nature OUTLOOK

PAIN

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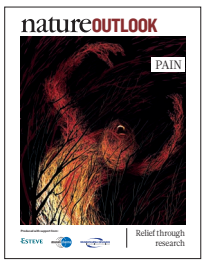

Cover art: Daniel Hertzberg

Pain is unpleasant but necessary. It signals danger, preventing us from harming ourselves, and alerts us to damage to our bodies. Yet for many people, their pain system is out of alignment. Too much pain is crippling and can make everyday living an agony. Even 'good' pain can turn bad, when the pain of an injury persists after the damage has healed.

To use only the term 'pain' is to ignore the full range of ways that people experience hurt. It might all start with the same basic pathways (see page S2), but the nuances change as acute pain becomes chronic and even the strongest analgesics stop working (S4). Damage to nerves has its own set of effects. Which sensation a person experiences might be a clue to the cause of their neuropathic pain — and how to treat it (S10).

The personal nature of pain complicates its study. Men and women even process pain through different immune cells in the spinal cord. Such an important distinction has a bearing on the sex of animals used in pain research (S7). And these variations have hampered genetic studies, which have so far shown only that pain is mediated by a mosaic of thousands of genes (S12). Brain imaging, however, is providing more leads. Researchers think that they have identified a neurological signature of pain that could be used in comparison studies (S8).

Researchers have come a long way in terms of understanding and controlling pain (S18). But although people in developed countries have access to the strongest opioids, billions elsewhere do not — even those in palliative care (S16). However, things are changing, with many drugs and devices in development, including the intriguing possibility of using honest placebos as painkillers (S14).

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Michelle Grayson
Senior editor, supplements

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CONTENTS

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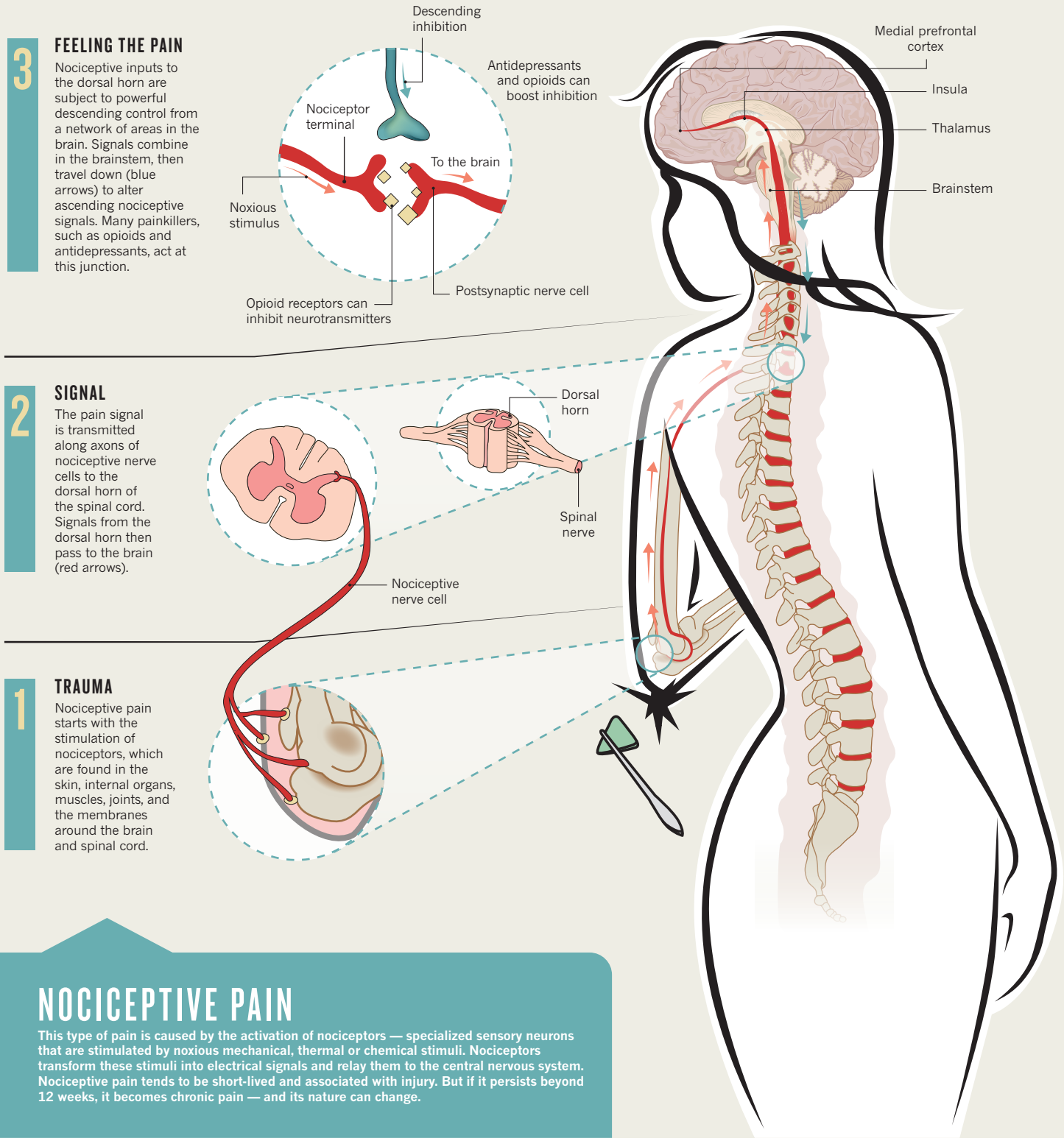
THE PAIN DRAIN

We can't live without it, but many of us struggle to live with it. Pain has an essential biological function, but too much — or the wrong sort — ruins lives and puts a sizeable dent in economic productivity. By **David Holmes**, *infographic by* **Mohamed Ashour**.



NOCICEPTIVE PAIN

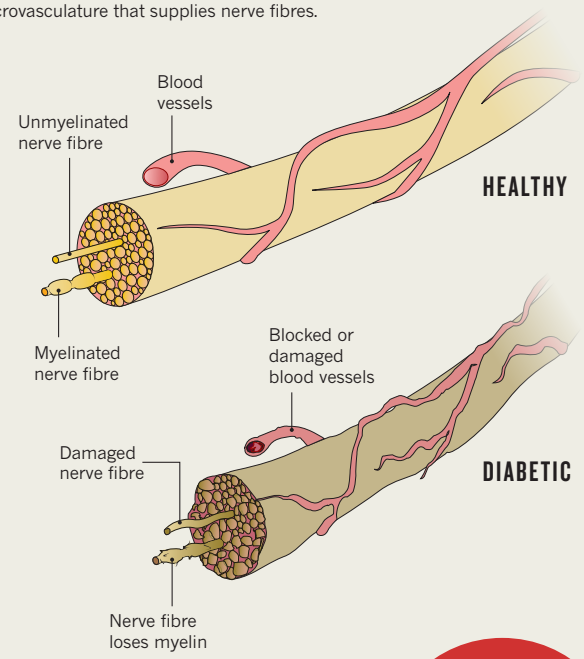
This type of pain is caused by the activation of nociceptors — specialized sensory neurons that are stimulated by noxious mechanical, thermal or chemical stimuli. Nociceptors transform these stimuli into electrical signals and relay them to the central nervous system. Nociceptive pain tends to be short-lived and associated with injury. But if it persists beyond 12 weeks, it becomes chronic pain — and its nature can change.

NEUROPATHIC PAIN

Unlike nociceptive pain, neuropathic pain is caused by damage to the somatosensory nervous system itself, as a result of trauma or disease. However, there is not always a clear link between disease states and neuropathic pain.

DIABETIC NEUROPATHY

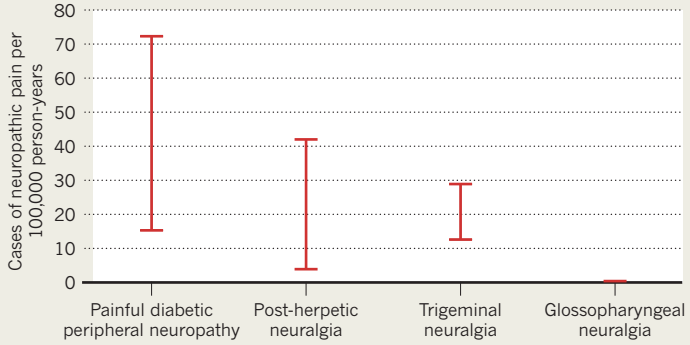
Painful diabetic peripheral neuropathy is one of the most common forms of neuropathic pain, with its incidence set to increase as the obesity and diabetes epidemics continue to grow. Neuropathy is caused by metabolic factors as well as by damage to the microvasculature that supplies nerve fibres.



7–10%
Population prevalence of neuropathic pain[1]

NEUROPATHIC PAIN INCIDENCE

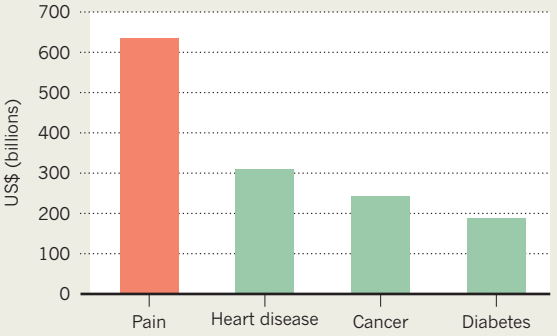
Definitions of neuropathic pain vary across studies, leading researchers to call for a unified nomenclature. The best evidence on incidence comes from studies of neuropathic pain linked to specific conditions, but even then ranges can vary widely[1].

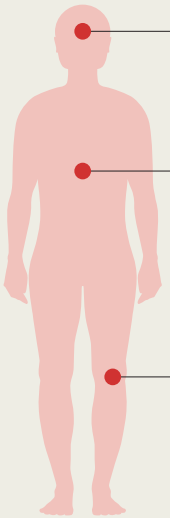


PRICE OF PAIN

BIGGEST BURDEN

Around 100 million adults in the United States are affected by chronic pain in a single year. The annual total cost of pain, including direct costs, decreased wages and lost productivity, eclipses that of any other condition[2].





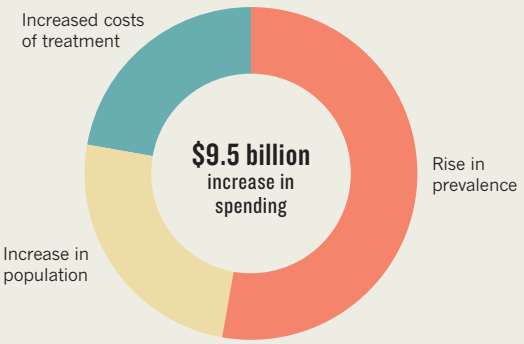
$14 BILLION
The estimated total cost of headache in the United States.

