A rare condition of excruciating eye pain

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Razor blades. Jabbing needles. Barbed wire. Screaming, howling, red-hot-poker-in-the-eye pain. The impulse to gouge your own eyes out or overdose on sleeping pills – anything to make the pain go away.

Blinking can be so excruciating that some people have had their eyelids partially sewn shut. One patient said the pain felt like shards of glass were jutting from her eyes. "Imagine a knife in your eye. Forever," wrote another.

Most causes of eye pain – a stray eyelash, a chemical burn, a dirty contact lens – are obvious and short-lived. But what happens if the source isn't immediately apparent and the agony doesn't stop? Ophthalmologists have made surprisingly little headway understanding the origins of severe and lasting eye pain. Many doctors, in fact, are outright dismissive of intense eye discomfort, deeming it of secondary importance to vision. Patients are often written off as being hyperbolic, narcissistic or even psychiatric.

At 82, Boston ophthalmologist Perry Rosenthal hears regularly from people who are desperate for answers. Although he no longer sees patients himself, he has become the nerve centre of a small but growing network of researchers and clinicians who are defying conventional wisdom and seeking out new explanations for the often jarring disconnect between brutal symptoms and a lack of clear signs.

Rosenthal's nearly singular focus on resolving the mystery has frayed professional relationships, forced him to leave his own charity and nearly

shut him out of a field in which he was once hailed as a hero. A recent burst of research, however, is prompting a new question about his unorthodox ideas: what if he's right?

Neil Brooks' problems began at birth. Colorado-based Brooks, 51, was born long-sighted with crossed eyes and pronounced astigmatism, or irregularly shaped corneas. But it took decades for an ophthalmologist to diagnose a painful eye spasm in the ciliary muscle that helps the eye shift its focus. When his condition forced him to quit his job in commercial real estate, Brooks began searching online for a potential cause and came across a condition called accommodative spasm.

An ophthalmologist finally agreed to test Brooks' hypothesis by treating him with drops used to dilate a patient's eyes before an examination. "About four months later, I woke up with tremendously less eye pain and significantly better vision," Brooks says. The dilating drops had finally broken his muscle cramp.

He went back to work, this time at an online flower shop, but the long hours of computer work required him to keep increasing the frequency and strength of the eye drops. Then a new kind of eye pain appeared – a burning sensation that steadily intensified, until it felt like his corneas had been seared by the sun. Bright light became nearly intolerable. Despite trying a range of standard therapies, the new symptoms eventually eclipsed his old ones and he was again declared disabled.

Brooks talked to doctors around the world. Finally, one realised that his eye drops contained a toxic preservative known as benzalkonium chloride. The preservative, which is widely used in artificial tears and eye drops for glaucoma, has been linked to dry eye symptoms, inflammation and cell damage in multiple studies; only some manufacturers have replaced it with other chemicals or preservative-free solutions, however.

An ophthalmologist in Paris who specialised in preservative-induced toxicity confirmed the worst: six years of using the drops had ravaged Brooks' corneas at the cellular level. Brooks searched online for what to do next and eventually came upon Perry Rosenthal and his charity, Boston Foundation for Sight.

Our clear, disc-shaped corneas serve two roles: first, as vision-enabling windows that refract incoming light and, second, as the foundations for protective films that fend off disease.

The protective 'tear film' contains three parts. First, the same kinds of cells that secrete the mucus lining our intestinal and respiratory tracts similarly coat the cornea with a thin layer of sticky mucus. Next, the lacrimal gland above each eye supplies a thicker gloss of tears. Finally, several dozen meibomian glands in the upper and lower eyelids pump out a mirror-smooth oil slick that keeps the tears from evaporating. In response to perceived threats, our eyes water or we blink, which replenishes the tears and oil. Any disruption of the tear film can result in blurred vision; repeated breaches can permanently damage the cornea.

In 2013, the nonprofit Tear Film & Ocular Surface Society launched an international public awareness campaign, Think Blink, about the importance of blinking regularly to maintain healthy eyes. The official campaign song 'Blink Around the World', a high-energy dance anthem sung by Italian pop star Sabrina, wouldn't have been out of place in the Eurovision Song Contest.

There's considerably less harmony among researchers struggling to reach a consensus on the main contributors to the condition targeted by the blinking campaign: an unwieldy catch-all of dysfunction known as 'dry eye disease'. Depending on how it's defined, studies suggest that up to one-third of the population of Japan and Taiwan may be afflicted; risk factors range from old age, smoking and low humidity to LASIK surgery

and use of contact lenses or video display terminals. Women make up roughly two-thirds of all patients, for unclear reasons.

