russian army band. He walked across the border and came to New York. My paternal grandfather, my namesake, labored as a coal miner in the Carpathian mountains until he emigrated with his family to work in the coal mines of Scranton, Pennsylvania. After he was diagnosed with black lung disease the family relocated to New York's lower east side, where he entered the dry goods business. Years later I learned from my mother that our relatives that remained in Russia were not as fortunate.



With my sisters and parents, 1940s

My grandparents brought very little with them from the “old country,” but they showered us with much love and affection, which is what truly matters. I was born in New York in 1942. My father, a physician, was away serving in the armed forces and I only met him for the first time at age 3, when Dad returned from Australia where he had been caring for wounded soldiers. Even after his return it was my mother who raised me, the second of four children, with help from her parents and sister's family who lived nearby.

When I was 10 we moved to the Rockaways, a remote part of Queens surrounded by ocean, to a home seven houses from the beach. It was a glorious place to grow up, with summers filled

with swimming and sports, especially baseball—between sunburns.



Me and my siblings at Bear Mt Park

I also developed a love of music, which I have sustained to this day, thanks to my mother, older sister and extended family. Not infrequently I took the bus and subway into Manhattan to buy records or hear concerts at Carnegie Hall, often with my mother. While in her 70s my mother learned jazz piano and played until she died at age 103 (I know she would enjoy having me mention this). I played the oboe and piano, and Saturdays were reserved for lessons and woodwind chamber playing with my family. To this day music remains my cathedral and medium for escape; family reunions at music festivals remain a highlight. I am forever thankful to my mom.



With my mom, Clara

I was educated in the public schools of Brooklyn and Queens and graduated from Far Rockaway High School in 1960—the alma mater of the Nobel Laureates Richard Feynman, Baruch Blumberg, and Burton Richter, well before my time. By then my interest in medicine was beginning to take hold.



My parents and I at college

My father, a general practitioner, had his office in the basement below our apartment and I would often accompany him on Saturday house calls. At age 14 I was thrown into the deep end of medicine when I took a summer job as a messenger boy at the Jewish Sanitarium for Chronic Diseases, a home for patients afflicted with severe developmental defects, dementia, end-stage neurodegenerative diseases, and debilitating strokes. I initially felt frightened and overwhelmed by such severe incapacity, but these desperate patients also roused my curiosity about how the human nervous system could go so awry. The memory of those extremely ill patients still lingers, and the experience drew me like a lodestone to an interest in neurology. I wanted to better understand and treat disorders of the brain, this mysterious organ. Working at the Sanitarium gave me a sense of purpose, and a goal.

I attended Johns Hopkins University and Tufts University School of Medicine, then trained at Yale in internal medicine. One of my attending physicians, Melvin van Woert, had worked with the Greek American scientist George Cotzias to discover L-DOPA for Parkinson's disease. Dr. van Woert regaled me with stories about one of the most exciting bench-to-bedside discoveries in the history of neurology. How ideal: to discover

a pathway, identify a deficient transmitter, develop animal and human models, and discover a transmitter-modifying therapy that had a huge impact on disease and greatly benefited patients. This strategy for deciphering complex disorders of the nervous system became a model for my own work.



My lab circa 1995, at MGH's historic Bulfinch building

While training in neurology in Boston at Peter Bent Brigham, Boston Children's, and Beth Israel Hospitals, I developed my interest in migraine, a mysterious and fascinating condition that lacked an obvious pathophysiology and explanation. The impact on quality of life was clear, and the illness presentation fascinating. I believed it could tell us something very important about the organization and function of the brain.

Also, though migraine afflicts some 100 million people worldwide, little was known about the disease at the time. There was no consensus on whether migraine headaches arose from inside or outside the cranium, or whether migraine was an organic or psychological disorder. There were no animal or tissue models and no pathology. Treatment options were suboptimal and the field lacked any coherent dogma to explain the origins of pain and aura or its diverse manifestations. If it had I probably wouldn't have been interested.

