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Philip Kass has dealt with pain for more than two decades.

CHRONIC PAIN: THE LONG ROAD TO DISCOVERY

Science is providing insights, and viable treatments are available. But millions of people are still without help. **By Lucy Odling-Smee**

Philip Kass spends 90% of his day lying on a twin bed in a sparsely decorated room that used to belong to his niece. He takes most meals with a plate balanced on his chest, and he usually watches television because reading is too stressful.

"I'm barely living," he told me on a warm night in June last year.

Ever since a back injury 23 years ago, pain has been eating away at Kass's life. It has cost him his career, his relationships, his mobility and his independence.

Now 55, Kass lives with his sister and her family in San Francisco, California. He occasionally joins them for dinner, which means he'll eat while standing. And once a day he tries to walk four or five blocks around the neighbourhood. But he worries that any activity, walking too briskly or sitting upright for more than a few minutes, will trigger a fresh round of torment that can take days or weeks to subside.

"It's just paralysed me," he says.

Some of what Kass describes is familiar. I have been pinned to the floor by spinal pain several times in my life. In my twenties, I was immobilized for three months. In my thirties and forties, each episode of severe pain lasted more than a year. I spent at least another half decade standing or pacing through meetings, meals and movies — for fear that even a few minutes spent sitting would result in weeks of disabling pain. For years, I read anything I could find to better understand why my pain persisted.

The picture that emerged was complex and surprising. Over the past few decades, a growing body of evidence has indicated that the very machinery that processes pain can

help to sustain the sensation or make it worse. Some researchers have explored unexpected interactions between the immune and nervous systems, showing, for instance, that inflammation, long considered a provocateur of pain, might also be crucial for resolving it. Others have shown how depression, anxiety and other kinds of emotional distress can both feed – and feed off – the experience of pain.

Although there are treatments that acknowledge this multifaceted, biopsychosocial nature of pain, medical practice hasn't kept pace with the science – not by a long shot.

Around the world, physicians are prescribing the same kinds of intervention for chronic pain conditions that they have offered for decades. Many people aren't getting treatment at all. And in North America and Australia, opioid overprescription and misuse have resulted in tight restrictions on one of the main tools long used by clinicians for managing pain. Kass, and the half-dozen other people I interviewed who live with pain, have spent years bouncing from doctor to doctor, trying to find someone who can eradicate their torment, or at least lessen it. And they're not alone.

In the last major survey, conducted in 2016, around 20% of adults in the United States – about 50 million people – had experienced pain on most days or every day in the previous 6 months. Around 8% – nearly 20 million people – had high-impact chronic pain, the kind that interferes with work or day-to-day activities[1]. Similar numbers have been reported from surveys conducted in Europe.

Although the pain research field is small, and fractured between different specialities, some researchers and clinicians argue that the knowledge and tools are already available to treat people with chronic pain conditions more efficiently and effectively than has been done in the past. What's needed, they say, is the will to get there – from both the medical establishment and society at large.

"We have a lot of treatments and approaches that already can make an impact, but we need to get them into people's hands, and we need to pay for it," says Sean Mackey, a physician-scientist at Stanford University in California.

The body's alarm

Pain often seems like a simple experience: grab a hot pan, and a harm alarm will sound. But in many cases where pain persists, the relationship between pain and harm is anything but simple.

In 1996, when Kass was 28, he was working as an acrobatics instructor with a travel and tourism company in the Bahamas. One morning, after a day of catching people on the flying trapeze, he was awoken by excruciating pain in his lower back.

He quit his job and flew back to the United States, where magnetic resonance imaging (MRI) revealed damage to a cartilaginous disc in his lower back, between his L5 and S1 vertebrae.

It's impossible to know exactly what was going on in Kass's body in the first hours and days after his injury. The specialists he saw in the United States told him that fragments of material from the damaged disc were probably pressing on his spinal nerves. But assuming Kass had experienced some kind of tissue damage, inflammation resulting from that would almost certainly have altered his pain-processing machinery.