$200 BILLION
The estimated total cost of back pain in the United States; about the same as the gross domestic product of Portugal.

$189 BILLION
The estimated total cost of arthritis to the United States.

GROWING PAIN

Health-care spending on back problems in the United States more than doubled between 1987 and 2000. Although treatment costs and population increases contributed, most of the $9.5-billion rise was due to an increase in the prevalence of back pain[3].



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DANIEL HERTZBERG

BIOMEDICINE

Move over, morphine

The dearth of treatment options for chronic pain has led to widespread over-prescription of strong opioids. But some innovative thinking is building a promising pipeline.

BY JAMES MITCHELL CROW

Michael was 15 when he was kicked in the back by another student at his school in Australia. The blow ruptured a disc in his lower spine, a painful injury that required surgery. In the weeks and months that followed, Michael had additional operations, but none were able to resolve his excruciating pain.

After 12 rounds of surgery — at the end of which, three-quarters of Michael's back had been fused with rods and screws — the pain was undimmed. Michael (not his real name) had spent most of his adolescence in hospital and had become morbidly obese.

"When I first met him at 20, he was essentially bed-bound, virtually no sleep from the pain, on crazy doses of strong opioids," says Marc Russo, who directs the Hunter Pain Clinic in Newcastle, Australia. "He was existing, but certainly not living."

Unfortunately, cases such as Michael's are not rare. Globally, around one in five adults — almost a billion people — has persistent pain, which is often accompanied by sleep loss, depression, unemployment and relationship breakdown.

And for most people, the pain does not start with a trauma, as it did for Michael, but rather with a small physical insult, says Lorimer Moseley, a chronic-pain researcher at the University of South Australia in Adelaide. "Maybe they bent over to pick something up and their back hurts." A bout of pain — whether it's back strain or post-surgical pain — is often short-lived. But for around 10% of these people, the pain does not go away; they have transitioned from acute to chronic pain.

As Michael found out, effective treatments are sorely lacking. "There are a range of options, and a lot of people don't respond to any of them," says Charles Brooker, a pain-management specialist at the Royal North Shore Hospital in Sydney, Australia. So acute was the shortage of effective drugs, that some doctors — particularly in the United States, but also in other Western countries, including Australia — began prescribing strong opioids for chronic pain.

That strategy has turned out to be tragically misguided, leading to an epidemic of opioid addiction. "Opioids almost never work in chronic pain, and cause untold misery," says pain specialist Andrew Moore at the University of Oxford, UK. The good news is that as researchers finally begin to understand the mechanisms of chronic pain, new therapies — both drugs and devices — promise a powerful set of alternatives to opioids.

FROM KILLING TO CAUSING PAIN

Opioids kill pain by targeting μ-opioid receptors on pain neurons in the spinal cord and brain. By binding to these receptors, opioids inhibit neurotransmitter release at the junction between pain neurons, blocking

the signal. "Strong opioids are wonderful for palliative care and acute pain," says Russo.

But for the long-term treatment of chronic pain, the side effects take a toll. The body quickly develops a tolerance, which doctors counter by escalating the dose. When Russo first began to see Michael for his back pain, one of his first interventions was to ease Michael off the opioids.

Understanding the mechanism of opioid tolerance may help researchers to find a way to avoid it. As more of the drug enters the body, non-neuronal cells known as glia take notice. Once thought to be nothing more than a scaffold for neurons, glia are now known to be active members of the central nervous system. One of the jobs of the glia is to keep watch for foreign invaders. High opioid doses seem to trigger a defensive response, causing the glia to release immune-signalling compounds called inflammatory cytokines, which stimulate the sensory neurons that the drugs are supposed to sooth. "The dose is so large it is now causing pain," Russo says.

But because μ-opioid receptors are such powerful targets for suppressing pain, research into new opioids has not been abandoned entirely. Researchers are looking for drugs that weakly activate the μ receptor, but also hit other targets, says Russo. Hitting the μ receptor disrupts the flow of pain signals to the brain. Ideally, dual-acting drugs would also activate inhibitory nerves that descend from the brain to suppress pain, he says. This is how two of the newer morphine-derived drugs, tramadol (approved in the United States in 1995) and tapentadol (approved in 2008), work.

James Zadina, a neuroscientist who studies novel opioids at Tulane University in New Orleans, Louisiana, has taken a different approach. "Instead of starting from the opium plant, we started from the brain," he says. The first big break came in 1997, when his team finally tracked down a peptide in the brain that binds to the μ receptor just as selectively as morphine does[1]. The compound, called endomorphin-1, is now recognized as the natural trigger of the μ receptor.

Endomorphin-1 elicited an analgesic response just as powerful as morphine, but without the side effects. "The old way of thinking was, any drug that hits that receptor is going to do pretty much the same thing," Zadina explains. In reality, however, drug molecules of different shapes can bind to the same receptor in different ways and trigger a different set of responses — a phenomenon known as biased agonism. In the case of the μ receptor, endomorphin-1 seems to selectively promote analgesia.

As drugs, natural endomorphins would be hopeless — they break down too rapidly in the bloodstream. Zadina and his colleagues have been testing endomorphin analogues with reinforced chemical structures. The hope is that these molecules will still trigger the same response as the parent compound. Zadina has identified four new analogues of endomorphin[2], and is now preparing to take the best-performing into clinical trials. That compound, dubbed analogue 4, provides "much longer duration of analgesia" than morphine, says Zadina. Tolerance is also reduced — and the compound does not seem to trigger the release of pain-stimulating cytokines.

"There are a range of options, and a lot of people don't respond to any of them."

In addition, analogue 4 does not seem to be addictive. The most compelling data, Zadina says, come from trials in which a rat can press a bar to self-administer the drug. A rat given access to morphine, he says, "will start pushing the bar like crazy. They don't do that for our compound."

CHRONIC-PAIN PROPHYLAXIS

However effective these pharmacological interventions prove to be, prevention will always be preferable. All chronic pain starts as acute pain. "It would be far better to extinguish it at origin," says Russo.

Several studies have pinpointed factors that predispose patients to chronic pain — susceptibilities that a simple questionnaire can flag. Pre-existing anxiety and depression put people at risk, as does pre-existing pain. "People with chronic migraine are more likely to get chronic knee pain after a knee operation," says Brooker. "Those people have a sensitized nervous system."

Multiple sensitization mechanisms could be at work. There is a simple test to see whether one particular gate in the pain pathway, called diffuse noxious inhibitory control (DNIC), is functioning. For most people, if you place their left hand in ice water, they don't feel mild pain induced by a laser shone on their right hand — the DNIC 'filter' in their spinal column is helping the brain to prioritize its response so that the person pays attention to the stimulus that is more likely to cause damage. "But 20% of people can still detect the pain on the right — which means they have an abnormal ability for pain signals to get through to the brain," Russo says. The DNIC filter is more likely to fail if a person is stressed, he adds.

A new type of spinal cord stimulation device is in clinical trials.

SALUDA MEDICAL

Another factor in whether a person develops chronic pain is the initial severity of the acute pain. The first 24 hours after a trauma or operation are thought to be crucial. "If your acute pain is very severe, your risk of chronic pain is much higher," says Moseley. "If we can reduce the activation of nerve cells that produce the danger message in the spinal cord, then we reduce the chance those nerve cells will sensitize and adapt." This provides a clue as to how to stop the nerve cells from firing after the injured tissue has healed.

Combine all these ideas, Moseley and Russo agree, and there's the possibility that doctors can intervene before chronic pain sets in. "If you come up positive on the risk-factor tests, a special rapid-response team will manage your pain in the first 24 hours," Russo says. These teams would use every pain-killing method at their disposal — from drugs to temporary nerve blocks — to make sure that the patient never rates their pain beyond mild on the pain scale, he adds.

Individuals at risk of developing chronic pain can also be offered targeted psychotherapy to help with the underlying issues that predispose them to it, and to educate them in the mechanisms of pain. In 2014, Toronto General Hospital in Canada became the first centre to implement such a comprehensive programme aimed at preventing chronic postsurgical pain. The team does not have randomized-controlled-trial data yet. But several hundred patients have taken part in the programme, and the results seem promising. "The data suggest we're doing something right," says Joel Katz, a pain researcher at the hospital.

NERVE ZAPPERS

For the patients that these early interventions don't catch — or the millions already living with chronic pain — there are other options in the pipeline, including one that is not a drug at all. Last year, Brooker carried out the first permanent implant of a smart electronic device that stimulates inhibitory neurons in the spine.

The main body of the device is a matchbox-sized titanium box housing all the electronics, which is placed in the fat layer just beneath the skin. A thin wire runs from the device to a metal electrode that is implanted next to the spinal cord.

Brooker's patient, Jaswir Grewal, had suffered debilitating back pain for decades. After the surgery, he said that the severity of his pain went from eight out of ten to about two or three with the flick of a switch.

CHILDBIRTH

Delivering more options for women

Most areas of medicine have changed radically since the 1940s. But women in labour have pretty much the same pain-relief options as their great grandmothers.

For generations, labour wards have offered a trio of escalating pain interventions: a mixture of oxygen and nitrous oxide (gas and air); an injection of the opioid pethidine, which can leave women feeling nauseated and 'out of it'; or an epidural anaesthetic that numbs the lower-body pain, but can restrict the woman to the bed.

But this could be about to change. Last year, midwifery researcher Julie Fleet (**pictured**) at the University of South Australia in Adelaide and her colleagues conducted a randomized clinical trial that compared pethidine with a nasal spray of the opioid fentanyl.

Fentanyl is not a new drug. But because the body clears it quickly, it was conventionally given through a drip, which restricts movement and limits its appeal on maternity wards.

Around a decade ago, a nasal version of the drug was developed for use by paramedics and on children's wards, where it is now used routinely. Fleet suspected that the reformulated drug could also make a difference in childbirth. The self-administered nasal formulation gives women effective pain relief and allows them to remain mobile during labour.

The researchers showed that although nasal fentanyl and pethidine both controlled pain equally, women who receive fentanyl had shorter labours, less difficulty establishing breastfeeding, and less sedation and nausea. More than 80% of women would use it again, compared with 44% for

pethidine[3], says Fleet. "They get the pain relief, but without the sedation, so could feel in control and be active in their labour."

The two hospitals involved in the trial now routinely offer nasal fentanyl to women in labour. Fleet is collecting data to assess whether women who take up this option are less likely to request an epidural.