My thinking about migraine began to crystallize as a postdoctoral fellow and junior faculty at Massachusetts Institute of Technology (MIT), in the Harvard-MIT Division of Health Science & Technology. I questioned the commonly-held hypothesis that migraine was caused by swelling of the blood vessels in the head and scalp, possibly due to vasoactive substances within the circulation. This failed to

explain why many migraine headaches were experienced on only one side, with pain sometimes stopping abruptly at the midline. I reasoned that headaches caused by circulating substances should trigger headache on both sides, since both receive the same arterial blood.



At Fenway park with Tali, daughter Jenna and Mattia

At MIT I became inspired by the published writings between 1910-1950 of Cushing, Penfield, Ray, Woolf, and Feindel at the Countway Library. It was fascinating to learn how they discovered that the connective tissue coverings of the brain (the meninges) were the only pain-sensitive structures within the cranium, as the brain itself is insensate. There was a striking lack of evidence of pain fibers in the arterial connections at the base of the brain, called the circle of Willis, but I was learning from patients that strokes in large meningeal vessels caused headaches. It was clear that a fresh look at the vascular innervation was needed. This is where I dropped my first scientific anchor. The field was awash with possibilities and I was hopeful that out of this chaos might come clarity.



Our annual photo in the daffodils

In 1979, my MIT colleagues and I proposed a hypothesis based on scant evidence. Little was known then about the role in nerve fibers of vasoactive peptides, substances that can dilate blood

vessels. Our hypothesis was based on meager evidence from other organ systems and included substance P, the only known vasoactive peptide, established in spinal sensory nerves. We emphasized in a seminal paper published that year in *The Lancet* the importance of the "release of substance P or as yet unidentified peptides and other transmitters from the fifth cranial nerve," and suggested that "peptides and other neurotransmitters may participate in the pathophysiology of migrainous headache and might suggest new strategies for prophylaxis and treatment."

The paper was a major breakthrough, the first to introduce the concept of the trigeminal nerve and vasoactive peptides stored and released from sensory fibers in meninges. It changed the direction and orientation of thought and focus in the field.



It doesn't get any better than this

Following publication of our *Lancet* hypothesis, my lab discovered the trigeminal (sensory) nerves supplying the circle of Willis by using novel axonal tracing techniques, aided by a polymeric slow-release system developed by MIT colleague Robert S Langer. Marc Mayberg ran this project; Lee-Yuan Liu Chen and he performed studies that identified the first vasoactive peptide within this pathway. We described these discoveries in seven papers between 1981 and 1984.

Because less than 50 percent of the trigeminal neurons projecting to the meningeal coverings of the brain contained substance P, we also anticipated the discovery of other vasoactive neuropeptides. Our work on this first candidate was accepted for publication or published before the discovery of a second and more therapeutically relevant vasoactive neuropeptide called CGRP, found in nerve fibers surrounding intracranial blood vessels, and before discovery of a third, PACAP. We

named this important pathway the trigeminovascular system.



With my wife upon hearing the news of The Brain Prize

Using the trigeminovascular system as a template, Gabriella Buzzi in my group was the first to provide pharmacological evidence that ergot alkaloids and triptans inhibited CGRP and substance P release, thus abrogating inflammation caused by peptide release. This work emphasized the expression of serotonin receptors on sensory fibers that led to the commercial discovery and development of a 5-HT_{1F} receptor agonist that relieves migraine headache but does not constrict blood vessels. It is now available clinically for acute therapy.

Summarizing the first decade of research, our team provided a template and roadmap leading to the present, but we still had much work to do. Although trigeminal activation, peptide release, and neurogenic inflammation were important in treating migraine, the upstream trigger was still unknown. My lab found such a trigger—an intense, metabolically-demanding brain activity called cortical spreading depression (CSD), the brain mechanism that underlies migraine auras.

