

Roberta Fulci, *Pain, Explained* (© 2023 Codice edizioni)

Chapter 2

You hurt here

For some time now I have often been reminded of a vignette that I no longer know where I have seen. The scene is one of those classic ones from “La Settimana Enigmistica”¹: doctor’s office, specialist standing with stethoscope, patient sitting on the couch. Top headline: *A neurologist consults the doctor*. Standing doctor turns to fellow neurologist: “Where is the pain?” he asks. “But in my head, of course,” he replies. A similar vignette in the past would have been different. If we go back far enough, the neurologist would have been rather a philosopher, and would have replied, “But in my heart, of course.” When I started wondering what pain is, the next question was just that: where is pain? If there is an on/off switch, one has to figure out where to look. When something hurts us, what is the center stage? Living in the 21st century, I do not have great suspicions about the heart, but the pool of suspects for me remains very large: will we have to look at the spot that hurts? The brain? What part of the brain? Or perhaps the whole nervous system? “The physiologist doesn’t care why you feel pain,” Gilberto Corbellini told me, “it matters to the geneticist.”

Living with Letizia

On a beautiful day in September 2021, Letizia Marsili, a 56 years old marine ecologist, is on a field trip to Castiglione della Pescaia. With her and her companion is another couple of friends walking a small dog. Suddenly, for no clear reason, the dog pounces on Letizia and imprints a deep bite on her leg. Her friends rush to her aid, while she dabs at the best of her ability the blood running down her shin. To the emergency room she won’t go: “It’s nothing, it’s nothing,” she repeats serenely a moment after being bitten. The next day, however, her leg is so swollen that Letizia cannot put on her shoe. In short order, it is clear that the wound has become infected and fourteen days of antibiotics are needed. At that point, does it hurt? “No, no, I don’t feel anything,” she assures. Friends and family are worried about the wound, but Letizia’s reaction does not surprise them all that much: they know she does not feel pain like others. Another Steven Pete? Not really.

Letizia knows pain, only that an injury such as a burn, a sprain, even a fracture, hurts her only the first few moments. A handful of seconds and then nothing more. Sometimes, as with the dog bite, the pain just isn’t there. Not all pain goes away immediately: she often suffers from back pain. “There are pains I feel, internal pains. For example, I suffer a lot from cystitis. Maybe I even feel it

¹ The most popular puzzles magazine in Italy [ed.]

more than other people because I'm not used to pain, so when I feel it it really sends me over the edge. Whereas in traumatic pain, like it can be a fall, a break, a sprain, there is the initial pain and then, I now know, I wait ten seconds and I don't feel anything. I used to think that was my character," she tells me smiling and expansive in her beautiful Tuscan accent.

"When I saw someone complaining about a pain, I always thought, 'What an exaggeration. What a stretch!'"

Things changed in 2000, when Letizia Marsili found herself collaborating on a project to monitor extractive platforms in the Val d'Agri, and thus meeting Anna Maria Aloisi. Now a full professor in physiology at the University of Siena, at that time Aloisi already had extensive experience in pain research. The first bell that alerted her to a possible peculiarity of her colleague, however, was not the pain: it was the clothes. I myself could verify that Letizia dresses unusually. The two of us met in December: "You have a sweater but I have a light, summer dress," she points out to me. "Anna Maria often saw me dressed like that in the middle of winter, and one day she asked me, 'But how do you do it? Are you not cold?'" Here, I have a thermoregulation problem. Like a snake," and burst out laughing, the big colorful earrings jingling. "I don't sweat: when we go walking, with my sister, after a whole day of walking our socks smell like soap! Since I don't sweat, if I stay in a room where there is a radiator on for a long time, I have to uncover myself; if I stay where it is cold, I have to cover myself. I hardly ever change clothes, I just increase or decrease the layers I put on."

Steven Pete doesn't sweat either. CIP (Congenital Insensitivity to Pain), often manifests as CIPA (Congenital Insensitivity to Pain with Anhidrosis), that is, with anhidrosis, the incapacity to sweat. Letizia Marsili is not completely insensitive to pain like Steven, but it is no accident that they share this characteristic. Anna Maria Aloisi knew well that pain tolerance and thermoregulation go hand in hand. On that day in 2000, she then asked her the question destined to make *Marsili syndrome* appear in the scientific literature, "And with pain, how do you cope?"

"Mah, I don't really feel the pain that much...."