"There is this big misconception that epidurals are very safe for the baby," Fleet says. "Epidural can be very effective, but it does have increased risks." An epidural is the only pain relief option that requires continual fetal monitoring, because it can cause the mother's blood pressure to drop, which reduces blood flow to the baby and increases the chance that a woman will need a caesarean or an assisted birth. "We think if we give them an option that's less invasive and still effective for pain, they won't need to go on to epidural." **J. M. C.**

Spinal cord stimulation was first trialled in 1967, but it has usually been a treatment of last resort. This is because the simple implants tend to move relative to the spinal cord as the patient moves — even when they breathe. The target nerve is therefore frequently under- or over-stimulated, and neighbouring nerves are hit, too. "You tend to pick up nerves to the ribs, which can be very painful," says Brooker. So people with the implant often turn it down, or even off.

"If your acute pain is very severe, your risk of chronic pain is much higher."

The device that Brooker implanted in Grewal is more sophisticated. Created by start-up company Saluda Medical in Artarmon, Australia, the device overcomes the problem of electrode movement by continually reading the electrical activity induced in the target nerve, and adjusting its output to keep nerve stimulation within the therapeutic range.

Saluda had already demonstrated the concept's potential using temporary implants, and in October 2015 the company began a multinational three-year clinical trial of permanent devices — which Grewal was part of. While this is taking place, the company is continuing to improve the device, including miniaturizing it. "Making it half as big is not out of the question," says senior vice-president Dan Brounstein.

The Saluda device has impressed pain researchers. "In theory, it's a very significant development," says Russo, whose pain clinic is participating in the trial. It used to be impossible to know how much of the time the correct level of activation was being delivered to the target nerve. "With this device, it's close to 100% of the time," says Russo.

A wave of similar technologies may be on the way, thanks to an explosion of innovations in spinal cord stimulation. Among the ideas being tested are whether the use of high-frequency electrical impulse patterns suppress pain more effectively, and the use of inductive coupling (the technology behind wireless mobile-phone charging) to power the implant — so that the mobile-phone-sized battery can be worn on the belt rather than implanted under the skin alongside the stimulation device. "It is far more comfortable," says Russo, adding that implanting the device "becomes an outpatient operation".

As the technology has improved, so has the clinical knowledge of which patients will benefit. Those with neuropathic pain from damaged nerves respond the best. "For many years, we were able to achieve 50% of patients achieving 50% pain reduction," Russo says. In the past 4 years, several clinical studies have got close to 75% of patients achieving 75% pain relief. "Once you get to those figures, it no longer makes sense to be a treatment of last resort."

The developments in medication and technology have been welcomed by Michael, who is now 28. He has a spinal implant, and is taking a tailored cocktail of drugs. Together, these therapies have reduced his pain significantly, allowing him to sleep. He has lost 30 kilograms and is mobile, independent, has overseas holidays and an active circle of friends. "Yes he still has pain," Russo says. "But he is living life."

It might be an age-old phenomenon (see page S18), but pain, says Russo, was only established as a medical speciality after the Second World War. "We are the youngest field of medicine," he says, "and changing probably faster than any other."

The fast-blowing winds of change carry the promise of new drugs, devices and early interventions, which many pain clinicians hope will soon translate into better pain-relief options for their patients (see 'Delivering more options for women'). "It's like everything has been thrown up in the air and we're waiting for the dust to settle," says Brooker. "We're waiting to see which of these new toys really is effective once the clinical research is complete." ■

CATHY KEMPSTER

James Mitchell Crow *is a freelance science writer based in Melbourne, Australia.*

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IMAGING

Show me where it hurts

Technology for peering into the brain is revealing a pattern of pain, and differences between the acute and chronic forms.

BY SIMON MAKIN

Researcher Tim Salomons examines brain scans as a person is subjected to laser stimulation in a scanner.

NATHAN CLARKE

David was lying in the brain scanner, showing no signs of reacting to an intense laser beam shining onto the back of his hand. Several minutes into the procedure, he said: "We should maybe stop this laser." When asked why, he replied: "It's starting to feel like when I used to burn my hand with a lighter."

Thanks to a rare genetic mutation, David cannot feel pain. "Most of us don't need to think: 'What does this feel like that I've experienced before?'," says Tim Salomons, a neuroscientist at the University of Reading, UK, who was part of the team running the study that David took part in. "It shows the role pain plays." Using a common brain-imaging technique called functional magnetic resonance imaging (fMRI) to measure brain activity, the team found that a painful stimulus activated the same regions in David's brain as it did in healthy controls[1].

Although this seems to cast doubt on the relationship between brain activity and pain, imaging studies in general have revealed much about how the brain processes pain. Some have found patterns that might offer a way to measure pain objectively, whereas others are exploring the differences between acute and chronic pain.

PATTERNS OF PAIN

In contrast with most other senses, conclusive evidence of a brain region dedicated to pain is lacking. Instead, pain is usually associated with activity in numerous areas — a 'pain matrix' of regions reliably activated by painful stimuli. These include the somatosensory cortices, which process sensory aspects of pain alongside sensations such as touch and temperature; and the anterior cingulate cortex and insula, which are thought to be important for emotional and motivational dimensions of pain (such as pulling your hand out of a fire). Other areas include the prefrontal cortex (the seat of higher cognitive processes) and the thalamus (a 'relay hub' for sensory and motor signals).

Pain-matrix regions are not specific to pain, they are also activated by attention-grabbing stimuli such as flashes of light and loud banging sounds. These stimuli trigger processes involved in detecting important events, directing attention and readying for a response. Because pain also grabs attention, Giandomenico Iannetti — a neuroscientist at University College London who worked with Salomons on the fMRI study — argues that pain-matrix activity may have more to do with the importance of painful events than with the pain itself.

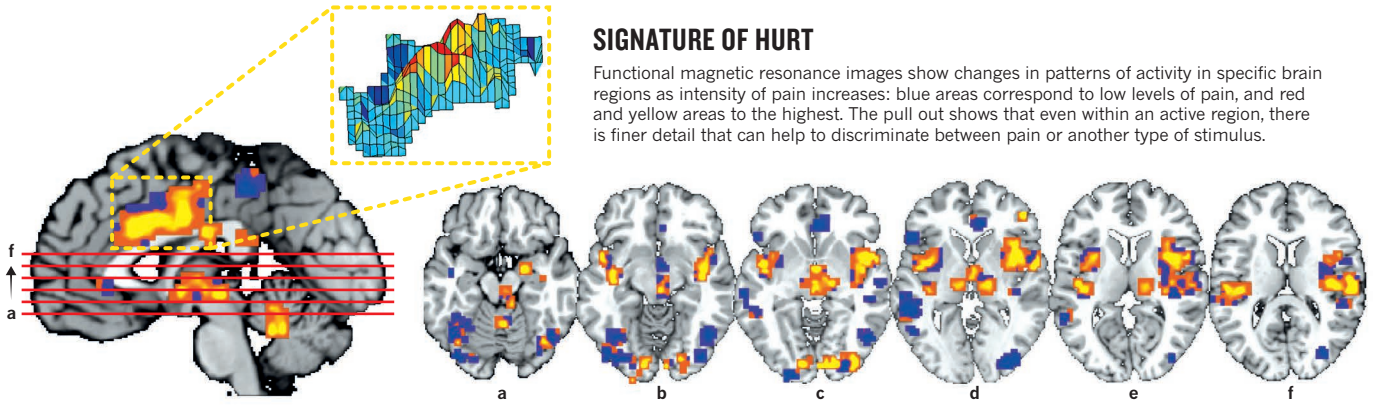
But others think that hidden within that general activity is something more specific. Tor Wager, a neuroscientist at the University of Colorado Boulder, used machine-learning techniques to classify patterns of activity over multiple brain regions — predominantly the pain matrix — to develop a 'neurological signature' of pain[2] (see 'Signature of hurt'). "We're showing very specific patterns within these regions that do encode pain," he says. "Other patterns encode other things, but we can separate them." For instance, among their other functions, pain-matrix regions are also activated by emotional experiences, such as social rejection and empathy for, or memory of, pain — leading some to say that those feelings also hurt, to some extent. But although rejection and physical pain share a dimension of emotional unpleasantness, heartache is clearly different from being stabbed in the chest — and this distinction can now be discerned in the fine detail of brain images. Wager's group used its system to distinguish painful heat from non-painful heat; actual pain from anticipation, or recall, of pain; and physical from emotional pain. The group's algorithm was able to correctly reject the non-pain experiences around 90% of the time, and determine actual pain with more than 90% accuracy — an impressive combination of specificity and sensitivity. Wager's system also predicted perceived pain levels and showed that administering a potent opioid drug significantly reduced activation.

"We're trying to develop measures that really track the pain that you feel, based on things that come up from the body," says Wager.

MIND OVER MISERY

Pain can also be influenced by factors such as expectation (which feeds into the placebo effect, see page S14), attention, emotion and even personality. Imaging is allowing researchers to investigate how these elements manifest in the human brain. The ability to exert control through willpower and imagination, known as self-regulation, can alter pain perception. But Wager's group found that self-regulation had no effect on the neurological signature[3]. It did, however, affect activity in other brain regions, most notably the nucleus accumbens, which operates through connections to the medial prefrontal cortex to form a circuit within the brain's reward network. The perception of pain, it seems, is not the result of one system. "The pain signature we developed is a really important component of pain," Wager says, "but it's not a complete description."

Imaging is already helping to determine those other components of pain. Researchers know from animal studies that attention and emotions can modulate pain through a descending system



TOR WAGER; SOURCE: REF. 2

SIGNATURE OF HURT

Functional magnetic resonance images show changes in patterns of activity in specific brain regions as intensity of pain increases: blue areas correspond to low levels of pain, and red and yellow areas to the highest. The pull out shows that even within an active region, there is finer detail that can help to discriminate between pain or another type of stimulus.

that connects parts of the brain's cortex and limbic system (the emotion centre) with various regions in the brainstem, which connects with the spinal cord (see page S2). This enables higher brain areas to enhance or inhibit pain signals. "What imaging has proven is when you're sad, anxious or distracted, it doesn't just change the way you express pain, it changes the physiological processing," says neuroscientist Irene Tracey. Her group at the University of Oxford, UK, has been using brain-imaging technologies to examine pain modulation in humans. One study[4] has already identified which brainstem regions reduce pain signals when a person is distracted, and they are now trying to identify risk factors and brain networks that might make someone more vulnerable to developing chronic pain. "We're using imaging to help explain why someone's painful experience is a particular way — and what mechanisms lock them into that state," says Tracey. "These provide exciting alternative targets for therapies." The hope is that a likely transition from acute to chronic pain can be prevented.

Chronic pain is a huge global burden, affecting around one in five people (see page S4). "We have no scientifically validated treatments for these patients," says physiologist Vania Apkarian at Northwestern University in Chicago, Illinois. "It's a massive health situation." Apkarian's group has found many functional and anatomical features that are unique to the brains of people with chronic pain, helping to establish that acute and chronic pain are fundamentally different. "By definition, that makes it a disease state," says Apkarian. Finding out whether such differences are the cause or consequence of chronic pain is trickier.

