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Migraine

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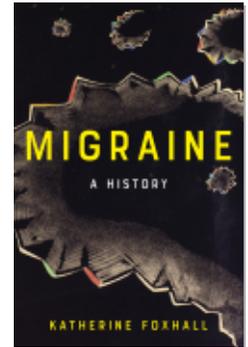
Published by Johns Hopkins University Press

Foxhall, Katherine.

Migraine: A History.

Baltimore: Johns Hopkins University Press, 2019.

Project MUSE., <https://muse.jhu.edu/>.



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Conclusion

At the annual scientific meeting of the American Headache Society (AHS) in June 2017, researchers were excited. Four different companies were announcing positive results from large-scale phase 3 trials for monoclonal antibody therapies to prevent migraine. The data were good: overall, the antibodies halved the number of days with migraine for almost 50 percent of the patients in the trials—a gold standard for preventive treatment.¹ All of the drugs (known as mAbs) target the neurotransmitter calcitonin gene-related peptide (CGRP) or its receptors.² CGRP is a molecule produced by nerve cells in the peripheral and central nervous systems. It is the most potent vasodilator we yet know of in the human body, plays a role in the transmission of pain, and is essential for the maintenance of normal brain circulation. CGRP is most concentrated in the nerves of the trigeminovascular system—the part of the brain responsible for head and face pain—where neuroscientists now think a migraine attack is initiated when the nerves are irritated or stimulated in some way. CGRP was first identified as playing a potentially important causative role in migraine attacks in the 1980s, when researchers observed that increased levels of CGRP (and only CGRP) were present in the cranial blood circulation and in saliva during acute migraine attacks.³ Intravenously infused CGRP was found to induce a migraine-like attack both in patients having migraine with aura and those without aura, supporting the theory that the mechanism of headache induction in both types of migraine could be similar. In chronic migraine, CGRP levels remain elevated.⁴

MABs are not the first migraine drugs to target CGRP. At the turn of the current millennium, migraine researchers hoped to develop a new class of

drugs—gepants—that would act as CGRP receptor blockers without the vascular complications of triptans. Enthusiasm for them was unexpectedly short lived, as these drugs were proven to have potentially serious side effects on the liver with prolonged use.⁵ It was then that scientists began to wonder whether monoclonal antibodies might provide an answer. This was a fast-growing sector of the pharmaceutical industry, promising treatments for diseases including cancer, multiple sclerosis, asthma, and rheumatoid arthritis.⁶ Could antibodies work for a disorder characterized by pain? It seemed unlikely if the molecules were too big to pass through the blood-brain barrier and into the brain, which is where most researchers thought any effective drug for migraine would need to act.⁷ Given these doubts, the announcement at the 2017 AHS meeting that a class of migraine-specific prophylactic mAbs had been successfully created—drugs that were able to prevent attacks over a period of several months—was “a genuine watershed moment,” Peter Goadsby declared.⁸ While further research was needed to understand their long-term effects and safety, in the short to medium term, all of the monoclonal antibody drugs, which are injected either under the skin or into a vein, appeared to be safe, effective, and more tolerable than triptans.

In May 2018, the FDA approved the first of these drugs (erenumab, marketed by Amgen and Novartis as Aimovig, a self-administered monthly injectable medication) for the preventive treatment of adult migraine. The drug was approved in Europe a few months later. In September 2018, a second FDA approval for Teva’s drug Ajovy (fremanezumab) followed. Drugs that target CGRP are not a panacea, however. They do not reduce pain in all cases, and—although at around \$7,000 per year the initial cost to consumers is lower than expected—such a price tag still raises pressing questions of access.⁹ Among those patients for whom the mAbs work, who will get treatment? Moreover, who will pay for it? In the United States, headache specialists are concerned that insurance companies are restricting access to new therapies that will need to be taken on a chronic basis, when cheaper existing drugs appear to offer similar effects.¹⁰ For anyone without insurance, the cost could be prohibitive. This question of access to pain relief is not a new one, nor is it likely to be resolved in the near future. Even triptans, now available in generic and over-the-counter form in some countries, can still be prohibitively expensive for people with a limited income, as well as in low- and middle-income countries. In 2010, a study published in *Neurology* concluded that uninsured American patients with migraine and those reliant on Medicaid were less likely to receive standard abortive or prophylactic migraine treatment, partly because