"Evolution took a piece of string and randomly – because it had millions of years – knotted it into a hellacious ball of yarn."

Researchers have known for decades that tissue damage can alter the sensitivity of neurons in the peripheral nervous system (all of the nerves that exist outside the spinal cord, brainstem and brain), as well as how the central nervous system interprets signals.

After a sunburn, for instance, warm water that felt pleasant the day before might seem scalding. This happens because the inflammation caused by the sunburn alters the sensitivity of nerves in the peripheral nervous system known as nociceptors, which recognize noxious stimuli – a phenomenon called peripheral sensitization. Similarly, days after surgery, well away from the site of the incision where there is no inflammation, a light touch of the skin might hurt. That's thanks to changes in the central nervous system. Multiple mechanisms drive this process, known as central sensitization, but in this case, firing from sensory neurons activated by innocuous stimuli is now perceived as pain.

In most people, most of the time, peripheral and central sensitization are temporary and adaptive. They prevent people from doing more harm to damaged tissues. But what if that amplified sensitivity persists after wounds have healed, or even in the absence of any detectable tissue damage?

Various studies, mainly in animals, have identified dozens of pathways and cell types involved in peripheral and central sensitization. Following damage – the cutting or crushing of a rat's sciatic nerve, say – a menagerie of cells get activated around the nociceptors, and release factors that make the neurons more sensitive. These include macrophages, neutrophils, T cells and B cells, as well as glial cells, which are non-neuronal cells that support and protect neurons.

It's a remarkably complex set of interactions, says Jeffrey Mogil, a neuroscientist at McGill University in Montreal, Canada. "Evolution took a piece of string and randomly – because it had millions of years – knotted it into a hellacious ball of yarn," he says.

And the communication between nociceptors and immune cells goes both ways. In certain contexts, pain-triggering neurons can block or ramp up the activities of neutrophils and other types of immune cell[2]. "The nervous system doesn't even have to go via the brain; it just signals directly to the immune system in the periphery," says Isaac Chiu, a neuroimmunologist at Harvard Medical School in Boston, Massachusetts.

In people with skin conditions such as eczema, where there is ongoing inflammation, these reciprocal interactions between the immune system and nociceptors might help to drive persistent inflammation, and with that, persistent pain.

Even a person's microbiome, which interacts with both the immune and nervous systems, could play a part in certain pain conditions. Several groups, for example, are exploring the use of probiotics to treat people with irritable bowel syndrome (which causes abdominal pain)[3].

Another emerging idea is that some immune-system processes that drive sensitization might also be important in driving pain away. Last year, scientists at McGill University published an analysis of gene-expression patterns in people with lower-back pain. Although clinical trials are needed to verify the results, their data indicate that if inflammation is blocked by drugs, neutrophils don't do what they are supposed to do to resolve pain[4].

This flies in the face of expectation, says Clifford Woolf, a neuroscientist also at Harvard Medical School – and the first to demonstrate central sensitization[5]. Physicians have long prescribed anti-inflammatory drugs on the premise that if pain is allowed to persist, it might become chronic. "This paper suggests the complete unexpected opposite, which is that the inflammation is actually helping," Woolf says.

Pain's amplifiers

Any one person's chronic pain develops in its own particular way.

After two years spent mainly lying on his back, Kass had surgeries to fuse several vertebrae. His condition stabilized enough for him to start a handyman business. He was still in pain most of the time, but as long as he limited his hours and the kinds of job he did, it was manageable.

Then, in 2008, for no apparent reason, Kass's pain worsened. To relieve it, he started taking Norco, a mix of hydrocodone and paracetamol (acetaminophen). He had another operation to insert a device that delivers pain medication directly to the spinal fluid. Over the years, he has had three steroid injections at different

points along his spine.

Nothing worked. By 2015, Kass had abandoned his business. Exercise was no longer worth the risk. There'd be "this awful lag", he says, where he'd do something – ride his bicycle for a few blocks, for example – only to be incapacitated the following day.