To tackle this question, Apkarian's group conducted the first longitudinal brain-imaging study of chronic pain[5]. The researchers followed 39 people with recent back pain for a year, periodically conducting brain scans. Over this period, those who developed chronic pain showed reductions in grey-matter density in the insula and nucleus accumbens. The researchers also found that measures of connectivity between the medial prefrontal cortex and nucleus accumbens taken at the start of the study predicted with around 80% accuracy who would develop chronic pain — stronger connections conferred higher risk. In a follow-up study, Apkarian's team tracked brain activity associated with perception of back pain and found that, as pain became chronic, activity shifted to brain regions associated with emotion and reward[6]. The extent of this shift was also related to the strength of the connectivity between the medial prefrontal cortex and the nucleus accumbens.

These findings reveal the circuitry that seems to trigger the transition from acute to chronic pain, together with the anatomical changes that are the consequences of it. "This disambiguates the chicken and egg of chronic pain," says Apkarian. His team has also shown that the main determinant of chronic pain is not the injury, but the properties of the person's brain, he adds. And, in rodents, the researchers have been able to block the transition from acute to chronic pain using drugs that inhibit neurons in the nucleus accumbens[7]; a trial is under way to see if this works in humans. "I'm confident we will quickly develop a whole series of new treatment options specific for different types of chronic pain," says Apkarian.

"The use of the technology is getting ahead of itself."

The brain regions that Apkarian identified are the same ones that Wager's group found to be involved in self-regulation. So, although this reward-learning and emotional circuitry is not part of the neurological signature for acute pain, it does seem to play a key part in chronic pain. "We're learning something about how different kinds of pain have different bases in the brain," says Wager. "What's driving your pain might not be the classic pain processes."

PAIN-O-METER

Could these developments bring us closer to being able to measure pain objectively? Such readings would be useful both for drug development and for people who can't express whether they are in pain, such as infants, people in a coma or those with dementia. Several companies in the United States are already offering a service that they say can detect a person's pain signature. And there has been at least one case in which brain scans have been accepted as evidence of chronic pain in US civil courts. But many researchers have grave concerns. Importantly, Wager's results don't apply to chronic pain. "The technologies Tor and others use involve recording how the brain responds to a stimulus," explains neuroscientist Karen Davis of the University of Toronto, Canada. "In chronic pain there's no stimulus, so we need a different approach."

Last December, the International Association for the Study of Pain, based in Washington DC, set up a task force, chaired by Davis, to study the use of brain imaging to identify pain. Over the next year it will produce guidelines on what the technology can and cannot do, whether it is accurate and reliable enough for legal settings, and what the ethical and social issues are. A key concern that Davis and many other researchers have is that fMRI might give misleading results. Certain drugs, for instance, can change vascular function and thus the fMRI signal without having changed brain activity. "Using a vascular-based technology has issues that people haven't been considering," says Davis. Getting this right will be crucial if brain imaging is going to play a part in evaluating pain. "The use of the technology is getting ahead of itself, and there are enormous legal and neuroethical implications," says Davis.

Put someone like David in the brain scanner and you get a false-positive result — he doesn't feel pain even though his pain matrix is active. Conversely, a lack of activity might seem to imply an absence of pain. But most researchers agree that such a conclusion would be unwarranted. "We can confirm pain of certain kinds," says Wager. "But you can never, even in principle, disconfirm pain — because a person's brain might just be unique." ■

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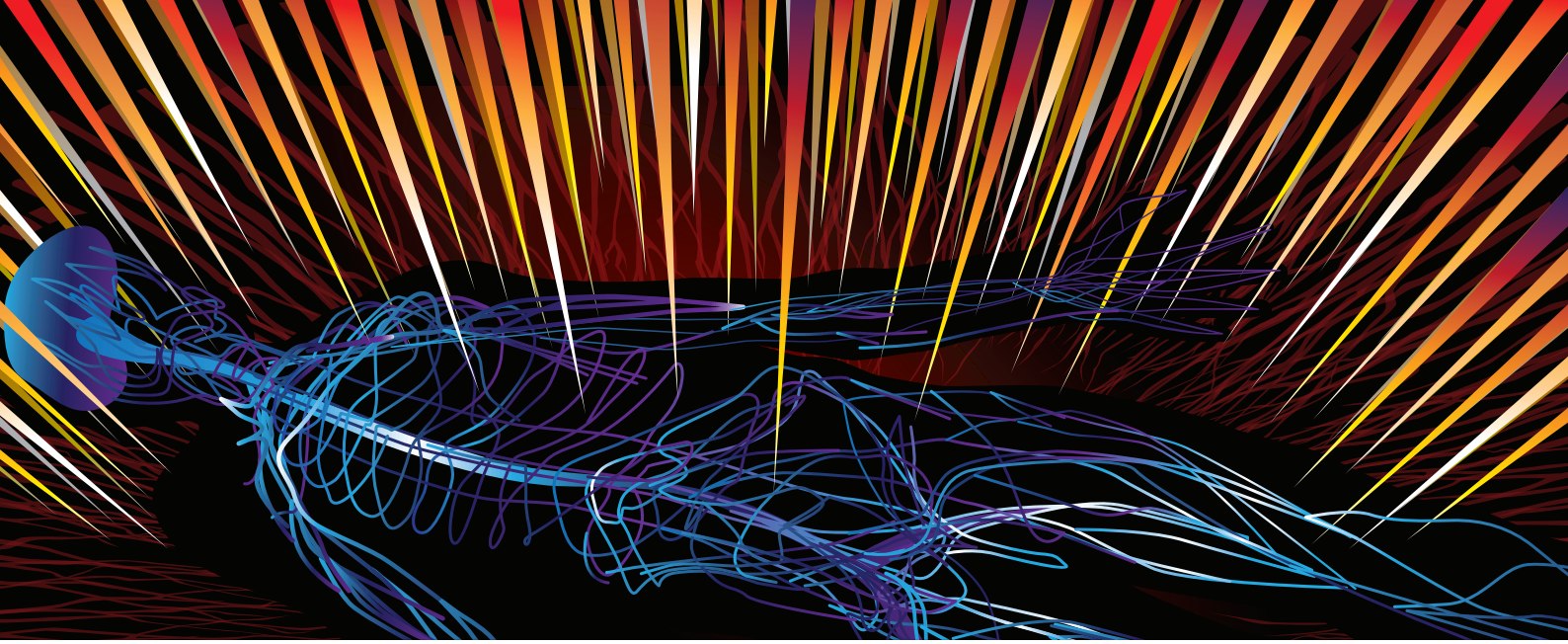


NEUROPATHY

A name for their pain

People with neuropathic pain have struggled to find relief with conventional drugs. Researchers are investigating whether more meaningful pain classifications could help.

BY MICHAEL EISENSTEIN

Two years ago, with little fanfare, neurologist Søren Sindrup reported the results of a successful clinical trial[1]. On the face of it, it was a modest success story. Instead of coming up with a wonder drug, Sindrup and his team repurposed an existing medication. Nevertheless, some pain researchers consider the trial a potential game-changer — one that marked a turning point in how researchers think about neuropathic pain.

This type of chronic pain arises from damage to the nerves that sense, transmit or process information about environmental stimuli. It can result from numerous initial insults, including spinal cord injury, diabetes and chemotherapy. Patients have generally been grouped on the basis of this initial trauma. But Sindrup, who is at Odense University Hospital in Denmark, and his colleagues took a different approach. They used diagnostic work-ups to cluster patients by their symptoms. This allowed the researchers to home in on a cohort that was more likely to respond to treatment. This is a huge step forward in an area where clinicians have struggled to help their patients. "The drugs we have relieve 50% of pain in somewhere between 1 in 4 and 1 in 7 of the patients we treat," says Andrew Rice, a pain researcher at Imperial College London. "That's for the best drugs — and that's not very good."

A growing number of pain researchers think that improvements can be found by analysing symptoms for clues about the underlying nerve damage. Neurologist Giorgio Cruccu of Sapienza University in Rome draws a comparison with another area of neurology. "There is no universal treatment for epilepsy," he says. Instead, "it depends on the type of seizures". Pain is a challenging medical target — doctors gain much of their insight from patients' reports rather than from external observations. But clinicians are attempting to devise more-sophisticated diagnostic tools to give the field a quantitative edge — and perhaps usher this patient population into a new era of evidence-based treatment.

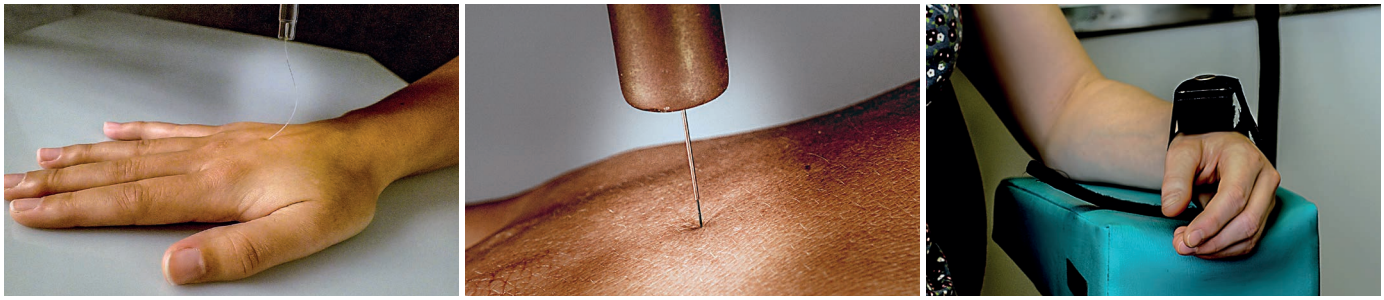
TESTING YOUR PATIENTS

Pain is initially recognized through peripheral sensors in the skin known as nociceptors, which react to potential sources of injury such as heat or mechanical trauma. Nociceptors send signals through specialized nerve fibres to the spinal cord, and from there to the brain (see page S2). Disruption to any part of this process can trigger enduring discomfort, although the severity and sensations experienced — burning or shock-like pain, numbness or tingling — can vary widely depending on the nature of the underlying damage. Not all injuries result in the same pain symptoms. For example, people with post-herpetic neuralgia (which can result after an outbreak of shingles) often have spontaneous pain that resembles an electric shock, but some experience allodynia — pain as a result of benign physical contact, such as clothing rubbing against skin. Over the past two decades, clinical researchers have come to appreciate that this variety of symptoms offers a way to understand how pain works. "There were hints in the literature that there are different mechanisms at work across various neuropathic pain entities, where patients have the same 'origin' of pain, but a different pain mechanism," says Christoph Maier, a pain specialist at University Hospital Bergmannsheil in Bochum, Germany. "Today, we know this idea is correct."