Many ophthalmologists have blamed the symptom that all patients have in common, dry-feeling eyes, on insufficient tear production or excessive tear evaporation. Other researchers suspect inflammation, and some are convinced that things still aren't that simple. The Tear Film & Ocular Surface Society has played the part of independent arbiter and recently launched its second round of workshops aiming to forge a better consensus on how dry eye disease should be defined and diagnosed. The intensive workshops are also delving deeply into subcategories such as surgery or drug-induced dry eye and abnormal pain and sensation.

Why all the bother? Studies suggest that moderate to severe dry eye can disrupt someone's quality of life just as much as hospital dialysis or moderate to severe angina, while mild dry eye can be as disruptive as severe migraines. And some researchers believe that the true spectrum of associated pain can range from occasionally scratchy eyes that could be alleviated with a simple change in lifestyle or environment to severe and unrelenting stabbing sensations that will resist nearly every intervention.

Perry Rosenthal has known two patients who committed suicide after finding no relief from the pain, and he has heard from many more who contemplated it. One woman told him that when she goes to sleep every night, she prays that she'll never wake up. "And nothing helped. Nothing helped," he says. "The worst was being abandoned by the medical profession, who say it's in your mind."

Rosenthal grew up in northern Ontario, Canada, and considered a career as a classical pianist – his mother's preference – before choosing medicine instead. In 1960, as a 26-year-old medical resident, he founded the contact lens service at the Massachusetts Eye and Ear Infirmary in

Boston. The "father of the gas-permeable contact lens", as he is sometimes known, pioneered the introduction of lenses that didn't smother the eyes – unlike other body parts, the surface of the eye depends on air instead of blood for its oxygen supply. From research begun in a garage with two chemists, he created the Boston Lens system that was eventually bought by eye care giant Bausch + Lomb.

In the mid-1980s, as an assistant clinical professor at Harvard Medical School, Rosenthal resurrected a peculiar type of oversized contact lens first developed in Germany and Switzerland a century earlier and initially made of glass. He modernised the lenses by fashioning them from permeable acrylic and made headlines when legally blind patients suffering from corneal diseases could suddenly see after trying on what amounted to custom-built prosthetic corneas inserted with the aid of miniature plungers.

Rosenthal founded the nonprofit Boston Foundation for Sight in 1992 to help get the expensive scleral lenses to patients who had run out of other options, regardless of their ability to pay. He was featured on The Oprah Winfrey Show in 2003 and lectured at medical centres around the USA. The dome-shaped Boston Scleral Lens, as he initially called it, acts like a reservoir for artificial tears and rests on the relatively insensitive sclera – the white of the eye – instead of the hypersensitive cornea. At the charity, some of Rosenthal's patients had such severe eye damage that the lenses couldn't restore their sight. But with the lenses on, they were no longer in agony.

For Rosenthal, the turning point came in 2007, when he examined a patient from Oregon who suffered from intense eye pain and light sensitivity after she was accidentally exposed to ultraviolet radiation at work. Insufficient or quickly evaporating tears seemed like a woefully inadequate explanation for her severe symptoms. When she removed her wide-brimmed hat and dark sunglasses in the dim light of his examining

room, Rosenthal watched as abundant tears spilled down her cheeks.

He fitted her with his oversized scleral lenses, which submerged the surface of each cornea in a pool of oxygen-rich artificial tears. Other specialists had accused her of lying – of malingering – to receive workers' compensation, but she responded immediately to the scleral lenses. "It was like magic. All of a sudden, she could open her eyes wide without any light sensitivity," Rosenthal says. Over time, however, the pain returned. "Her response was dramatic. Why? And why did the lenses soon become much less effective? I became obsessed with the need to find an answer."

Ophthalmologists are still unable to fit cases like this into the traditional definition of dry eye disease, Rosenthal contends, because the existing framework largely ignores the significant contribution of corneal nerves or wiring in the brain that may be sending faulty information. Eyes that feel dry, in other words, may not necessarily be dry.

Our corneas have a far higher concentration of nerve endings than anywhere else in the body – one reason why corneal pain can be so intense. A recent description of corneal nerve anatomy, based in part on corneas from donated cadavers, suggested that 44 thickly branched nerve bundles are crammed into a space only slightly wider than the home button on an iPhone.

"It's not leaving a single point in the cornea in which there is no possibility of stimulating a pain fibre," says Carlos Belmonte, founder of the Institute of Neurosciences in Alicante, Spain, and among the first to study the physiological basis of eye pain. The dozens of meibomian glands lining our eyelids are likewise among the most sensitive glands in the body.