Letizia Marsili is not the only one in her family who is so little exposed to pain. Her mother, her two sons, her sister, and her sister's daughter all share a curious resilience. The anecdotes are dozens: "My son Bernardo, he was a child... he fell off his bicycle in the brambles and continued pedaling for ten kilometers with a broken elbow. We didn't notice it until a month later, when his arm had calcified bent and he could no longer stretch it out. Luckily a very good doctor knew how to treat him!", "My son Ludovico plays soccer, I always follow him. As a child they called him Highlander! The other day he had hurt his hand, drove home, had dinner, slept, the next day he saw that his hand was swollen and, well, he had broken his scaphoid," "I must have been seven years old, I was climbing a pole, I was such a tomboy when I was a child... I got a rusty nail stuck in my

chest and I didn't tell anyone because I was afraid I'd get beaten up. My mom noticed days later, they had to give me an emergency tetanus shot.”, “My sister burns her whole mouth, she really peels, because she can't feel the heat of tea and soups, and her daughter burns her feet in the summer at the beach, because she doesn't notice that the sand is hot...”

In 2008, when it was now clear to Anna Maria Aloisi that Letizia and her blood relatives could be a remarkable case study, she discussed it with her colleague John Wood, a pain geneticist at University College London. An entire family to analyze? Wood was over the moon. He immediately asked for DNA samples from all six members of the Marsili clan and had them sent to London. Once he received that treasure, he placed it in the hands of his young collaborator, James Cox. To the expert eye of Anna Maria Aloisi we owe all the discoveries that followed.

Wood&Woods

Marsili syndrome is not the first form of pain resistance to be studied genetically. When “gene hunter” James Cox was tasked by his mentor John Wood with reviewing the genome of his entire family, a mutation associated with special pain resistance was already known. Cox and Wood themselves, in collaboration with their Cambridge University colleague Geoffrey Woods – the homonymy, or nearly so, does not help – had published in 2006 a finding that caused a huge stir: three Pakistani families with congenital analgesia had mutations in a gene called SCN9A². Steven Pete's condition is also due to a mutation of this type: when he was a child in the 1980s, there was no means to do genetic analysis, but in 2012 Geoffrey Woods was able to confirm his diagnosis with a simple blood draw.

The 2006 research won the pages of “Nature” and was destined to become the leader of a long series. In 2010, a group from the University of Florida published a new study³ showing how other mutations in the same gene could trigger similar effects. It was then the turn of a second gene, SCN11A, identified by German research in 2013⁴. Many more findings were added, and to date Geoffrey Woods and his colleagues have mapped the genomes of no fewer than eleven families (158 individuals), adding to the list of mutations of interest a dozen more abnormalities in a third gene, called PRDM12.

James Cox's investigation of the Marsili family's genetic material was a titanic undertaking and required ten years of

² James J. Cox *et al*, *An SCN9A Channelopathy Causes Congenital Inability to Experience Pain*, “Nature,” 444, December 2006, pp. 894-898.

³ Roland Staud *et al*, *Two Novel Mutations of SCN9A (Nav1.7) Are Associated with Partial Congenital Insensitivity to Pain*, “European Journal of Pain,” 15, 3, March 2011, pp. 223-230.

⁴ Enrico Leipold *et al*, *A De Novo Gain-of-Function Mutation in SCN11A Causes Loss of Pain Perception*, “Nature Genetics,” 45, September 2013, pp. 1399-1404.

work⁵. Letizia's blood relatives share several genetic mutations, and identifying those responsible for their unusual resistance to pain was the proverbial hunt for the needle in the haystack, punctuated by trial and error and failure. Finally, in 2018, after several experiments in vitro and in the animal model, the scientific truth emerged in the guise of a new mutated gene, ZFHX2⁶.

Letizia rarely feels pain, but when she does get hurt, she almost always has a few seconds' discomfort that warns her of danger.

Her childhood was very different from Steven's, and both she and her relatives lead normal lives: her family's case does not collide with cases of total congenital analgesia and genetics confirms this. As is clear from Steven's words, knowing pain makes all the difference in the world. That little bit of discomfort that the Marsili family has access to has allowed them all to receive a negative stimulus in the face of danger and develop a fear, albeit limited, of getting hurt. Cystitis and back pain are not the only pains Letizia really fears. She remembers another one very well, which lasted only a minute but was well etched in her memory. From 2000 onward, before even being genetically analyzed, she and her family underwent a huge number of tests: MRIs, blood tests, concentration tests, and, of course, pain threshold experiments. Letizia lent herself more than any other family member, and at times these were invasive tests. Certain experiments, conducted early in the course, left her with some scars: "I had to say when I felt burning. Since this burning I never felt, they burned me." In one particular case she was left with the fear of pain, real fear. It happened with an injection of capsaicin, the substance that makes chili peppers spicy: normally, she explains to me, such an injection triggers pain after a few minutes. For her, however, the pain was immediate and very strong, although as always it lasted only a few moments. "There I felt the most intense pain of my life. I tell you the truth: I would not do that test again. And after they did it to me, I prevented them from doing it to any other person in the family. It is not right to try a feeling like this just to be studied."