It's anyone's guess as to whether immune-system processes, nerve damage or some other pathology in his lower back are helping to keep Kass in pain today. But neuroscientists have been uncovering all sorts of ways in which, over time, the experience of pain can be sustained and even amplified.

In the past few decades, brain-imaging studies have revealed changes to different areas of the brain in people who have experienced prolonged pain – including in the limbic system, the part involved in behavioural and emotional responses[6]. And experiments using animal models suggest that some of the neural networks that get reorganized by chronic pain might, in turn, affect how pain is perceived. In 2019, researchers at Stanford University used a technique called chemogenetics to engineer mice so that their neuronal activity could be finely tuned using various drugs. When the researchers turned off certain neurons in a part of the limbic system called the amygdala, the mice could still sense pain, but behaved as if that pain was less bothersome[7].

These findings raise questions about whether a new type of painkiller could be developed that acts on the unpleasantness of pain rather than on pain sensation, explains Grégory Scherrer, who led the study and is now at the University of North Carolina at Chapel Hill.

Another area of work involves looking for associations between certain properties of people's brains – as shown by functional MRI (fMRI) – and how they had previously responded to questionnaires assessing their levels of depression or anxiety. These studies have revealed that attention, expectations, anxiety, depression, catastrophic thinking and more can all influence pain perception[8].

Anyone who has been in severe pain knows that with enough discomfort, one thought will dominate all others: 'make it stop'. But at least in certain situations, there might be some truth in the saying that attitude is everything. "There's no doubt that the context in which you experience pain – your expectations and your attentional focus on it – will dramatically influence your perception of it, through real physiological neural networks," says neuroscientist Irene Tracey, vice-chancellor of the University of Oxford, UK.

> **"I try to do anything possible to help me cope every day with my pain."**

That context can include the people around you and the attitudes they bring. Among the things that can heighten anxiety and depression – which can, in turn, escalate pain – is scepticism from doctors, friends, partners and family. Many people with chronic pain face biases, which can be exacerbated by factors such as race, stigma around opioid use and misuse and the source of pain not being visible or obvious.

Quána Madison, a 42-year-old artist living in Denver, Colorado, has felt severe pain in different parts of her body every day since 2016. In that one year, she had surgeries to remove her breasts, womb and ovaries. These were followed by breast reconstructions and another emergency operation to repair a potentially life-threatening complication of hysterectomy.

Madison, who is African American, has had to deal with the pain, but also with suspicion and bias from others. During one of her visits to an emergency department in 2017, a nurse, who had been trying to draw her blood, called the police after Madison warned her that because of her heightened sensitivity to pain, she might scream if the nurse didn't use a small-gauge needle and a hot pad.

Predictors of pain

Faced with unrelenting pain and other people's doubts, it's easy to start ruminating: 'Why me? What is it about my body, my brain, my past, that makes this pain soar, not subside?'

Researchers have begun to unpick some of the factors that correlate with a heightened risk of chronic pain using genomics, epidemiological surveys and brain imaging.

Studies of twins indicate that the heritability of common chronic pain conditions (irritable bowel syndrome, back and neck pain and migraines) ranges from around 25% to 50% (ref. 9). But genomics studies, mainly involving people experiencing migraines, have generally uncovered gene variants that, individually, have small effects on a person's risk of developing chronic pain[10].

Various risk factors for chronic pain have been identified by epidemiological surveys, in which thousands of people are given questionnaires. The main factors that affect risk are: age; sex; socio-economic status; levels of anxiety, depression, sleep and physical activity; and body mass index[11]. For reasons that have yet to be worked out, persistent pain is more likely to be reported by people identifying as women than by those identifying as men. In the case of fibromyalgia, a disorder characterized by widespread musculoskeletal pain and fatigue, and problems with sleep, memory and mood, women are nine times more likely to have the condition than are men[12]. Also, people's likelihood of developing a chronic pain condition increases as they age, until about 60.

Separating cause and effect is a challenge. Are people who report high levels of depression and anxiety more likely to develop a pain condition? Or is their pain making them depressed and anxious?