Several multidisciplinary studies have shown that CSD activates the trigeminovascular system and causes pain. Hayrunnisa Bolay along with collaborator David Boas provided convincing evidence that CSD activates a pain reflex and causes meningeal inflammation. Moreover, my close associate Turgay Dalkara discovered in his lab a signaling pathway to inflammation in the brain that activates the trigeminovascular system after CSD. Hong-Wei Jin and Cenk Ayata on my team found that drugs used in migraine prevention make the brain more resistant to CSD,

possibly explaining why treatment reduces the frequency of migraine episodes. In addition to genes, more than likely vascular, metabolic, and psychological stresses will be recognized that modulate and contribute to CSD susceptibility as well as novel mechanisms to be discovered that activate the trigeminovascular system.

Recently, by linking migraine aura with meningeal inflammation, Nouchine Hadjikhani and colleagues at the MGH Athinoula A. Martinos Center for Biomedical Imaging discovered upregulated inflammatory signaling within the meninges and surrounding tissues following repeated episodes of migraine aura in 11 patients, opening promising new avenues to investigate. Much future study remains but advances over the past 40 years represent a triumph of translational medicine and a near-seamless transition from bench to bedside in the service of providing better treatments and a roadmap for future discovery.

For my work with trainees, I am immensely proud to have been recognized by Harvard Medical School with the William Silen Lifetime Achievement in Mentoring in 2007. One of the most rewarding aspects of my research has been training and mentoring more than 110 postdoctoral fellows and graduate students. More than a quarter are now full professors, department chairs, institute directors, and world-wide research directors; a number have become close colleagues and friends.

My most enduring relationships, however, have been family, especially my daughter Jenna who lives just four miles from me with her husband Jacob and my grandchildren Mattia and Tali. They bring great joy and meaning to my life. My wife Mary has kept it all together and has been my constant companion, plus a wonderful stepmom and grandmother. I cannot imagine a more generous and loving partner.

I write this autobiography from home during a raging pandemic. It makes me realize how interconnected we all are, and how fortunate I am to belong to an international community of medical scientists who recognize and respond to the needs of the suffering. That 14-year-old messenger boy could never have imagined the scientific journey he would embark on, nor how well served he would be by the legacy of his parents and grandparents.

Jes Olesen

I was born in a small town in the western part of Denmark called Jylland. There were no gymnasiums (the Danish equivalent of high school) so instead I went to the boarding school called Herlufsholm, far away from my hometown. The school made me very independent and, since it was full of pupils from the higher circles of Danish society, it also made me ambitious if this had not always been my nature. My dad was a general practitioner in the countryside and my mom a dentist, so my choice of medicine at the University of Copenhagen was no big surprise.

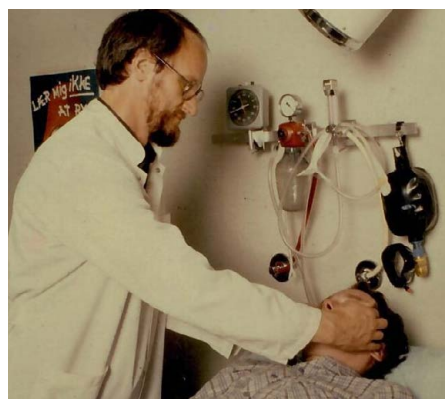


Here at my confirmation party with Mom and Dad

After medical school, the only thing I knew was that I should not be a surgeon. Internal medicine was an obvious choice, but I was not quite sure that I was intelligent enough to match all the extremely clever people I met at the Department of Internal Medicine and Hematology. I sought something easier and considered pediatrics but ended up with neurology. The choice was strongly influenced by my close friend professor Olaf B. Paulson who was already engaged in an advanced research project lead by the world-famous scientist and expert in brain circulation, Niels A. Lassen. Olaf told stories about many foreign and particularly about American visitors to the lab, trips to international conferences which in those days were a very rare thing and first and foremost about the exciting studies of brain blood flow in real human beings. I got accepted in Lassen's group and was the first to use a new type of equipment, the only one in the world, that allowed the measurement of regional cerebral blood flow from 35 areas of a hemisphere. We used the intracarotid injection of radioactive xenon and I did several studies of the pharmacology of the cerebral circulation and of the physiological regulation of human brain blood flow. Rather happily I became the first person to show that when a person opened and

closed his fist, the regional brain blood flow increased in the hand area of the corresponding hemisphere. I also showed that during visual stimulation blood flow increased in the visual cortex, but I thought that it was hardly worthwhile to publish when I had already published the effect of hand movement. It was a complete misjudgment because the relation between brain functioning and brain blood flow and metabolism has later become a huge avenue of research with thousands of publications. My own findings have more or less been forgotten because they were published already in 1970.