If these symptoms do represent different underlying mechanisms, that would help to explain why people in the same patient group respond differently to the same drugs — and that might have implications for treatment. "We have tried to develop a classification that is based on symptoms, which may give some indirect clue about the pain mechanism," says Nadine Attal, a neurologist at Versailles Saint-Quentin-en-Yvelines University in France. Over the past decade, several questionnaires have been developed, including painDETECT and Douleur Neuropathique 4, which help to distinguish pain associated with nerve injury from that brought on by other causes, and the more detailed Neuropathic Pain Symptom Inventory (NPSI), for further subclassification of patients. These can be completed by patients in minutes, and have proved to be a reliable way to assess the nature and intensity of their pain.

But questionnaires do not objectively measure pain, nor can they zero in on the factors that trigger it. To provide such insights, Maier and other researchers affiliated with the

DANIEL HERTZBERG



Left to right, a whisker-like fibre, pin prick and thermal stimulus are used to test pain sensitivity as part of the quantitative sensory testing protocol.

CHRISTOPH MAIER

German Research Network on Neuropathic Pain (DFNS) have devised a standardized battery of assessments known as quantitative sensory testing (QST). The QST protocol includes components such as hot and cold probes, to determine whether pain is triggered by thermal stimuli, and thin, whisker-like filaments that are applied to the skin to assess sensitivity to touch. "If you have somebody with allodynia, that small filament would feel painful," says Ian Gilron, an anaesthesiologist at Queen's University in Kingston, Canada. QST can help researchers to measure the response of different types of sensory nerve, including both the small fibres that detect painful stimuli and the large ones that transmit information about movement and vibration. Although QST enables clinicians to measure and monitor pain symptoms, it is a labour-intensive process that requires extensive training. Furthermore, the variability in pain response across or even within individuals means that QST is better suited to identifying subgroups in a population than for diagnosing individuals.

Skin biopsies taken from the area of pain can provide a more detailed picture of what is happening at the tissue level. "You can demonstrate the loss of small fibres by directly counting how many free nerve endings can be found in the epidermis," says Cruccu. He also advocates the use of tests that directly measure how well individual nerves function. Such techniques, says Cruccu, "provide objective measures unpolluted by cognitive biases". Although this type of neurophysiological testing can reveal the nature of nerve damage, it requires costly, specialized equipment and expertise — and some of the more cutting-edge tools have yet to be validated for clinical use.

IN SEARCH OF SUBGROUPS

Researchers are still deciding how to rewrite the diagnostic rule book, but preliminary studies support the idea that a deeper assessment of pain symptoms can lead to more effective care. For example, in Sindrup's clinical trial[1], although the team recruited patients with diverse neuropathic traumas, it used QST to identify common characteristics that might predict drug efficacy. The researchers found that people with nerves that had become hyper-responsive to temperature or physical probing — the 'irritable nociceptor' phenotype — were more than three times as likely to have pain relief from the anticonvulsant drug oxcarbazepine as those who had the non-irritable phenotype. This response also makes mechanistic sense: Sindrup and colleagues noted that oxcarbazepine blocks the sodium channel proteins that are responsible for nerve signalling, which could well be hyperactive in patients with irritable nociceptors.

This study is one of the few to select patients up front on the basis of pain characteristics, but others have applied similar techniques retrospectively. By using QST and skin-biopsy data collected during a trial of botulinum toxin A, which inhibits the firing of pain nerves, Attal and her colleagues found that people with both allodynia and a higher density of epidermal pain-sensing fibres were more likely to benefit from this treatment[2]. And a team led by Didier Bouhassira, a colleague of Attal's at Versailles, is preparing to report a study that re-examined data from 1,200 patients who previously participated in unsuccessful clinical trials for a heavily studied neuropathic pain drug. These findings offer hope for improved patient–drug 'matchmaking', whereby symptom profiles inform smarter trial design and help doctors to prescribe the treatments that are most likely to be effective.

> ***"There were hints in the literature that there are different mechanisms at work."***

Integrating data sets from multiple diagnostic approaches offers a way to improve this process. One such effort, by neurologist Roy Freeman at the Beth Israel Deaconess Medical Center in Boston, Massachusetts, and colleagues, analysed QST and NPSI data from past clinical trials to identify four distinct patterns of pain symptoms that seem to correlate in different groups of patients[3]. These profiles could be developed into 'fingerprints' for specific types of neuropathic injury by, for instance, connecting specific pain triggers such as pressure or cold with manifestations of pain such as stabbing or tingling sensations.

Researchers hope that such correlations will reveal information about the roots of pain pathology. A large European patient registry maintained by the DFNS and the public–private organization the Innovative Medicines Initiative (IMI) is enabling a more thorough hunt for such patterns. "It contains about 4,000 patients," says Maier, who manages the data set as part of the IMI's Europain project. "It includes somatosensory profiles, clinical data, QST data, microscopy and skin-biopsy data and, in some cases, genetic data."

Despite having only a handful of trials to serve as proof of concept, several consortia — including the US-based Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) — are planning on using these phenotyping tools in clinical trials. For now, most of the enthusiasm is coming from the academic sector; pharmaceutical companies expect much stronger evidence before taking on the additional cost. There is also the likelihood that more refined testing will shrink the patient population that drug companies can target with new analgesic drugs. "Instead of getting an approval for all of post-herpetic neuralgia, for example, they'd get one just for post-herpetic neuralgia with allodynia," Rice says.

Nevertheless, according to Cruccu, a growing number of trials now use the quick questionnaires as a cost-effective fail-safe. Even if, overall, a trial seems unsuccessful, the availability of these data could enable a later search for specific subgroups in which efficacy can be demonstrated. Maier says that findings such as those from Sindrup's trial suggest that many 'failures' may be masking successes: small numbers of patients whose positive response to a drug is drowned out by the sea of people whose pain is poorly matched to the therapy being tested.

For now, the diagnostic tools available give only basic signposts for clinicians who treat people with neuropathic pain. But, given the dearth of effective treatments, even modest gains could have an outsized impact — especially once a next generation of analgesics enters the pipeline. "If there was a way to know who was most likely to respond to a drug and really focus on that in a clinical trial," says Rice, "that would be magic." ■

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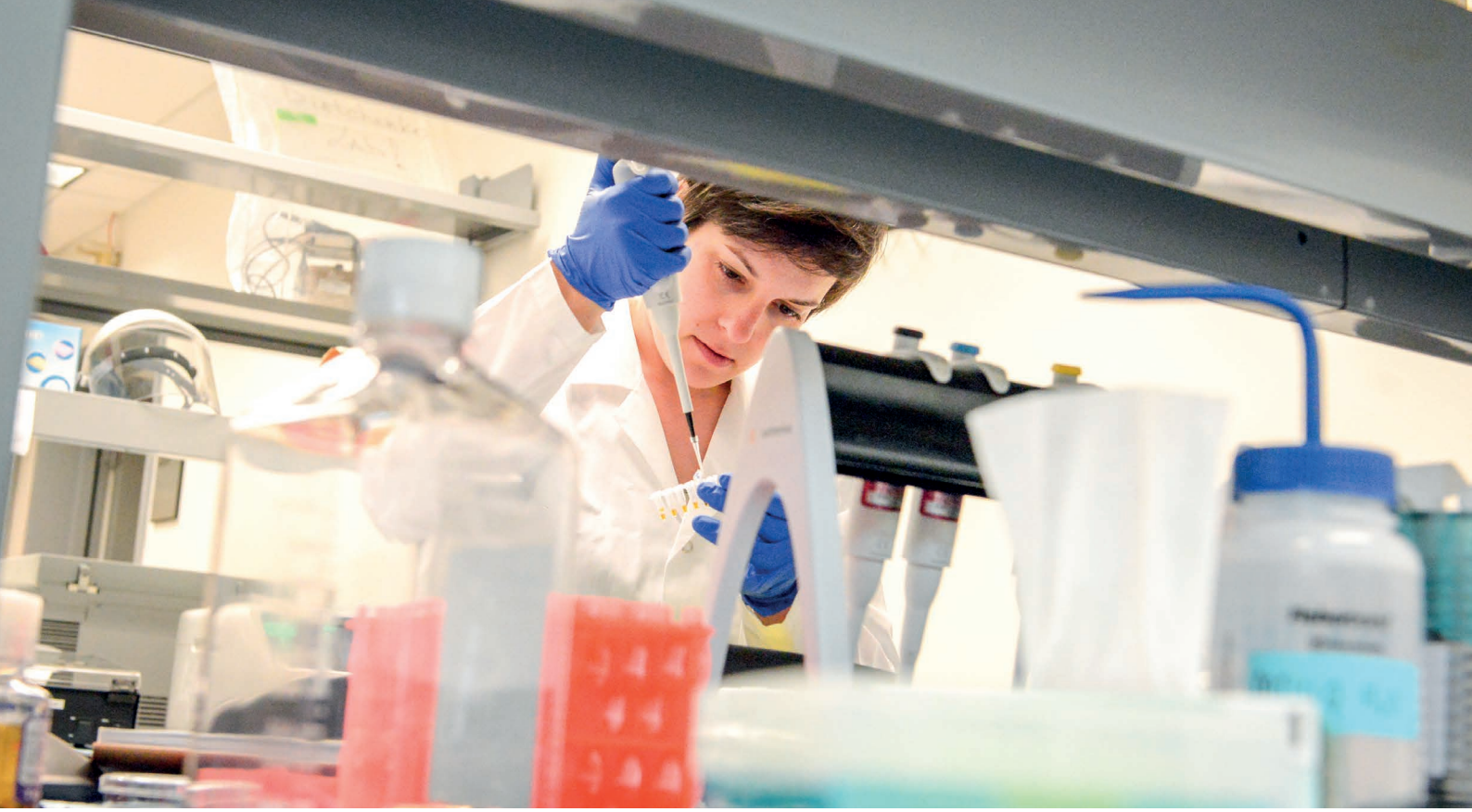


Researchers such as Anne-Julie Chabot-Doré, pictured in Luda Diatchenko's lab at McGill University in Montreal, Canada, are searching for chronic pain genes.

LUDA DIATCHENKO

GENETICS

An incomplete mosaic

Although genetics studies have so far failed to revolutionize pain treatments, some researchers think that a host of discoveries are just around the corner.

BY ERYN BROWN

Neurologist Stephen Waxman wants to understand how genes influence chronic pain. He hopes that unravelling the mystery will offer relief to the patients he studies. Some are in agony because of old injuries, others because of diabetic nerve damage. And there are those who battle rare disorders such as inherited erythromelalgia, experiencing searing pain in their extremities when they come into contact with mild warmth or engage in moderate exercise. "For these people, putting on socks is like having hot lava poured on their bodies," Waxman says.