According to Daniel Clauw, a physician-scientist at the University of Michigan in Ann Arbor, many studies show that "if you do make someone's pain dramatically better", say with knee replacement surgery, "you often make anxiety, depression, catastrophizing dramatically better".

But there might also be something about people's brains that predisposes them to chronic pain.

Using fMRI, Tracey and others have assessed the brain properties of groups of people with a pain condition (back pain or osteoarthritis, say). After surgery to treat the condition, or

Kass worries that he might lose access to some of the drugs that offer him relief.

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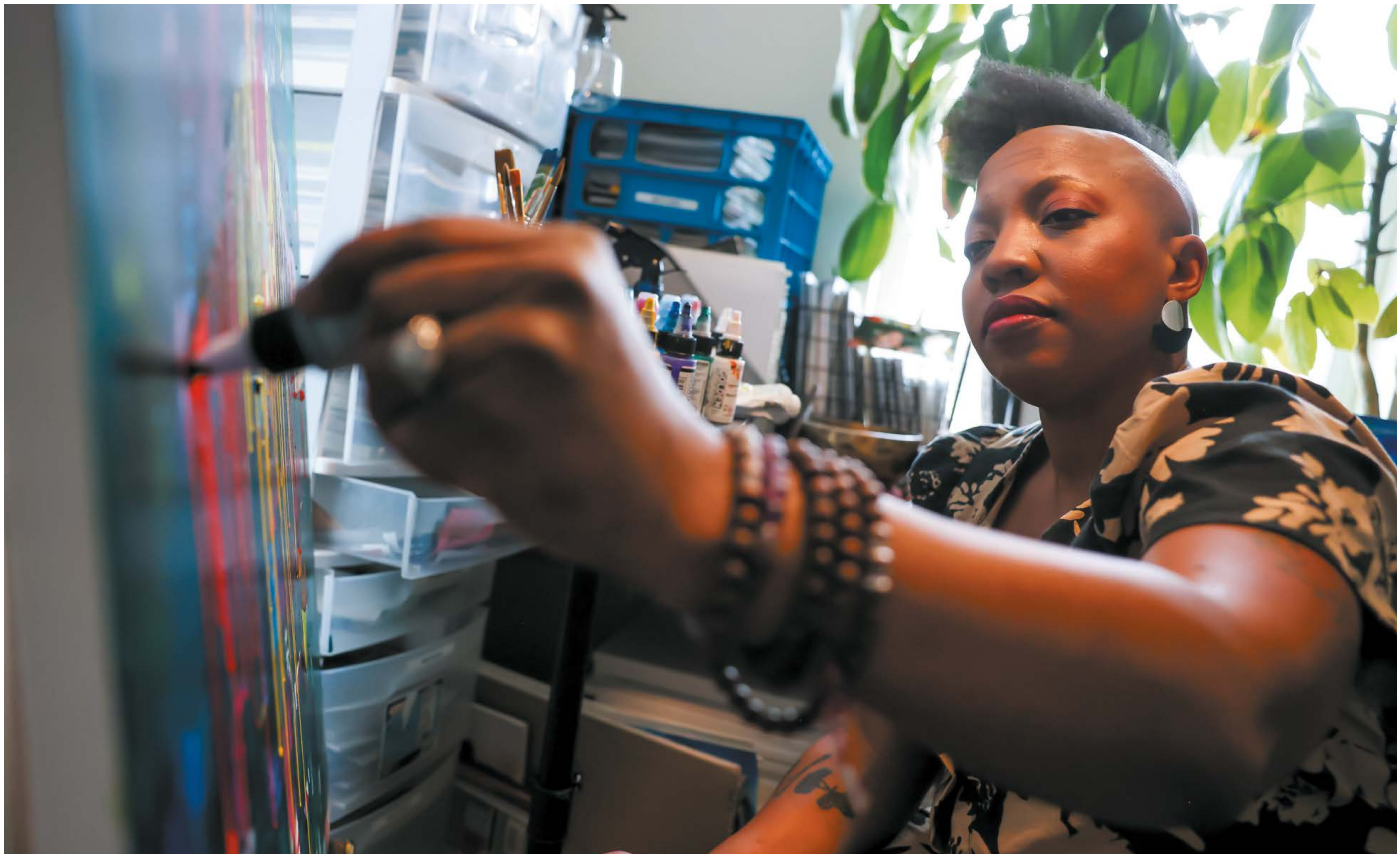