One point of all those pain-producing nerves, according to evolutionary

biologists, is self-preservation. The stronger the pain, the more unmistakable the message: reduce the threat now! The density of nerves in and around the cornea may help the brain send a clear warning if it senses a threat to the protective tear film that keeps our eyes healthy.

One type of pain, known as nociceptive pain, follows a relatively straightforward cause-and-effect chain of action. "You poke me in my eye and it hurts," says Anat Galor, an ophthalmologist at the Bascom Palmer Eye Institute at the University of Miami in Florida. Ditto for staring too long at a computer screen or exposing your eyes to a strong wind.

Belmonte's research has suggested that sensors at the ends of specialised corneal nerves can indirectly measure the thickness of the eye's tear film by sensing a drop in temperature at the corneal surface. As the tear film evaporates and exposes more of the cornea to air, Belmonte says, these sensors detect a colder surface temperature and trigger an alarm that's perceived as a dry, painful sensation. For most people, crying or blinking restores the tear film to its normal thickness, and the pain fades away. In mice missing a crucial part of the cold temperature sensor warning of dryness, Belmonte found that the normal rate of tear production fell by up to half.

A second type of pain, called neuropathic pain, transmits sensations linked to damaged, diseased or otherwise altered nerve fibres that fire spontaneously or react to light or other signals that wouldn't usually bother us. A poke in the eye hurts much more than it should; even a light touch can be excruciating. "The nerves have kind of taken on a life of their own," Galor says.

Rosenthal likens this system to a faulty fire alarm that's been set to go off at a certain temperature. Based on Belmonte's research, he believes damaged nerve sensors can become so hypersensitive that they send pain

signals to the brain even with a normal surface temperature and an intact tear film. In other words, they continually raise a 'false dry-eye alarm' that results in chronic pain.

In what he calls his "last hurrah", Rosenthal teamed up with Harvard University pain specialist David Borsook to lay out his ideas in a May 2015 review in the *British Journal of Ophthalmology*. The publication makes the case for ocular neuropathic pain – eye sensation rooted in dysfunctional corneal nerves – and for a related type of pain, dubbed oculofacial pain, that is instead initiated by faulty pathways in the brain. The latter condition, which Rosenthal refers to as an "invisible, suicide-provoking eye pain", may explain some of the most extreme cases lumped under the dry-eye disease umbrella, including the woman from Oregon.

His explanation goes something like this: the patient's scleral lenses covered her tear film and temporarily quieted the pain-provoking dry eye alarm by preventing even a slight drop in the surface temperature due to tear evaporation. If the damage had been limited to her corneal nerves, maybe it would have been enough. But Rosenthal believes years of heightened pain and light sensitivity can rewire the brain, unplugging some connections and reinforcing others. Although his treatment may have initially disrupted her pain signals, he suspects her brain gradually reset its faulty connections and overrode the dampened alarm.

With this type of centralised pain, in fact, many patients cannot tolerate scleral lenses at all: "The eyeball itself is tender," he says. The unusually sharp, burning sensation, he believes, may originate from abnormal signals in the brain's pain-control centres that radiate out through the three branches of the trigeminal nerve supplying sensation to the head and face. "Even though they feel it in their eyes, it's not coming from their eyes; it's projected to their eyes," Rosenthal says. Or put another way: just as nearly one in four Danish patients in a 2010 study felt

phantom pain after having their eyes amputated, some patients with oculofacial pain might still feel the intense cutting sensations even if they were to have their own eyes removed.

None of his ideas are proven, Rosenthal concedes; they're still only hypotheses. And in any one patient, multiple problems on or under the eye's surface could be contributing to the discomfort. Nonetheless, he and his supporters are taking direct aim at lingering scepticism over whether nerve-mediated eye pain is even a real phenomenon. As Borsook points out, few doctors now doubt the existence of similar sensations in an amputated arm or leg.

"Yes, if you have your limb blown off, I see something missing and it's more tangible that you have pain and I've heard about phantom pain," he says. "But if you've just had a small incision in your body and you have incredible pain – it could be a tooth removal or the eye, and you still look normal – you know, what's wrong with you?"

Most ophthalmologists, Galor says, have been trained to identify evidence of cataracts or defects in the retina, not the less visible signs of abnormal nerve function. The idea that many patients with dry eye symptoms have chronic pain, then, is "completely new and radical", she says. "They look at it like, 'If I don't see it, it doesn't exist'."