Instead, I pursued my interest in neurology and watched out for a big neurological disease where brain blood flow was expected to contribute.



Young dr. Jes examining a headache patient

My chief, professor of neurology Erik Skinhøj, and my friend Olaf B. Paulson had already done a study in migraine patients demonstrating reduced brain blood flow during the aura using relatively simple equipment. Their findings seemed to support the then popular ischemic theory proposing that the aura symptoms were due to arterial vasospasm and cerebral ischemia and the headache due to reactive hyperemia. Soon after I was able to show, with equipment allowing 254 hemispheric areas to be measured, that blood flow changes started at the back of the brain and spread gradually forward not respecting territorial supply of major cerebral arteries. These changes were very similar to the animal experimental phenomenon called cortical spreading depression and soon after Olaf B. Paulson and Martin Lauritzen did more detailed studies further validating the idea of cortical spreading depression as the underlying phenomenon of the migraine aura. Finally, in 1990 I combined several studies and showed that

brain blood flow was decreased during the aura and into the headache phase after which it normalizes and then increases above normal but without temporal relation to the headache. The ischemic theory of migraine was eradicated but lingered on in textbooks for another 25 years.

At the end of the eighties, I realized that with existing technologies there was nothing more to gain from studies of patients during attacks since spontaneous attacks cannot be studied at onset. There had also already been several negative biochemical studies confirming this view. I decided to focus on provocation of migraine attacks. Migraine attacks are very unpleasant and painful but cause no damage and are treatable. These unique features made it ethically possible to experimentally induce attacks in volunteer patients. I therefore developed an experimental human model for the study of migraine provoking substances. The first study was on histamine, already known to cause headache. In migraine patients it caused a migraine-like attack while in tension-type headache patients it caused less severe headache and in normal controls even less headache. Later, in a double-blind trial, we showed that headache induction was caused by activation of the H1-receptor independently of nitric oxide. Unfortunately, it was also clear that anti antihistamines did not work in migraine. So, the experimental model did not always predict the effect of an antagonist. The next series of studies focused on the gaseous neurotransmitter nitric oxide (NO). The NO donor nitroglycerin caused a short-lasting headache in normal individuals and in migraineurs, but the migraineurs also got a delayed more severe headache attack that fulfilled the diagnostic criteria for a migraine attack. Several studies investigated different aspects of NO-induced headache/migraine. Nitric oxide was thus of importance in generation of migraine attacks. It was, however, also important for the entire duration of the attack because an inhibitor of all 3 nitric oxide synthase (NOS) enzymes was effective in treating spontaneous migraine attacks. Unfortunately, non-selective NOS inhibitors are not suitable as drugs. Selective inhibitors of inducible NOS were not effective in migraine. No good selective compounds have been developed for eNOS and nNOS and no drugs have been tested that modulate the further downstream reactions in the NO-cyclic guanylyl cyclase cascade. Several possibilities are

right there waiting for the pharma industry. Next, we studied the influence of calcitonin gene-related peptide (CGRP). Like nitroglycerin, it caused headache in normal individuals and migraine attacks in migraine sufferers. This was a crucial finding for the industry in combination with Goadsby's and Edvinsson's finding of increased secretion of CGRP from the head during migraine attacks. Together they led to the development of a CGRP receptor antagonist, olcegepant. We showed that olcegepant did not affect hemodynamic parameters or brain blood flow and therefore was safe. Olcegepant in a double-blind study was highly effective in the treatment of migraine attacks. The first CGRP receptor antagonist olcegepant was however not developed because of its unsuitable pharmacokinetic characteristics. But the proof of concept had been made, and it greatly stimulated the development of human monoclonal antibodies against CGRP or its receptor. They are now widely used and represent a revolution in migraine prophylaxis. Small molecule CGRP receptor antagonists that are orally available have also now been marketed. Pituitary adenylate cyclase activating peptide (PACAP), like CGRP, is present in trigeminal nerve fibers. It has several similarities with CGRP. It also induced headache in normal volunteers and migraine in migraine sufferers. That was not the case, however, for the related peptide vasoactive intestinal peptide (VIP).



