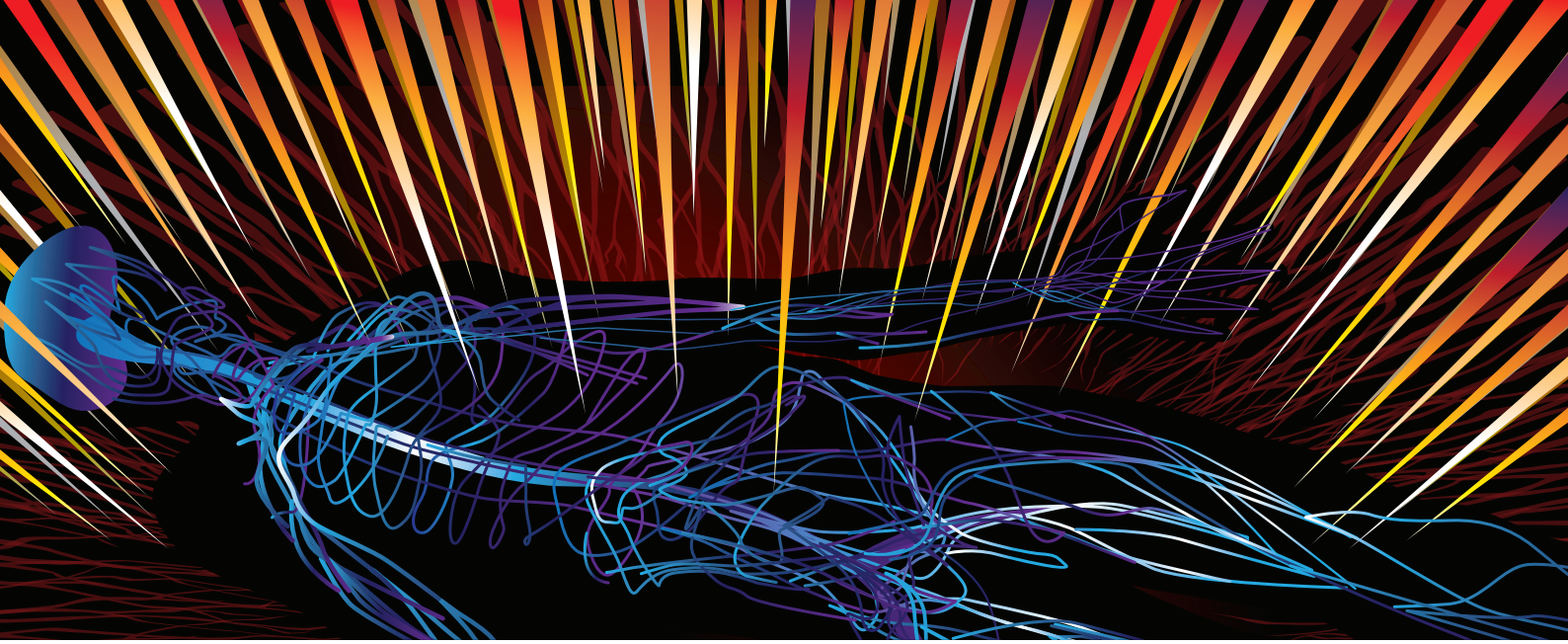

NEUROPATHY

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

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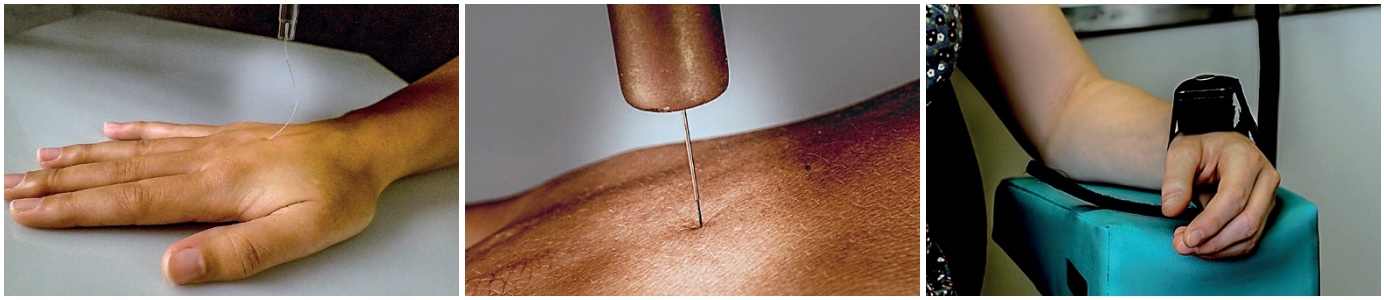

Left to right, a whisker-like fibre, pin prick and thermal stimulus are used to test pain sensitivity as part of the quantitative sensory testing protocol.

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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1. Demant, D. T. *et al. Pain* **155,** 2263–2273 (2014).
2. Attal, N. *et al. Lancet Neurol.* **15,** 555–565 (2016).
3. Freeman, R., Baron, R., Bouhassira, D., Cabrera, J. & Emir, B. *Pain* **155,** 367–376 (2014).