Patient advocates hail Rosenthal's 2009 study, 'Corneal pain without stain: is it real?' as a breakthrough in advancing the argument that debilitating pain could occur without the clinical signs detected by using fluorescent stains on the cornea and other standard tests. Citing his pioneering work, Galor calls Rosenthal "the father of this field".

After his initial study on chronic eye pain, however, Rosenthal says the ophthalmology community largely censored his views. Even his own charity, the Boston Foundation for Sight, was roiled by internal conflicts.

When the foundation fired his son, Bill, in 2011, Rosenthal was briefly arrested for trespassing in Bill's office to gather up some belongings, according to a police report of the incident. Bill sued over his dismissal and recently reached an undisclosed settlement with the foundation. Then in 2012, after a 20-year tenure, Rosenthal was forced out of the foundation too – an abrupt firing that he alleges was linked to his focus on eye pain and what some at the charity referred to as his "off the wall" treatments.

"Boston Foundation for Sight has had numerous disputes with Dr Rosenthal over the past many years, some of which involved his son," responds foundation spokesperson Karen Schwartzman. "All disputes were settled to the satisfaction of all parties in May 2015.

"With respect to Dr Rosenthal's ideas about the neuropathic origins of severe and lasting eye pain, we hope his work will encourage research on this paradigm to the benefit of patients suffering from severe eye pain."

Based on his clinical observations at the foundation, Rosenthal wrote a paper describing 21 patients who underwent LASIK or similar laser-based surgeries and subsequently had severe eye pain lasting more than two years. After two ophthalmology journals rejected the article, he published it himself on the website of the Boston EyePain Foundation, another nonprofit that he launched in 2013 to continue his work. Since then, he has regularly posted patients' stories and railed against what he alleges is the medical community's willful suppression of mounting evidence that much of what is considered dry eye disease is instead a broken alarm mediated by faulty nerves and circuits in the brain.

David Sullivan, a Harvard ophthalmologist and founder of the Tear Film & Ocular Surface Society, is cautious about the details of Rosenthal's hypotheses, which he says are based mainly on clinical observations and may or may not be supported by further studies. "But I think the bottom

line is this whole area of pain and sensation is very, very important," he says. And so far, he concedes, doctors don't have answers for many patients.

In his crusade for a solution, Rosenthal is finding himself increasingly accompanied by other researchers who say the general outlines of his ideas fit many of their own observations. Twenty years ago, for example, a group led by Japanese ophthalmologist Kazuo Tsubota described an unusual form of dry eye disease in which patients had no injury to the corneal surface and no drop in tear production but an unstable tear film and intense pain. "This is a very interesting group because the symptoms, very bad. But signs? Almost nothing," says Tsubota, who practices at Tokyo's Keio University School of Medicine. "I love Perry Rosenthal's idea because his hypothesis can explain our findings."

Donald Korb, an expert on meibomian gland dysfunction, says Rosenthal likewise opened his eyes to the concept of neuropathic pain. "When I think back about how ignorant I was seven years ago, I'm appalled," says Korb, a clinical professor of optometry at the University of California at Berkeley and a long-time friend of Rosenthal's.

"What I like about the argument that Perry has put forward is that it's shaking the field to ask the question, 'Is this a true neuropathic syndrome with pain?'" Borsook says. "And if it is, then the current treatment of [eye] drops is not that useful."

Eye drops are by far the most common over-the-counter remedy for dry eye, representing a multi-billion dollar global industry. The only prescription drug to win widespread regulatory approval so far, however, is ciclosporin – sold as Restasis by Dublin, Ireland-based Allergan and billed as an anti-inflammatory medication that can increase tear production. Within the past decade, more than a dozen other companies have failed in their bids to win FDA approval for a dry eye drug,

although a handful of candidates are showing promise in clinical trials.

The links between corneal nerves and the brain may be more difficult to study, but Galor says most treatment strategies based on the prevailing understanding of dry eye disease haven't shown a sufficient connection between treating the signs and resolving the symptoms. Other efforts have recruited patients who may be suffering from vastly different conditions. "We need to rethink the biology of dry eye when we design our studies," she says.

Several groups already are. Galor says she is finding "fantastic" success with patient-derived autologous tears, or drops made from a patient's own blood serum and filled with growth factors that might aid nerve regeneration. Others are refining the use of anticonvulsant drugs to reduce the spontaneous activity of neurons.

Sullivan is investigating a lubricating, anti-friction protein called lubricin that may reduce symptoms by preventing the tear film from becoming abnormally concentrated and unstable. Tsubota and Korb have reported promising results with goggle-like moisture chambers for some of their patients, and Korb has developed a device called LipiFlow that uses heat and pressure to relieve painfully clogged meibomian glands.