Researchers such as Waxman, who is at Yale University's Center for Neuroscience and Regeneration Research in West Haven, Connecticut, are betting that analysing patients' DNA will help to explain the underlying causes and mechanics of chronic pain, which now afflicts around one billion people worldwide. Ultimately, researchers hope that such explorations will lead to better treatments for those who have chronic pain, by revealing targets for a new generation of drugs that are capable of targeting pain without dulling the senses or promoting addiction.

But this is a search that has already gone on for a couple of decades. And although scientists have discovered that genetics have a significant role in pain — anywhere from around 20% to 60% of the variability in how people experience pain is attributable to differences in genes — no one has yet pinpointed any crucial smoking guns in DNA. And the complexity of the problem can be a bit depressing. "Once you realize something is mediated by, say, 1,000 genes, you wonder if it's even possible to figure it out," says Jeffrey Mogil, a pain researcher at McGill University in Montreal, Canada. But other researchers are more optimistic, and suggest that continuing with the approach, with some refinements, will yield useful discoveries.

ELEMENTAL CONCERNS

Across the campus from Mogil's office, molecular geneticist Luda Diatchenko is undeterred in her search for pain genes. Diatchenko thinks that the large number of unknowns means that scientists are actually on the verge of a flood of discoveries. It took time, she says, to design pain-genetics experiments and to develop methods for studying the genome that were not prohibitively expensive. "The studies have not been done yet," Diatchenko says. "It will be an explosion — soon."

Pain-genetics researchers have pursued two main avenues of inquiry, says neuroscientist Stephen McMahon at King's College London. The first strategy, taken by researchers such as Waxman, is to study rare pain disorders that run in families to identify single-gene mutations. This approach has produced a handful of tantalizing leads. For instance, inherited erythromelalgia, which Waxman says affects around 30–40 families worldwide, is caused by a mutation in a gene that causes the sodium-ion channel $Na_V1.7$ to become overactive. This protein is crucial for conducting pain signals in peripheral nerves, but not, it is thought, in the central nervous system.

If drug developers could use this information to come up with a way to dial down $Na_V1.7$ in people with chronic pain, they could develop systemic treatments that would dampen pain signals in nerve cells without causing side effects such as sleepiness, confusion, loss of balance or addiction, says Waxman. Drug companies such as Amgen, Pfizer and Convergence Pharmaceuticals are

working on $Na_V1.7$ inhibitors, but Waxman doesn't expect to see any therapies approved for several years. "Finding a drug that's selective for this sodium channel is tricky," says McMahon. And accidentally hitting another subtype of sodium channel — such as the ones that are essential for controlling heartbeat — would be dangerous.

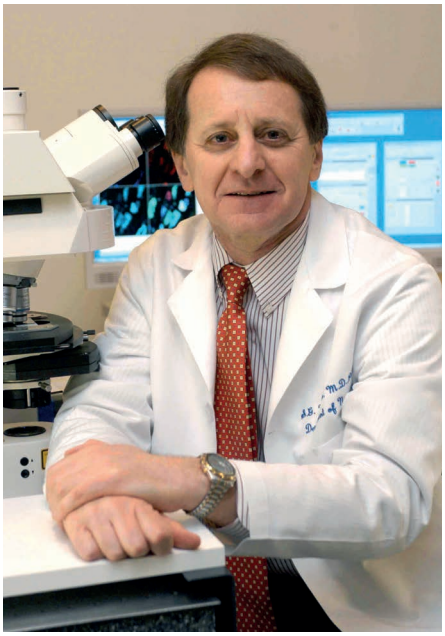
The second approach is broader: rather than just looking at rare inherited conditions, the DNA from large cohorts of patients is sequenced to try to identify genetic variants and the traits, or phenotypes, that correlate with them. The hope was that such studies would reveal a small number of key pain genes — those shared by all or many people with various chronic pain disorders. But what researchers found instead was that pain, like many chronic conditions, is caused by a complex interaction between genes and the environment, influenced by hundreds, if not thousands, of genes in each individual.

William Maixner, director of the Center for Translational Pain Medicine at Duke University in Durham, North Carolina, refers to the causes of chronic pain as "a mosaic of pathways" within each individual that change over time owing to environmental factors, and that affect psychological processes as well as those related to nerve damage. Maixner is working with Diatchenko and others to tease out the genetic mechanisms that are at work in a number of pain disorders, including irritable bowel syndrome, fibromyalgia and lower back pain.

Their Orofacial Pain: Prospective Evaluation and Risk Assessment, or OPPERA, study focuses on people with temporomandibular disorder (TMD), a common facial-pain condition of unclear origin. The team collected data for up to 5 years from just over 2,700 TMD-free men and women, 260 of whom developed TMD during the study. Maixner's group examined DNA variations known as single nucleotide polymorphisms (SNPs) in 358 genes that regulate pain, and tracked 202 phenotypes in the volunteers[1]. The initial findings underscored the complexity of TMD. The researchers failed to identify any single genetic variation associated with the condition, but did find five SNPs linked with risk factors for TMD, including ones related to non-specific facial pain, physical symptoms, stress and negative mood. The team has since expanded its analysis to the entire genome of the OPPERA participants, and hopes to publish updated results by 2017.

"The studies have not been done yet. It will be an explosion — soon."

Researchers such as Mogil and McMahon, who are vexed by the slow progress in pain genomics, say that genome-wide association studies have been too small to detect culprit variants — and that the funding isn't there to support larger-scale efforts.



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Neurologist Stephen Waxman studies the genetics of rare pain disorders.

Compounding the problem is the difficulty of correctly phenotyping people with chronic pain. Christopher Sivert Nielsen, a pain psychologist at the Norwegian Institute of Public Health in Oslo, says that pain disorders that receive separate diagnoses are often not that different from each other. Furthermore, chronic pain is very common, making the identification of controls challenging. In this sense, chronic pain is very different from well-characterized diseases such as multiple sclerosis (MS). "If you study MS, you go into the clinic, you collect cases and the rest of the world provides your controls," Nielsen says. "But this doesn't work for pain." Because many types of pain have common genetic origins, it's easy for a person with a related pain type to end up in a control group, disrupting an association study. To pin down phenotypes, Nielsen adds, researchers will need to screen study participants much more rigorously — a difficult task in the large groups required to do genome-wide association studies well.

Maixner says that OPPERA researchers are trying to cut through the noise in their data by devising new methodologies to understand how genes relate to symptoms. Bioinformaticians are working on stratification procedures that divide the study population into three distinct subgroups — a pain-sensitive cluster of people with heightened sensitivity to experimental pain stimuli, a global-symptoms cluster with pain sensitivity and psychological distress, and a third group with neither[2]. Most people with TMD fall into the first and second groups. By analysing these clusters instead of the entire population, Maixner suggests that scientists will find it easier to tease out how genes contribute to the development and to the manifestation of symptoms in each group.

Some researchers are looking beyond the genome to the epigenome — the markers on DNA that have been added by processes such as methylation. Epigenetic changes alter gene expression and therefore affect various biochemical events. "The hope is to discover a whole new number of cellular processes that control the dynamics of a chronic pain state — the 'on' switches," says McMahon.

He says that studying epigenetics could help scientists to understand the environmental influences that make a person more likely to develop chronic pain. He thinks it could also improve treatments, reasoning that drugs that interfere higher up the chain of biological events should prove more effective than therapies that operate at the periphery. "Using Na_V blockers is like attacking the foot soldiers, whereas disrupting epigenetic processes is like taking out a general giving an order to the whole army," he says.

In 2014, McMahon collaborated on a study that looked at identical twins with different levels of pain sensitivity. The team found[3] methylation differences connected to several genes, including the pain gene *TRPA1*. But epigenetics is dizzyingly complex, and other researchers note that it is not yet possible to link epigenetic changes to the environmental factors that might have caused them. "It's early days," concedes McMahon, who stresses that merely finding epigenetic or genetic targets isn't enough — such work must be accompanied by experiments in cells and model organisms that explain the biology going on in the cells.

And Mogil wonders if "epigenetics is a bit of a flavour of the month". Genetics failed, so researchers are now asking "Where will we bet all our chips now?" he says. For now, Mogil has largely shifted the focus of his research from identifying pain genes to validating known candidates in rodent studies, and to understanding how sex impacts pain processing (see page S7). This is the type of follow-up work that could help researchers to understand the fundamental mechanisms of pain and what the genetic and epigenetic findings have to do with them.

Researchers are not yet close to understanding the genetic components of pain well enough to produce tailored pain therapies to satisfy the push for precision medicine, says Mogil. But he is not pessimistic — just realistic. There is still a lot to learn, and for a researcher that is good news. "What I love about genetics is, you can find interesting proteins to study without even knowing what you're looking for." ■

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PLACEBOS

Honest fakery

Armed with a clearer understanding of how placebos work, researchers are suggesting that inactive substances might be used to mitigate chronic pain.

BY JO MARCHANT

In April, Ted Kaptchuk addressed hundreds of physicians and scientists at the Behind and Beyond the Brain symposium in Porto, Portugal. Within minutes, ripples of laughter were spreading around the conference hall.

Kaptchuk, a researcher at Harvard Medical School in Boston, Massachusetts, was showing the audience a cartoon in which a doctor hands over a prescription note. "I want you to take this placebo," says the white-coated medic to her bemused patient. "If your condition doesn't improve, I'll give you a stronger one." The chuckles were a response to the absurdity of openly treating a patient with fake pills. By definition, placebos have no active ingredient, so the idea that someone might benefit from knowingly taking one — let alone that different placebos could have different effects — seems nonsensical. But Kaptchuk invited his audience to take the scene seriously. Honest placebos can work, he insisted. And some placebos really are stronger than others.

Kaptchuk's trials are overturning many assumptions about the best way to care for patients, particularly those in pain. After four decades of probing the mechanisms of placebo responses, researchers are advancing the argument that inert pills are more than just negative controls in clinical trials: they can be a treatment in their own right.

PLEASING MEDICINE

The modern idea of the placebo effect stems from 1955, when US physician Henry Beecher analysed the results of 15 studies and concluded that, regardless of a patient's complaint, around one-third showed a significant response to a placebo[1]. The effect is now well-established, particularly for conditions that rely on subjective reports, such as pain.

There are lots of reasons why someone in a clinical trial might feel better. Symptoms often ease with time, or trial participants might report an improvement to please the experimenters. Because of this, placebo responses are commonly viewed as illusory — a baseline against which to compare the action of new drugs. But there is now a large body of research showing that the effects of placebos can be very real.

Fabrizio Benedetti, a placebo researcher at the University of Turin, Italy, points to a 1978 study[2] by neuroscientist Jon Levine that, he says, represents the moment that "the biology of placebo was born". Levine and his colleagues administered intravenous infusions of saline to patients who were recovering from surgery, telling them that it might be morphine. One-third of them reported a significant reduction in pain. Then, the researchers secretly added naloxone, which blocks the action of painkillers such as morphine by binding to opioid receptors in the brain, to the infusions and the patients' pain returned. Levine had shown that a placebo response could be biochemically blocked.

