outlook

ILLUSTRATION BY TAJ FRANCIS

The puzzle of chronification

Scientists are trying to work out why migraines become more and more frequent in some people — and how to reverse the process. **By Neil Savage**

Len Barbieri started getting migraine headaches when he was 9 years old, although it was many years before they were labelled as such. The condition ran in his family; both his father and his aunt experienced migraines. As a teenager, Barbieri remembers driving his father to the hospital, where only a shot of morphine could provide relief.

By the age of 16, Barbieri was also taking a prescription opioid for the pain. Unlike his relatives, he didn't experience neurological disturbances known as aura before the headache (see page S7), or the sensitivity to light that confined them to darkened rooms. "I just had terrible, terrible headaches," he says. Often the pain would start on one side of his head, then spread to both sides. Over a wider area, the pain felt more diffuse, but when it concentrated down to just one temple, it felt like he was being stabbed. "I remember miserable days," he says.

The attacks persisted through university, and became more frequent during his career working in criminal justice — first as a parole officer, then eventually becoming a warden in the state of Connecticut. Eventually he was having two attacks a week, some lasting two or three days, totalling 10–20 headache days a month. Barbieri powered through them, working his way through various prescriptions that provided some relief. The drugs did not stop the cycle — in fact, they might even have increased the frequency and length of his headaches — but Barbieri felt he had no option but to take what little immediate relief they provided. "Otherwise it was unbearable," he says.

Migraine is estimated to affect more than one billion people, and can vary widely from person to person. However, one notable feature of the condition is that some people see a persistent increase in the frequency of attacks, known as chronification. Every year, about 2.5% of people with episodic migraine, which is defined as fewer than 15 headache days a month, move to chronic migraine, experiencing 15 or more headache days monthly.

Cutting the frequency of a person's migraine attacks can have a considerable effect on their lives — migraines are estimated to be the third leading cause of disability in people under 50 worldwide. For Barbieri, the breakthrough came when he visited Christopher Gottschalk, a neurologist at Yale School of Medicine in New Haven, Connecticut, who established the school's first programme in headache medicine. Gottschalk prescribed an anti-epileptic drug called topiramate, which he says has "phenomenal anti-migraine properties", and nadolol, a beta-adrenergic blocker that is usually used to treat hypertension. Now 73 and living with his wife in Florida, Barbieri has had perhaps three or four headaches a year for the past five or six years, and those that he does have are mild. "I don't think about it any more.

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That's a really big deal," he says.

Barbieri is one of the lucky ones. Only around one-quarter of people with chronic migraine go back to episodic headache or experience complete remission. The drugs that worked so well for Barbieri do not help everyone, Gottschalk says, and their mechanisms are partially understood at best. To stop migraine attacks from becoming more frequent, or even to reverse the progression, researchers first need to out why they become more numerous in the first place. Some are investigating links between headache frequency and common comorbidities, whereas others are looking for physical differences between the brains of people with chronic and episodic migraine. But it's hard to know whether such factors are the cause or the result of more-frequent headaches. And some researchers are concerned that their work might be hampered by the very way that the field defines chronic migraine.

The hunt begins

In search of reasons why only some people progress from episodic to chronic migraine, researchers are asking why certain other conditions are more common in people with more-frequent headaches. Among the most common comorbidities are psychiatric disorders, such as depression and anxiety. In one study, around 30% of people with chronic migraine also experienced depression, compared with about 17% of people with episodic migraine[1]. The proportion of people experiencing anxiety followed the same pattern.

Chronic pain syndromes, such as back pain or post-concussion headache, are more than twice as likely to develop alongside chronic migraine compared with episodic migraine. Factors as varied as obesity, poor sleep and low socioeconomic status are also predictive of chronic migraine. Even a history of childhood sexual abuse might contribute. A 2015 study by the Diamond Headache Clinic in Chicago, Illinois, looked for a history of sexual abuse in 329 people with migraine. Whereas only around 4% of people with episodic migraine had anything to report, nearly 16% of those with chronic migraine had experienced some form of sexual abuse as a child[2].

However, there is an unresolved question in nearly all of these apparent risk factors, says Hans-Christoph Diener, a neurologist at the University of Duisberg-Essen in Germany. "The problem is we have no idea what is the cause," he says. "Are people getting depressed because they have so many headache days, or is migraine getting worse because they independently have depression?" Researchers might see a correlation in the statistics, but it is difficult to say whether these risk factors actually cause the movement towards more frequent headaches in any particular person.