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Quána Madison, in severe pain since 2016, says her concerns about pain have sometimes been met with suspicion.

after a certain amount of time has elapsed, only some people in each group continue to have pain. Across multiple studies, researchers have been able to make predictions about who will fall into which group, using the patterns of neural activity in people's brains when they first enrolled.

This January, Tracey and her colleagues assessed people who were about to receive chemotherapy for various types of cancer. Around 30% of cancer survivors develop a chronic pain condition called chemotherapy-induced peripheral neuropathy. In this study, the researchers were able to use people's fMRI brain-imaging data, collected before chemotherapy, to predict which group they would fall into[13].

Tracey says that the hope is to identify which individuals are most at risk of neuropathy from chemotherapeutic agents, and then to adjust the treatments to reduce the risk.

Targeting treatments

The approaches currently used to treat common pain conditions generally entail medications and interventions such as surgical procedures or nerve blocks — the injection of a local anaesthetic close to a nerve or group of nerves. There are also behaviourally and psychologically oriented approaches, such as cognitive behavioural therapy, which involves trying to alter patterns of thinking and behaviour around the pain, and physical therapy to increase levels of activity and functionality.

"All these things help some people some," says David Clark, an anaesthesiologist at Stanford University School of Medicine.

Clinicians and others estimate that treatments available today can help one in three to one in four people, such that the levels of pain they report could decrease by about 30–50%.

Some researchers think that better efforts to match people with pain to the right treatments could make these options more effective.

One example comes from a multi-year project called the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network. Data from this study[14] suggest that people diagnosed with bladder pain syndrome (formally known as interstitial cystitis), but who have pain confined to their pelvis, essentially have a different disease from those given the same diagnosis but who have widespread pain throughout their body.

In neuroimaging, the brains of those with confined pelvic pain appear healthy, whereas people with widespread pain have brains that look similar to those of individuals diagnosed with fibromyalgia, explains Clauw, who was involved in the study. This suggests that the group with widespread pain might respond better to drugs than to physical therapy for the pelvis[14].

"Within the next couple of years, we'll take a lot of commonly used treatments that work in one out of three individuals, and just by getting smarter about who we give those treatments to, they will work in one out of two people," says Clauw.

Similarly motivated by the idea of better matching treatments to individuals, Mackey at Stanford is using a US$12-million grant from the US National Institutes of Health to develop biomarkers for pain.

Around ten years ago, to improve care for people with chronic pain, Mackey created a digital platform called CHOIR (Collaborative Health Outcomes Information Registry). This characterizes people according to their physical, psychological and social functioning — largely on the basis of clinicians' reports and participants' responses to health questionnaires. Ultimately, Mackey's goal is to incorporate brain-based biomarkers of pain into the CHOIR system, as well as other information distilled from metabolomics, proteomics, genomics, the microbiome and even from wearable fitness trackers such as Fitbit.

Mackey and his colleagues are still trying to map associations between the vast array of biomarkers that can be measured and the experience of pain. But he's convinced of the promise of the basic approach: "I'm growing more and more optimistic that we're going to be able to do this," he says.

Most researchers and clinicians agree that better-tailored treatments could help. But many people with persistent pain have difficulty accessing any care at all.

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Painting is one of the ways that Madison copes with her pain.

"When I see the challenges facing patients," says Mackey, who has co-led a US effort to change how people in pain are assessed and treated, "I see this as more of a societal implementation issue."