Levine's study was revolutionary because it suggested that patients don't simply imagine or pretend that their pain is eased with placebos. Their analgesia reflects a measurable, physical change — mediated by the release in the brain of endogenous opioids called endorphins[2]. This finding has since been confirmed by dozens of brain-imaging studies, which show increased binding of endorphins to opioid receptors in response to placebo painkillers, as well as reduced activity in areas of the brain involved in processing pain[3].

DANIEL HERTZBERG

Endorphins aren't the only neurotransmitters involved. Placebos can activate endocannabinoids (which bind to the same receptors as the psychoactive constituents of cannabis) or dopamine, or they can reduce the levels of prostaglandins (which dilate blood vessels and increase sensitivity to pain). In general, Benedetti says, "placebos can modulate the same biochemical pathways that are modulated by drugs".

Inert substances cannot, of course, create biological changes. A placebo's active ingredient, says Kaptchuk, is a person's psychological response to being treated. Tor Wager, a neuroscientist at the University of Colorado Boulder, agrees. His functional magnetic resonance imaging (fMRI) studies were among the first to show that placebos reduce activity in relevant brain areas when people are subjected to pain. But before the onset of pain, his fMRI scans show something different: receiving a placebo increases activity in the two parts of the brain involved in emotion and valuation, the prefrontal cortex and the ventral striatum[3]. "We think the placebo is causing a re-evaluation of the pain," concludes Wager. "It doesn't mean the same thing to you."

LEARNING NOTHING

Placebos influence expectation: how good or bad we think our pain is going to be. This expectation is influenced by what we're told about a treatment and also its nature — invasive treatments (such as surgery or acupuncture) often elicit larger placebo responses than interventions that seem more modest (such as pills). Social factors including the attitude of the practitioner can also influence patients' symptoms[4,5]. What's now coming to light, however, is that placebo responses can also be learned. Just as Russian physiologist Ivan Pavlov discovered that dogs salivate in response to a buzzer associated with food, similar mechanisms are thought to drive placebo responses previously assumed to rely purely on conscious expectation.

For example, giving volunteers several doses of a real painkiller — or surreptitiously reducing the strength of experimental pain — makes subsequent placebo responses to the same stimulus stronger and more consistent. Benedetti calls this process "pre-conditioning". When he and neuroscientist Luana Colloca, now at the University of Maryland in Baltimore, subjected volunteers to electric shocks, pre-conditioning resulted in a five-fold boost to the average pain relief conferred by a placebo[6].

In some circumstances, such learned responses can override conscious expectations. Wager and his colleagues reported that after four episodes of pre-conditioning, an inert cream reduced pain in volunteers even when they knew it was a placebo[7]. "Eventually, it doesn't matter what you think, because your brain has learned," says Wager.

Different drug memories can trigger different neurochemical pathways. Benedetti demonstrated this effect by pre-conditioning some volunteers with morphine and others with the non-opioid painkiller ketorolac[8]. The subsequent placebo response of those in the morphine group involved endorphin release, whereas in the ketorolac group it was mediated by endocannabinoids. "It shows that not all placebos are equal," says Benedetti.

The key question is whether these drug-like placebo responses can be harnessed in medical care. Patients could benefit from measures such as using language designed to boost expectations or to strengthen the social bond between doctor and patient[4]. But researchers are now suggesting something previously unthinkable — a role for placebos themselves.

Colloca suggests that, by taking advantage of learning mechanisms, doctors could give placebos honestly and reduce the amount of medication. For example, a doctor might prescribe a blister pack of painkillers, and tell the patient that it contains both drugs and placebos — but not which pills are which. Earlier this year, Colloca and her colleagues reviewed 22 studies that used similar techniques, covering conditions such as insomnia, autoimmune diseases and pain[9]. They concluded that these approaches have the potential to reduce side effects (although some of these may be conditioned responses, too), limit problems with drug dependency and toxicity, and reduce costs.

"The assumption has been that deception or concealment is necessary for placebos to work."

Benedetti loves the idea. "This is one of best applications of placebos in clinical practice," he says. In a trial published in February, he showed that in people with Parkinson's disease, pre-conditioning with the drug apomorphine made patients respond to a placebo just as strongly as they did to the active drug[10]. Alternating drugs and placebos might delay the development of tolerance, he suggests.

Kaptchuk is going one step further. For conditions such as chronic pain, for which placebo effects are large, drugs aren't very effective and taking them can have downsides (see page S4), he suggests sometimes ditching medication altogether and openly giving placebos. He made headlines in 2010 with a placebo study for irritable bowel syndrome (IBS) in which patients were told that they were receiving a sugar pill[11]. "Historically, the assumption has been that deception or concealment is necessary for placebos to work," Kaptchuk says. "My logic was that maybe we could tell patients upfront that placebos may work and tell them to give it a try." The results were startling: 59% of patients who knowingly took sugar pills reported adequate relief from their symptoms, compared with 35% in the no-treatment group — better than most IBS drugs, he adds. "I was very surprised by the results," says Kaptchuk, "even though I hoped it would work."

And it wasn't a fluke. At the symposium in Porto, Kaptchuk followed the cartoon with the results of a new test of an open-label placebo. The trial included 97 patients with chronic lower back pain who had not responded to previous therapies. All continued their usual treatment, but those randomized to the open-label placebo group were also given twice-daily sugar pills, along with an explanation of the research behind why these might help them.

Over three weeks, patients in the placebo group reported a marked drop in pain, whereas the pain of the treatment-as-usual group didn't significantly change. The open-label placebo triggered "sometimes modest, sometimes dramatic, improvements in pain and disability that had major impacts on people's lives", says lead researcher Cláudia Carvalho, a psychologist at the ISPA-University Institute in Lisbon.

Carvalho and her co-authors are still not sure why placebos seem to help patients who haven't responded to treatments in the past. Carvalho suspects that for some, knowingly taking placebos may have made them more aware of the role of the mind in controlling pain. "It empowered them and changed their relationship with their pain," she says.

More studies of honest placebos are in the pipeline — other teams are conducting trials in cancer-related fatigue and depression, and Kaptchuk is recruiting for a trial that aims to replicate and extend his original findings in IBS. If the results continue to be positive, Kaptchuk suggests that for appropriate conditions, placebos — honestly prescribed by clinicians — could become a routine part of medical care. "Placebos have always been a negative for medicine," he says, "but for many patients, trying open-label placebos could be a first line of treatment before any drugs are prescribed." ■

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Painful progress

~2000 BC

Mesopotamians and Egyptians recognize different types of pain, such as burning and stabbing. Where there is no obvious injury, pain is attributed to demons, ghosts or gods. Mesopotamians think that these attack by touching or striking the body; Egyptians say that the spirits enter the body through the ears and nostrils. Physicians sometimes use narcotics such as opium or the poisonous plant henbane (*Hyoscyamus niger*) to relieve pain, but treatment consists mainly of spells or prayers.

~410 BC

Greek physician Hippocrates and his followers dismiss supernatural causes of pain, arguing that it is a symptom of disease. Hippocratic medicine considers pain to be a useful clue to what is wrong with the patient. Among the texts known as the Hippocratic Corpus are instructions in the art of diagnosis. High on the list of questions that physicians were to ask patients are the familiar "Are you in pain?" and "Where does it hurt?"

1664

French philosopher René Descartes proposes specific pain pathways from the point of origin to the brain; the concept holds for 300 years. He illustrates the mechanism in his book *Treatise of Man* — a boy with his foot near a flame is hit by "particles of fire", which speed along a nerve to the spinal cord and on to the brain, where his soul lies. The soul transforms the signals to a perception of pain, releasing "animal spirits" that course through the nerves to the leg, prompting it to move. The book is published posthumously so that Descartes can avoid the wrath of the Church, which teaches that pain is a gift from God.

1798

English chemist Humphry Davy tests the effects of inhaling nitrous oxide. It makes him giggly and dizzy, but also eases the agony of an erupting wisdom tooth. "The pain always diminished after the first four or five inspirations," he says. Later, Davy reports how a mix of nitrous oxide and oxygen produces reversible unconsciousness in animals. He suggests that the gas "may probably be used with advantage during surgical operations", although the idea of gaseous anaesthesia languishes until the 1840s.

1805

German pharmacist Friedrich Sertürner isolates morphine, the active ingredient of opium. The milky gum tapped from unripe seed pods of poppies (**pictured**) had been used to deaden pain since prehistoric times, but despite improved preparations (such as laudanum) the variable potency of plant products made their effects unpredictable. Morphine proves ten times as potent and more reliable than opium, making it a mainstay of pain relief.

~6000 BC LEAF RELIEF

People of the Nanchoc Valley in Peru are the earliest known users of cocaine. Archaeological evidence suggests that they chewed coca leaves (**pictured**) with quicklime to speed the release of the drug — a traditional painkiller in parts of South America.

~2250 BC EARLY WORMS

A Babylonian clay tablet advises treating the pain of a burrowing 'tooth worm', which is thought to be the cause of caries, by plugging the hole with gum mastic and powdered henbane seeds. This is the earliest known written prescription for a painkiller.

47 BRIGHT SPARK

Roman physician Scribonius Largus prescribes electrotherapy for headaches and gout. In his medical text *Compositiones,* he recommends placing the electric ray *Torpedo marmorata* on the brow or under the feet, allowing it to discharge its electricity "until the patient's senses were benumbed".

1898 TRIAL BY ORDEAL

German surgeon August Bier proves the effectiveness of spinal anaesthesia. He administers cocaine to his assistant through a lumbar puncture, then burns and hammers the assistant's legs, finishing by twisting and squashing his testicles. The assistant feels nothing — until the anaesthetic wears off.

CLOCKWISE FROM TOP LEFT: DE AGOSTINI PICTURE LIBRARY/GETTY; AIZAR RALDES/AFP/GETTY; JERRY MASON/SPL

For thousands of years people have sought explanations for pain and ways to ease it. Despite a better understanding of the mechanisms behind the sensation, much remains baffling, and the search for better treatments continues. By **Stephanie Pain**

1899 BARK WITH BITE

German company Bayer creates aspirin. The drug has its origins in an age-old remedy for aches and pains — willow bark. The powdered bark contains the analgesic salicin, which Bayer modifies to create the less-toxic acetylsalicylic acid. Aspirin is now one of the world's most widely used drugs.

1906 ALARM SYSTEM

British neurophysiologist Charles Sherrington proposes the existence of nociceptors — specialized nerves that detect potentially harmful stimuli, such as extreme temperature. If the intensity is enough to cause injury, the nerves relay a pain signal to the brain.