they were more often treated in emergency rooms than in a physician's office. The result of the study, the authors comment, is "a reminder that access to some forms of insurance is not the same as access to adequate care." Moreover, they acknowledge that "inadequate insurance magnifies the already high burden of migraine on low-income families."¹¹ In England, the National Institute for Health and Clinical Excellence (NICE, the licensing body for NHS treatments) has agreed to include prescriptions for Botox injections for chronic migraine since 2012, and in Scotland, approval was granted in 2017. The NHS has also funded occipital nerve stimulation for adult patients with intractable chronic migraine since 2015. But this new generation of monoclonal antibodies will have to prove their cost effectiveness to be accepted by insurance companies, the NHS, and other medical systems under a great deal of political, social, and fiscal pressure.¹² Financial and ethical decisions will need to be made about whose migraine is treated. If these discussions are difficult in wealthy countries that experience socioeconomic, racial, and gender disparities in population health and medical care, they will be even harder in resource-poor countries facing other pressing public health crises, such as HIV, tuberculosis, or malaria. Migraine-specific drugs are not included in the WHO lists of essential medicines, and, as Paulo Martelletti argues, unless we are to treat a billion such sufferers worldwide, the priority will be in preventing and reducing chronic migraine.¹³

Our understanding of migraine, and its global burden, has changed rapidly in recent decades. During the 1970s, neurologists undertaking hospital-based studies had assumed that migraine was rare in Africa. Later research presented a more complicated picture but nevertheless suggested that a lower prevalence among Africans might be attributable to a variety of reasons, including underdiagnosis, greater pain tolerance in rural communities, and genetic factors. In the 1990s, studies conducted in the United States indicated that migraine prevalence was lower among African Americans and Asian Americans than populations with a Caucasian background—a finding for which the authors suggested race-related differences in genetic vulnerability were a likely explanatory factor.¹⁴ More recently, surveys carried out in the United States using the *ICHD* criteria have indicated that inequalities in migraine diagnoses, medical care, and treatments are likely to account for disparate burdens across different racial and ethnic groups. While confirmed migraine is more prevalent in non-Hispanic whites, researchers have found the incidence of *probable* migraine to be higher among African Americans. Moreover, African Americans experience a greater burden from migraine,

with it being “more frequent, more severe, more likely to become chronic and associated with more depression and lower quality of life.”¹⁵ Other research has indicated that the occurrence of migraine might be greatest among Native Americans, a highly disadvantaged group.¹⁶ These results should not be surprising. Minorities have been systematically underrepresented in clinical trials for migraine, while women (unusually) are overrepresented. As a result, the clinical trial population does not adequately characterize either the general population with migraine or the multiple varieties of the disease.¹⁷ We also know that persistent racial and ethnic disparities and biases lead to the systematic undertreatment of minorities for all kinds of pain, whether that pain is acute, chronic, caused by cancer, or amenable to palliative care.¹⁸

In 2003, in *World Health Report 2001*, the World Health Organization published the results of its first Global Burden of Disease (GBD) survey, conducted in 2000, and ranked migraine nineteenth in global causes of disability, responsible for 1.4 percent of all years lived with disability (YLD).¹⁹ For the headache research community, the report’s recognition of migraine’s public health burden gave credibility to their repeated calls for greater research investment, funding, and political action. Nevertheless, leading experts in the field of headache disorders argued that disability from migraine (with and without aura) remained underreported. In an editorial published simultaneously in the journals *Cephalalgia*, *Headache*, and the *Journal of Headache and Pain* in 2010, three leading experts criticized the 2000 Global Burden report for considerably underreporting migraine disability and for generally giving a “very poor account” of headache disorders. Primarily, this had been because of a lack of evidence, particularly for China, India, Southeast Asia, Africa, the Eastern Mediterranean and Eastern Europe.²⁰ In the years since the first GBD survey, Lifting the Burden’s Global Campaign Against Headache, a worldwide collaboration between the World Health Organization, nongovernmental organizations, academic institutions, and individuals, has collected a great deal of new evidence.²¹ As a result of this effort, as well as the increasing international acceptance of standardized criteria for migraine, the 2010 Global Burden of Disease report radically updated earlier findings related to the burden of headache disorders. Steiner and colleagues cited the 2010 survey’s estimated worldwide prevalence of migraine to be 14.7 percent—making it the third most common disease in the world, behind dental caries and tension-type headaches, and the seventh highest specific cause of disability globally. Migraine had become, “by a large margin, the leading cause of disability among neurological disorders.”²² While this recognition was a breakthrough for the

field, the implications of this new status for headache disorders were unwelcome. Experts were “appalled” to find largely treatable headache disorders “among these ignominious top ten.”²³