One area in which it might be possible to identify cause is the link between chronic migraine and head and neck injuries. Over the past decade, Gottschalk says, researchers have increasingly come to recognize undetected leaks of cerebrospinal fluid — which could be caused by trauma to the head and neck or by ageing — as a cause of chronic headache. "When you find one and you patch the leak, the problem goes away instantaneously," he says. Now that such leaks have become easier to detect, he would like to see prospective studies that check everyone who comes to a headache centre to work out what percentage of headaches could be attributed to this issue.

"People with headache every day are afraid of it getting worse. That's going to exercise the amygdala."

As well as leaks of cerebrospinal fluid, researchers have gone looking for other physical differences between people who suffer from chronic migraines and those who don't. Todd Schwedt, a neurologist at the Mayo Clinic in Phoenix, Arizona, has used magnetic resonance imaging (MRI) to look for structural differences in the brains of people with migraine. Layers of the cerebral cortex can vary in thickness from point to point, and the thicknesses change as the brain ages. In a 2015 paper[3], Schwedt compared the brains of 15 people with chronic migraine with those of 51 individuals with episodic migraine and 54 healthy controls. He found that variations in structure, with some areas thinner and others thicker, followed a characteristic pattern in people with chronic migraine that was distinct from the patterns seen in people with episodic headaches and healthy controls.

Studies looking at cortical thickness have returned inconsistent results, possibly owing to small sample sizes in some cases. But last year, a large, multi-site study[4] by neurologist Till Sprenger at the University of Basel in Switzerland reached similar conclusions to Schwedt's team. Looking at the brains of 131 people with migraine and 115 controls, Sprenger and his colleagues saw cortical layers in areas of the brain that were thinner in people with migraine than in healthy controls, and also showed a correlation with headache frequency. Again, however, the study did not resolve the question of cause and effect or determine what the mechanism might be, although the researchers surmise that at least some of the cortical abnormalities they saw could be the result of genetic differences that made people more susceptible to migraines.

Chicken and egg

The question of cause and effect is a big problem in migraine research, says Robert Cowan, a neurologist at Stanford University in California. As part of his research, he performed MRI scans on 44 people with chronic migraine and 44 with episodic migraine[5], and found that the right amygdala was 13% larger in the former group. The amygdala is part of the limbic system and is involved in assigning emotional significance to sensory input, so Cowan also asked the participants a detailed series of questions related to their mental state. People with chronic migraine tended to be more anxious and were more likely to see their pain as catastrophic — as might be expected. "People with headache every day are afraid of it getting worse," Cowan says. "That's going to exercise the amygdala, and it's going to get bigger." But it is also possible that cause and effect run in the other direction, and a large amygdala predisposes people to develop more frequent migraines, he adds.

To get to the truth of the matter, Cowan and his colleagues are tracking people with chronic migraine who have been successfully treated and returned to an episodic pattern to see whether their amygdala shrinks. The researchers are also providing behavioural therapy to people with episodic migraine who have high anxiety scores that might indicate a tendency for chronification, with the aim of seeing whether reducing their anxiety and catastrophic thinking makes them less likely to progress to chronic migraines. Cowan isn't sure how much time it will take for either intervention to show an effect.

All of this work is part of a larger study that Cowan's laboratory is conducting to determine the impact of treatment on patients moving from episodic to chronic migraines, or back from chronic to episodic. Over the past five years the researchers have enrolled about 250 people; they would like to get closer to 500. The researchers perform annual MRI scans of each person's brain, and a 'deep phenotyping' group collects about 500 data points on each participant. They assess them on scales of anxiety, depression and stress, record any history of abuse, take a detailed work history, measure their weight, ask about their sleep habits, and more. Researchers also collect samples of blood, saliva and cerebrospinal fluid, and use machine-learning algorithms to examine the data for commonalities. One goal is to predict which people with only a few monthly headaches can manage their attacks

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Len Barbieri was at one point experiencing 10–20 headache days every month.

with just acute pain relief, and which ought to be on longer-term treatment to prevent the headaches from growing more frequent.

Split the difference

Another goal of Cowan's research is to group patients more precisely than the broad categories of chronic and episodic migraine to identify any differences that might increase headache frequency. He thinks that migraine research is hampered by rigidly classifying the condition as either chronic or episodic – the more important question, he argues, is whether the number of headache days is increasing.