1936 RIGHT JAB

Anaesthesiologist Emery Rovenstine establishes the first pain clinic at New York City's Bellevue Hospital, where he pioneers new methods for nerve blocking. Injections of anaesthetic into nerves ease the pain of angina, sciatica, neuralgia and some cancers.

2004 BRAIN DRAIN

People with chronic back pain are shown to lose as much as 11% of their brain tissue (A. V. Apkarian *et al. J. Neurosci.* **24,** 10410–10415; 2004). Subsequent studies find that other causes of chronic pain, such as persistent headaches and irritable bowel syndrome, also lead to shrinkage of grey matter.

2014 BACK TO THE FUTURE

An analgesic is discovered in the herb *Corydalis yanhusuo* (**pictured**), used for centuries in China to treat back pain. The compound, dehydrocorybulbine, binds to dopamine receptors and offers longer-term relief than opiate drugs.

CLOCKWISE FROM TOP LEFT: ULLSTEIN BILD/GETTY; MONTREAL NEUROLOGICAL INST./SPL; BON APPETIT/ALAMY STOCK PHOTO

1864

During the American Civil War, Silas Weir Mitchell and two fellow surgeons identify an excruciating form of chronic pain that stems from damaged peripheral nerves, a condition that Mitchell calls causalgia (now called complex regional pain syndrome). Even minor injuries cause unbearable burning pain, which soldiers liken to a "red-hot file rasping the skin". They become hypersensitive to the slightest touch; exposure to air or heat, or even the sound of a rustling newspaper increases their pain. Some are still suffering decades later.

1965

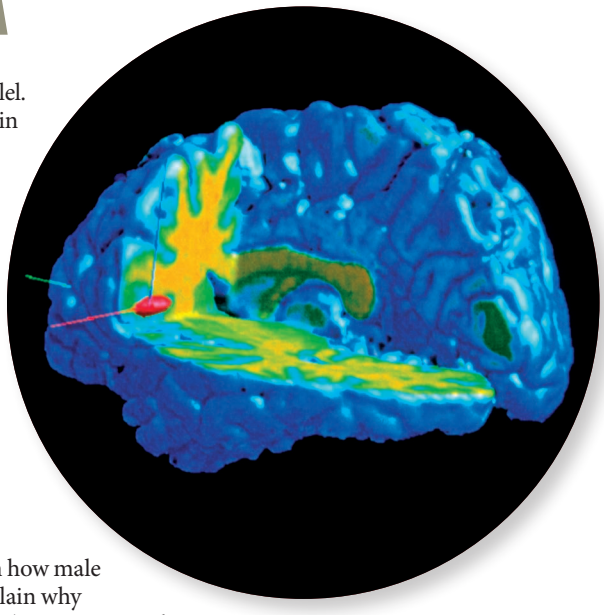
Psychologist Ronald Melzack and neuroscientist Patrick Wall propose their gate-control theory of pain. They suggest that the spinal cord has a 'gate' mechanism: messages from the source, other nerves and the brain converge to determine whether the gate opens to allow pain messages to reach the brain or closes to prevent them. This suggests that the perception of pain is influenced by a combination of physiological and psychological factors, such as mood. Although the details of their mechanism later prove flawed, the theory revolutionizes the field.

1973

US researchers discover a receptor in the brain through which morphine exerts its effects. This suggests that opiate drugs work by mimicking natural painkillers made by the body. Two years later, British biologists discover enkephalins, a group of endogenous opioids — or endorphins. Endorphins form part of the body's natural mechanism for managing pain, providing analgesia by reducing the perception of pain.

1991

Neuroimaging techniques reveal that pain is processed in several areas of the brain in parallel. Positron emission tomography (the brain's pain response is pictured in red) and functional magnetic resonance imaging have since provided a deeper understanding of this phenomenon, as well as how the perception of pain is influenced by emotion, experience and expectation. Some think that these techniques may make it possible to measure pain objectively and to distinguish physical from emotional pain. Imaging could help in the search for new drugs for chronic pain (see page S8).



2015

Researchers find a fundamental difference in how male and female mice process pain, helping to explain why men and women seem to feel pain differently (R. E. Sorge *et al. Nature Neurosci.* **18,** 1081–1083; 2015). Women are more sensitive to pain than men, are more likely to have chronic pain and respond differently to some painkillers. Past studies showed that the immune cells microglia play a key part in pain perception, but this is now found to be true only in males. T cells serve the same function in female mice (see page S7).

the musical discrimination of the Tsimane' villagers, the listeners experienced consonant and dissonant intervals as equally pleasant (J. H. McDermott *et al. Nature* http://dx.doi.org/10.1038/nature18635; 2016). This is not a deficiency of affect, because the villagers can distinguish cheerful sounds (laughter) from less cheerful ones (gasps). They also recognize physically unpleasant sonic 'roughness' — the beating sensation when two tones close in frequency are played at once.

The reason for the villagers' inability to distinguish what others would call pleasant sounds from unpleasant ones might be, in large measure, one of culture. The Tsimane' do have music, but it is purely one of melody rather than harmony. They play or sing in single lines, and do not adhere to Western scales. This seems odd to those immersed in the European musical tradition, with its clear differences between pleasant and disagreeable harmonies.

The differences are so clear, in fact, that we are inclined to think of them as innate. The mathematics behind the music seems to back this up. Consonant intervals, such as an octave, perfect fourth or perfect fifth, are integral ratios of harmonics — 2:1, 4:3 and 3:2, respectively. A reliably dissonant interval such as the augmented fourth, or tritone, has an irrational ratio of $\sqrt{2}$:1. Consonance and dissonance seem to be written into the fabric of the Universe. But the Tsimane' results show that these structures are a human interpretation, and one that seems to be learned by experience.

The tale of the Tsimane' should remind us that Western music was not always as richly polyphonic as it is now. In medieval times, music was as melodic as that of the Tsimane'. Chords were unknown, and so were modern musical scales. There were just eight notes, corresponding to the white notes on a keyboard. The earliest keyboard instruments had no black keys, and indeed no such thing as a musical key. Instead, there were 'modes', each determined by the unequal spacing of intervals, depending on which note you started from.

But then the Devil arrived, in jumps of three whole tones, in particular between F and B. This was the tritone, so obnoxious that ecclesiastical authorities described it as *diabolus in musica* ('the Devil in music') and banned it. Choristers presented with singing a tritone preferred to flatten the B, making a much more agreeable perfect fourth. Keyboard technology caught up by inserting the first black key, a B flat. The other black keys followed in time, and modal music evolved into the system of keys that we have today, followed rapidly by that most daring of innovations — polyphony.

"The Tsimane' of Bolivia know nothing of Bernstein, let alone Birtwistle."

It is fair to say that the entire edifice of Western music has been built on the tension between consonance and dissonance. The music of Beethoven and Queen's 'Bohemian Rhapsody' take the listener on journeys that make sense only within that framework. Composers Harrison Birtwistle and Pierre Boulez travel routes that redefine the meaning of dissonance and (it must be acknowledged) thrill smaller audiences. Most readers of *Nature*, we hope, can resonate with the heartache and absolution in the song 'Maria' from Leonard Bernstein's *West Side Story*, in which Tony sings the name of his inamorata — using a tritone that immediately resolves into a perfect fifth.

The Tsimane' of Bolivia know nothing of Bernstein, let alone Birtwistle. Even when their traditional tunes were recorded, shifted in pitch and harmonized to make polyphonic arrangements and create consonance and dissonance, the listeners could not tell the difference between the two. One hopes that their patience wasn't tried too sorely by outsiders playing fast and loose with their heritage (there are those of us who still bear the scars of hearing Bach murdered by The Beach Boys).

But the key finding, the resolution, the crescendo, the cadenza, the Tierce de Picardie — one is tempted to say — is that the Tsimane' do not find the tritone any more or less pleasant than any other interval. The Devil has not reached that part of Bolivia, it seems, and the tunes of the Tsimane' might be such as those played in Eden. ■

Fifty shades of pain

The push to find reliable ways to measure pain is proving harder than generating it.

Science has produced such a bewildering array of tools and techniques to cause gentle pain that to list them all can seem like describing a torture chamber in Toytown. To study the body's responses, people are prodded with fingers, pricked with needles and pressed with ice. Toes are squeezed and ear lobes pinched. Muscles can be poked with sticks and zapped with electricity. Mustard oil is spread on the skin and capsaicin injected beneath it. Laser pulses offer a double hit: an initial prick followed by a burning sensation.

When properly performed, these human experimental pain models help researchers to understand both the mechanisms of pain and the effectiveness of new compounds that could help to relieve it. The translational bridge from animal experiments to human trials is built on the backs of countless volunteers who sign up for a little lab-based agony. (Special thanks indeed must go to the anonymous 18 brave souls who had "two series of rectal balloon distensions performed on two separate days" to help to study "cortical processing of visceral sensations and pain" (D. Lelic *et al. Neurogastroenterol. Motil.* **27,** 832–840; 2015).)

Similar studies check on the pain caused by fully inflating a balloon inside other internal organs. Although, as a review of these pain models noted in 2012, it is (perhaps counter-intuitively) more difficult to find people who are willing to take such balloons through the mouth to stretch the oesophagus: "Difficulties in tolerating balloon distension commonly results in poor recruitment rates as well as the potential for esophageal perforation" (K. S. Reddy *et al. J. Res. Med. Sci.* **17,** 587–595; 2012).

When it comes to assessing, measuring and reducing pain, the science toolbox is less well stocked. We have thankfully moved on from the earnest 1950s debates about how the pain tolerance of patients was linked to eye colour — discussions that were themselves coloured by racism. But there is much about pain that we still do not realize, and important knowledge remains beyond the reach of even the best-placed balloon.

Some of what we do know is presented this week in an Outlook supplement (www.nature.com/pain). A series of articles describes the physical, neurological and psychological factors that seem to contribute, and offers a snapshot of current thinking on the best forms of relief.

Science and medicine no longer use a person's ethnicity and religion to mark how well they will tolerate the pain of a procedure, but equally, researchers have not yet found a reliable way to measure pain tolerance. The search for quantifiable ways to compare painful sensations, and to diagnose pain in those who are unable to communicate it, mirrors the effort in psychiatric research to find useful biomarkers for mental-health disorders.

For pain, expression of inflammatory mediators in the blood and the presence of metabolites in saliva could be biological guides to a person's distress. So, too, could brain scans that reveal the neural signature of chronic pain. However, as *Nature* pointed out last year (*Nature* **518,** 456; 2015), such techniques must be introduced with care, not least because they could be used by insurance companies and others to demand 'proof' of pain as a way to overrule reported personal experience.

Science has already developed some weird and wonderful ways to deliberately cause pain. It should be wary that it does not inadvertently create some more. ■