By the 2013 Global Burden of Disease report, migraine, by itself, was up to sixth in the leading causes of disability worldwide. When combined with “medication overuse headache” (at eighteenth), headache disorders ranked third among all causes of disability worldwide. While data on migraine in earlier reports had predominantly come from Europe and the Americas, the 2015 Global Burden of Disease report confirmed that migraine ranked between fifth and eighth among causes of disability in *all* regions of the world, an important rebuttal to racialized assumptions about lower migraine prevalence among Africans, in particular. As new studies provide more accurate data, researchers predict that the proportion of global disability correctly attributed to headache disorders will continue to rise.²⁴ Nonetheless, much more research is needed to understand how migraine burdens around the world relate to gender, socioeconomic status, race and ethnicity, and access to effective treatments.

Having easy access to modern drugs is not the only answer, however. Increasingly, physicians and researchers interested in migraine are concerned that the frequent use of acute medication can lead to medication overuse headache, which can be a major factor in the transformation from episodic to chronic migraine. Perhaps the most significant change in the second edition of the *International Classification of Headache Disorders* in 2004 was the introduction of chronic migraine as a diagnosis for patients who fulfilled diagnostic criteria for migraine (without medication overuse) on more than fifteen days per month for three months or more.²⁵ Most recently, *ICHD-3* has incorporated chronic migraine into the main body of its classification, identifying it as a major type of migraine, alongside migraine without and with aura.²⁶ As recent research has shown, however, what the distinction between episodic and chronic migraine actually means in practice is not clear. One study argues that patients with ten days of migraine a month (high frequency episodic migraine) experience as great a level of emotional and functional impact through disability, loss of quality of life, and direct and indirect costs as patients who reach fifteen days and come into the official chronic category.²⁷

Moreover, we are still by no means certain what migraine actually is. While some researchers hope to discover a common biochemical pathway in the brain that will eventually unify all of migraine’s diverse symptoms into a single mechanism, genetic research suggests an alternative picture. Early on, this

research into migraine identified three ion channel genes that could cause rare and severe forms of migraine disorder, such as familial hemiplegic migraine. These “simple” gene mutations for specific subtypes, however, did not appear to be linked to common migraine. Following the completion of the human genome project in 2003, researchers have been able to undertake much larger genome-wide association studies that identify genetic contributions to a whole range of diseases. At the time of this writing, in 2018, more than forty genetic variations have been found to affect susceptibility to common migraine. Significantly, these genes appear to be involved with vascular and neuronal processes in the two main types of migraine (with and without aura), a finding that opens the door to yet another potential reassessment of the role of vascular processes in migraine.²⁸ Advances in genetics promise greater insight into the molecular mechanisms of migraine attacks, which, in turn, may help improve patient care and individualized treatment. But, yet again, a great deal remains unknown, including how genetic variations might interact with environmental or socioeconomic factors.²⁹ Determining the extent to which global regional differences in migraine prevalence might be genetic—rather than the result of underreporting, disparities in the provision of healthcare, political decisions about funding and drug approval, and the inherent weaknesses and biases of diagnostic models that rely on self-reported pain—will require very carefully considered research, robust data, and sensitive interpretation.³⁰ As the authors of one recent paper point out, undertaking population studies large enough to enable convincing genetic conclusions will require a huge amount of resources, as well as international collaborations across a range of academic, clinical, and commercial partners.³¹