If he can secure funding, Borsook hopes to conduct an MRI imaging study of LASIK patients that might show differences in the brains of those with chronic eye pain. "There's certainly a neuroscience interest in it," he says, "but the biggest thing is, can you help patients get to a point where doctors believe them?"

That point cannot come soon enough for patients who tell remarkably similar stories about being accused of lying, of having psychiatric issues, of wasting their doctors' time.

For these patients, "there is nothing that is more damaging to their psyche than being dismissed and invalidated by eye doctors, and they've all been through it,", Neil Brooks says. Doctor after doctor told him that because he had tears and an intact tear film, his severe pain couldn't be as bad as he described. "And I had to come up with comebacks," he says. "I found myself never making progress on why my eyes might hurt because I was spending all my time trying to convince a doctor that [they did]."

In the absence of help from the medical community, Facebook has become a vital hub for many patients to share tips, encouragement and information. So have websites like the Dry Eye Zone, a collection of community forums, patient stories, blogs and an online shop run by Rebecca Petris, a former financier for the airline industry turned off-the-grid homesteader in rural Washington State.

Since her own LASIK surgery in 2001, Petris has faced more than a decade of experimental therapies and corrective surgeries to resolve chronic vision and dry eye symptoms, although she counts herself lucky that she doesn't have severe stabbing sensations.

With no common language for chronic pain, she says, patients who aren't taken seriously may use increasingly dramatic descriptions, only to have the strategy backfire when doctors view them with mounting suspicion. Petris now advises patients to go to their appointments armed with standardised questionnaires like the Ocular Surface Disease Index, a 12-question survey on the severity of symptoms that's now available as a smartphone app. "The difficulty of putting pain in terms that doctors can understand is huge," she says. "I don't know how you get over that."

For relief, Petris sometimes recommends one of the Dry Eye Shop remedies she's curated over the years. Sometimes she becomes an impromptu therapist instead, urging callers to hang on and seek help

before they take their own lives. "People find me on the internet because no one's listening to them," she says. "They're at the end of their rope."

Both patients and researchers say the message may finally be getting through. Every big advancement in medicine seems to follow the same cycle, Neil Brooks says: people don't believe it and then an avant-garde researcher questions the prevailing truth and pushes the envelope to find out what's really happening. "Perry Rosenthal, to my knowledge, was at the vanguard of saying, 'What if these people aren't crazy?'" he says.

After reaching out to Rosenthal, Brooks agreed to see whether a pair of custom-built scleral lenses might relieve his symptoms. He endured long and painful fitting sessions but immediately noticed a difference when he left with a new pair. "There are no miracles when you've gotten to the point where my eyes are, but it was the single best, most effective treatment," Brooks says. The lenses not only reduced his pain but also made them less sensitive to the dry, bright and windy conditions back home in Colorado.

The relief wouldn't last. Because Brooks had undergone multiple surgeries to correct his crossed eyes, three specialists told him that the suction of the scleral lenses was putting his eyes at risk for even more damage. A "life-changing" transformation was once again cut short. "So I went from [being] that guy who could do things back to being the guy who can't," he says. At the same time, the "invisible disease" was wreaking havoc with his personal life: a simple disagreement over barking dogs that continually interrupted his desperately needed sleep – he didn't seem sick to his neighbours – spiralled out of control and eventually forced him out of his house.

Brooks made one last big push to reclaim his life: he sold his house, put everything in storage and immersed himself in the ultra-humid tropics of Central America. For the first ten weeks, life was great; the high

humidity helped to keep his tear film intact. Then the effect began to wear off, and the pain returned. The body is a self-regulating mechanism, Rosenthal told him. Eventually, his brain may have instructed his lacrimal glands to acclimate to the new environment by reducing their tear production.

He has since retreated to Colorado, where he lives with relatives. Nearly two years later, his remaining strategy is avoidance. "I don't do anything," Brooks says. "If I am lucky, I get the dog out for a walk four or five times a week."

Perry Rosenthal is still in battle mode and pessimistic about whether ophthalmologists are truly motivated to get at the root cause of chronic eye pain. Even his supporters aren't in full agreement on the chain of events triggering the sensitivity. But more researchers are at least coalescing around the idea that neuropathic eye pain may be caused by an accident, disease, drug use or surgery.

What Brooks has left, he says himself, is hope. "A once full and big and wonderful life has been reduced to next to nothing," he says. "And I know that's true of a lot of other people, and I have to tell myself the same thing I would tell them, which is don't give up – the same doctor you saw today might read a paper tomorrow that lets him help you next week."

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