Wife Inger and daughter Astrid during sabbatical in Boston in 1999 visiting New York. We all love the United States and come back very often



The second headache classification committee left. Top right meeting of the management committee of the European Federation of Neurological Societies and bottom right explaining the coalition European Brain Council



In asthma trials during the 1990s, openers of the ATP-sensitive potassium channel Katp had headache as a very prominent side-effect. At the time we could not get a Katp channel opener because companies producing it tried to find other clinical indications, but it was possible to study the channel in our animal experimental models. Together with my wife Inger Jansen-Olesen we showed that one of many isoforms of the Katp channel, the SUR2B/Kir6.1 channel was most likely responsible for headache induction. Colleague professor Messoud Ashina managed a couple of years ago to get the Katp channel opener levcromakalim in a form that could be used in human patients. He showed that every single patient in a double-blind cross-over trial developed migraine after infusion of levcromakalim. Unfortunately, there are no Katp channel antagonists that selectively block the SUR2B/Kir6.1 isoform available for human use. We were able, however, to validate non-selective KATP channel inhibition in animal models of migraine by demonstrating that it had a significant therapeutic effect on spontaneous allodynia in rats and on allodynia induced by nitroglycerin injection in mice. Currently we are further exploring these channels in animal studies.

These were my most important scientific achievements in a nutshell. Along with my scientific work I have always been interested in professional organizations. I started a patient organization for Danish stroke patients and was president of the International Headache Society. I chaired the International Headache Classification Committee for almost 30 years and published 3 subsequent versions of the International

Classification of Headache Disorders. The fact that different headache disorders became clearly defined by explicit diagnostic criteria has had a great impact on headache science throughout the world. I was also the prime organizer of the European Federation of Neurological Societies EFNS, later fused with the European Neurological Society into the European Academy of Neurology. Finally, I took the initiative to form and was the first president of the European Brain Council EBC which is a coalition of European-wide organizations of neurologists, psychiatrists, neurosurgeons, basic neuroscientists and patient organizations within neurology and psychiatry. The activity of this organization over a decade in Brussels has been a significant factor behind a twenty-fold increase of funding for brain research by the European Union.

What about my private life? It is probably not a surprise that I have been a workaholic all my life, usually working around 70 hours a week. It has had its consequences in the form of two broken marriages but fortunately ending happily with my present wife whom I married 27 years ago. She is also an internationally recognized scientist in the migraine field. Thus, we share not only our bed but also our scientific interests. I also have 4 wonderful children who are all successful. At my present age of 79 I have decreased my workload to maybe 40 hours a week which has allowed more time for my children and grandchildren. Apart from a prostate cancer and a vascular stenosis that were successfully operated I have enjoyed excellent health. I still play tennis 4 hours a week and I bicycle around 100 kilometers a week.



In the middle of my family a few years ago

Fortunately, there are still new horizons to explore. One of them is the genetics of migraine in which I have been increasingly active over the last 20 years, but now we have an extremely strong group lead by Thomas Folkmann Hansen and fantastic materials that will allow, I hope, to solve at least part of the mystery of the inheritance of the prevalent types of migraine, migraine with

typical aura and migraine without aura. The other major horizon I want to explore together with senior scientist David Møhbjerg Kristensen is to finally get the puzzle about migraine's biochemical mechanisms a bit more together. Three decades of provocations and experimental work have revealed many substances that can induce a migraine attack and substances that

cannot. Therefore, it should soon be possible to find out how all the signaling molecules work together in causing a migraine attack. But if that is to be achieved, I must continue a bit longer and why not? Is anything in life more interesting than science? Family of course, but apart from that my answer is no.

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