Standardized, globally accepted classifications have allowed more robust, comparable analyses, and new neurobiological frameworks for migraine have afforded better recognition and increased funding, improving the professional status of an unfashionable field. Neuroimaging of patients both during and between attacks offers the possibility for much greater understandings of how drugs act in the brain; how episodic and chronic migraine affect brain structure, function, and neurochemistry; and why patients respond differently to therapies.³² Yet, as Joanna Kempner argues, greater understanding of migraine’s biological reality does not necessarily endow legitimacy or reduce stigma. People with migraine continue to be seen in terms of moral and social failure—weak, excitable, sensitive, neurotic hypochondriacs who are unable to cope with everyday life.³³ As our knowledge continues to evolve, and in whatever biological leads we choose to follow in the hunt for migraine’s causes and

mechanisms, we must take care that we don't ignore the varied experiences of people who are in pain, as well as the conditions in which they live their lives and access medical care. In particular, we should not sideline people whose pain (especially chronic pain) is *not* reduced by pharmaceutical advances, or whose symptoms do not conveniently fit the classificatory boundaries we select in order to define what does, or does not, constitute migraine at any given moment.

At various times and places, migraine has meant a number of things, and changing definitions have emphasized different symptoms to fit explanatory models. Yet the constancy and severity of pain at the heart of migraine, and people's attempts to manage that pain, have woven their way through the entire history this book has recounted. From the classical period, throughout the Middle Ages, and into the early modern period, pain was the central component of a disease understood in terms of humors. Descriptions of it are visceral, and sometimes violent, and they provide a compelling logic for its severity. In the seventeenth century, concepts of migraine began to broaden. First, we can see a shift in the vernacular meaning of *megrim* to incorporate sensations of dizziness, turning, or nausea. Then, by the late eighteenth century, European medical writers began to emphasize visual symptoms, while, in the wider culture, migraine came to imply nervous weakness, effeminacy, and even an association with quackery. As lay and professional medical understandings of sick headache and bilious headache diverged in the nineteenth century, the records of how working-class patients talked about their own chronic pain (and the way that pain was used in the service of pharmacological development) is in marked contrast to accounts of a painless visual aura that captivated an intellectual elite. The assumption that migraine was a hereditary disorder of educated, scientific men was only one aspect of wider discussions about the disease, but it suited physicians to emphasize migraine's class-related credentials in an age of concern about the role of nervous disorders in social and moral degeneration. Even as more-standardized pharmaceutical sedative treatments for pain became available in the late nineteenth century, physicians were elevating visual aura as the key diagnostic characteristic of migraine. The conceptual primacy that has since been accorded to the visual manifestations of aura can be seen in the diagnosis of Hildegard of Bingen, the persistent celebration of Hubert Airy, and in the Migraine Art competitions, when organizers simply did not anticipate the extent to which entrants (the vast majority of whom were women) would be motivated to represent pain with such visceral clarity. Tellingly, the winning image in the first

competition conformed to a very particular neurological aesthetic of representing migraine “objectively”: one detached from the body, in which pain was absent. On the one hand, emphasizing the visual element of migraine adds important weight to the claim that it is much more than “just a headache.” On the other hand, it paradoxically deflects attention from the aspect of the migraine experience that most requires our attention—severe, debilitating, and radically undertreated pain.

One of the key contributions of this book has been to show how the widely accepted statistic that women account for two-thirds of the people with migraine has been formalized only in the past few decades, despite a long history of discussion about the kinds of people migraine affects. Such an apparently straightforward figure hides a great deal of complexity. Overall, migraine seems not only to be more common, but also be fundamentally more painful and less visual for women, a finding that has real significance when we consider the way migraine has been represented and researched as a highly gendered neurological disorder since the nineteenth century.

If people with migraine are to receive consistent, appropriate, and, most importantly, effective treatment, those driving health research and policy, whether in individual clinics or at the level of long-term global initiatives to address health inequalities, need to be interested in and well informed about how our current understanding of migraine’s neurobiology is founded on a centuries-long social, cultural, and medical history, of which neurology is only a part. That history has shaped our knowledge about the disease, our attitudes towards the people who become patients, and the measures we take to address pain. Even more to the point, when we attempt to comprehend historical ideas and practices on their own terms—particularly when those ideas seem alien to our own concepts, or when the implications of past practices might still resonate uncomfortably—such a history reminds us that our own ideas (not to mention our medicines), however confident we may be now of their value, are also contingent, temporary, and—above all—can be bettered.