Lars Edvinsson, a neurologist at Lund University in Sweden, says that the definition for chronic migraine – as set by the International Headache Society in London – is based more on clinical experience than physiological differences. Doctors and drug companies simply wanted some way to distinguish between the more and less severely ill patients, he explains – there is no sudden difference at the molecular level.

Cowan is even more adamant. "The notion of chronic and episodic is ridiculous," he says. "Somebody with 14 headache days a month is not going to be different than somebody with 16 headache days a month." Clinicians, he explains, are more concerned about an increase from four headache days to ten than they are about a smaller increase that carries a patient over the boundary into chronic migraine. Once someone hits 14 headache days per month, Diener adds, further increase is likely, so managing the frequency early is crucial.

One suspect in chronification is overuse of pain medication, particularly opioids, which suggests that cutting back on drugs could avoid the problem. But Gottschalk says that this view has been tempered by evidence that decreasing medication does not always diminish headache frequency. In one small study, for instance, around half of people who stopped taking pain medication for two months saw no improvement in the frequency of their headaches without further treatment[6]. "That's certainly not a home run. It says that maybe sometimes that's the issue, but I don't think that's the main problem," he says.

Instead, he says, it might be the timing of a treatment that is key to preventing an increase in headache frequency. A class of migraine drug called triptans, introduced in the 1990s, can interfere with receptors for a neurotransmitter found in the brain called serotonin to stop a migraine in its tracks if given early enough in the attack. But once the headache has spread through the brain, these drugs don't work. "Migraine is episodic, progressive sensitization of the nervous system," Gottschalk explains. It starts on the edge of the nervous system, where triptans can interrupt it, but quickly triggers further sensitization in the brain. With each migraine, the nervous system grows more sensitive to the stimuli that trigger pain, and future headaches become more likely. Missing the initial window to stop an attack therefore leads to headaches becoming more frequent, more severe and less responsive to early treatment.

Interventions to reverse sensitization seem to back up this understanding of the process. Administration of dihydroergotamine (DHE), an intravenous migraine drug that acts in a deeper part of the brain than triptans, leaves patients headache-free, Gottschalk says. DHE had been used in the past, but it is cumbersome to administer and can have negative effects on blood vessels, so it fell out of favour when triptans were discovered. Now, some companies are developing easier-to-use formulations. DHE is known to interact with receptors for several neurotransmitters, such as serotonin and dopamine. It is not clear exactly what effect the drug has on these pathways, Gottschalk says, but the fact that targeting these receptors can alleviate headaches is a strong sign that they have an important role in migraine. Interrupting the sensitization process might not only treat individual headaches, but also halt the march towards chronification.

Future directions

There is much still to be learned about the causes of chronification and how to reverse it. Cowan hopes that the hunt for interventions to control chronification will be aided by efforts like his to group people with migraine more precisely than simply by whether they have more or fewer than 15 headache days a month. It might, for instance, turn out that people with migraines who have experienced head trauma will do better with a particular drug because their blood–brain barrier has been compromised, which could simultaneously provide both a treatment and an explanation for their specific illness. Other promising paths include working out what part various brain structures play in chronification, and examining the effect of certain molecules in the body, such as peptides that alter the dilation of blood vessels.

Some headache specialists suggest that migraine research is running behind that for many other disabling conditions because people have not taken this invisible, non-fatal illness as seriously as they should. But those already in the field know just how debilitating the condition can be when attacks become more frequent. Chronic migraine might not be fatal, but "it ruins your life", Cowan says. "It's not a silent killer. It's a silent disabler."

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1. Katsarava, Z., Buse, D. C., Manack, A. N. & Lipton, R. B. *Curr. Pain Headache Rep.* **16**, 86–92 (2012).
2. Torphy, B. & Grossman, D. *Austin J. Clin. Neurol.* **2**, 1070 (2015).
3. Schwedt, T. J. *et al. Headache* **55**, 762–777 (2015).
4. Magon, S. *et al. Cephalalgia* **39**, 665–673 (2019).
5. DeSouza, D. D. *et al.* Preprint at medRxiv https://doi.org/10.1101/2020.08.31.20185397 (2020).
6. Zeeburg, P., Olesen, J. & Jensen, R. *Cephalalgia* **26**, 1192–1198 (2006).

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