Thanks to clinicians discovering that drugs developed for other conditions, such as seizures or depression, can help treat pain, there are actually many more treatments for chronic pain today than there were 20 years ago. Among the ones Mackey lists are more than 200 medications, most of which are non-opioids; mind-body therapies, such as acceptance and commitment therapy; and a host of procedures such as those involving spinal-cord stimulators — implanted devices that send low levels of electricity into the spinal cord.

They just aren't getting to the people who might be helped by them — at least to some degree.

Madison, and some of the other people I spoke to who live with pain, told me similar stories: unable to get much assistance from the health-care system, they have eventually cobbled together their own forms of treatment, born of years of trial and error.

"I do meditation. I use aromatherapy. I do abstract painting. I try to do anything possible to help me cope every day with my pain," says Madison.

Clinicians say a host of changes are needed to improve the situation. These include a shift in attitudes towards chronic pain conditions; insurance companies being persuaded to cover integrative care involving multidisciplinary teams; better education and training about pain in medical schools; and a lot more investment in the problem.

Researchers who continue to chip away at the mechanisms underlying chronic pain conditions could gradually change the narrative around chronic pain. And it's not unthinkable that, some day, providers of pain care will be trained in a very different way from how they are today. But right now, "it's really hard to find good quality care for people with chronic pain", acknowledges Clauw.

Breaking point

In the winter of 2020, whatever it was that had been holding Kass together through 23 years of pain broke down. In the mornings, he would cry. At some point, the crying turned into screaming. One of the tenants in Kass's building in Berkeley, California, closed his shop for a few weeks because of the noise.

That tenant, who was also Kass's friend, would visit him now and again to try to help. But one day in early 2021, Kass overdosed on medication with the intention of killing himself.

Kass thinks he was unconscious for about 24 hours before his friend found him.

A team of emergency doctors at Alta Bates Summit Medical Center in Berkeley revived him, and kept him under observation for three days.

"It was awful," he says. "I was scared. I was in terrible pain. And I couldn't leave the hospital."

After days of Kass begging the hospital staff to give him pain medication, a psychiatrist prescribed him an opioid called buprenorphine. Along with mirtazapine, other antidepressants and an antipsychotic called Latuda (lurasidone), he's still taking the opioid: eight milligrams three times a day.

Kass worries, however, that because of the kind of health insurance he has and doctors' wariness about prescribing opioids in the United States, his prescription could be stopped any day. "So there's that fear," he says. "Without the buprenorphine, I'm back to screaming every day."

Pain is a universal experience. Yet it's hard to comprehend what being ruled by fear and wracked by a continually sounding alarm can do to a person — even for those of us who have, at some point, experienced a long stretch of severe pain.

For almost all of 2020 and some of 2021, I limited my standing or walking to 5–10-minute sessions. After each attempt to move — often walking the block just a few streets from where Kass lives now — I would lie down for an hour. While on my feet, I wouldn't let my sons, then aged six and eight, touch me in case their pulling triggered another two-week-long flare. I wore ski gloves while lying on the floor because cold worsened the stabbing in my arms. And at night, I couldn't sleep for more than a two-hour stretch.

In that winter of 2020, I had screamed too.

Although I still have pain every day, and periodic flares, I've clawed a full life back little by little, using approaches similar to those a multidisciplinary UK team had introduced me to more than a decade ago. I've used medication, meditation and psychotherapy. I've used cognitive behavioural therapy to monitor my thinking around the pain, and eventually to alter it. I've used a timer to pace my activities, initially increasing the spells on my feet by a few seconds. I've used physical therapy and exercise to recondition my body — and to keep pushing back against the 'something is wrong' alarm that's been endlessly looping.

But pain takes a different course for every person. And as I listen to Kass, whose skin is so pale it's almost translucent, and who sometimes strains for a date or a word more than I'd expect for a man his age, I struggle to understand why the health-care systems of the world's richest countries are not yet using all the knowledge that science has provided to bring more help to him and millions of others living with pain.

Lucy Odling-Smee is a Senior Comment Editor for *Nature* in San Francisco, California.

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