Not all genetic mutations found so far that prove insensitivity to pain, partial or total, act in the same way: from the specificity theory, in vogue in the 19th century, to the present day, a much more complex chain has emerged. To tamper with it may be sufficient to boycott one of its many steps.³

Do not open that gate

In January 1944, Allied troops landed at Anzio with the aim of weakening the German presence in Italy. The Germans

⁵ Matthew Shaer, *The Family That Feels Almost No Pain*, "Smithsonian Magazine," May 2019.

⁶ Abdella M. Habib *et al*, *A Novel Human Pain Insensitivity Disorder Caused by a Point Mutation in ZFHX2*, "Brain," 141, 2, February 2018, pp. 365-376.

reacted more effectively than expected and, until May, the Anglo-Americans had to withstand a series of attacks that cost them many casualties and a number of wounded soldiers. On duty at the military hospital on the beach was an American anesthesiologist named Harry K. Beecher, who during his stay in Anzio as a medical officer found himself treating dozens of soldiers. When asked, “Do you feel pain? Do you want something to ease the pain?” 70 percent of the wounded answered no. We are talking about very serious injuries: gunshot wounds and amputations. Conversely, in peacetime, when he asked the same questions of a sample of civilians freshly operated at Massachusetts General Hospital in Boston – men of comparable age to the soldiers at Anzio – the proportion reversed: 70 percent answered yes.

The specificity theory had trumped the intensity theory, but it did not quite explain everything. It postulated that the intensity of pain was proportional to the stimulus: if the same stimulus corresponds to the same pain, Beecher thought, how come comparable wounds result in such different reactions? His experience and observations are so crucial that they practically constitute the incipit of *Pain. The Science of Suffering*⁷. This book – a great classic of contemporary pain literature – is intended for the general public and constitutes a kind of testament of one of the most influential pain scholars of the last century: the British neuroscientist Patrick David Wall. He wrote it in 1999, already ill with the cancer that within two years would kill him. When I started reading it my enthusiasm grew from page to page. Here, I thought, it touches on the very questions that trouble me! It answers so many doubts! It clarifies a lot of gray areas! I have now read *Pain* two and a half times and I think I will need another dozen to really assimilate its content. What matters is that Beecher raised a fundamental objection to the specificity theory, and it was Patrick Wall, together with Canadian psychologist Ronald Melzack, who proposed an alternative hypothesis in 1962: the gate control theory, or gate theory. Wall and Melzack started from a fundamental problem, namely, that no existing theory of pain could explain Beecher’s observations.

According to Hippocrates, pain was due to the excess or deficiency of one of the humors of the body (blood, phlegm, yellow bile and black bile). This idea of imbalance, of alteration of a status quo, recurs in so many conceptions of pain: for example, in ancient Chinese medicine, in which pain is caused by the prevalence of yin over yang or vice versa. The Muslim tradition, with Avicenna, refers to a more materialistic change in the physical state of the body. Does your arm hurt? Compared to before, something in your arm has changed. Well, exemplary. But the most iconic image of all on the science of pain is made by Louis De Forge and illustrates the mechanism of pain as Descartes

⁷Published in Italian as: Patrick Wall, *Perché proviamo dolore*, Einaudi, Turin 1999. Unfortunately, it is out of print.

describes it in his *L'homme*: we are in the 1730s. It shows a boy bringing his foot close to a flame; from the foot starts a kind of cord that goes up the leg and along the spine, until it reaches the brain. Descartes imagined the nerves as if they were the strings of a bell tower: if you pull, the bell rings. If you bring a foot close to the fire, like the unfortunate little boy in De Forge's illustration, the "heat particles" that come in contact with the nerve endings of the foot stimulate the nerve and the brain realizes that someone is pulling on the other end of the cord.

In short, there is an ascending phase of the pain mechanism that, although not in detail, has been clear for centuries: the stimulus awakens a receptor that sends the signal to a relay of neurons up to the brain. Today we know that, when faced with a painful stimulus, peripheral neurons send an electrical signal to those in the spinal cord, which in turn communicate with the brain. This relay acts even in the case of grazed damage: the pain we feel by bringing a finger close to the flame, if we move in time, can end before even one cell has been damaged. That is why the pain is compatible with tissue damage even if only "potential," as the IASP definition reads. What Wall and Melzack hypothesized is a control mechanism at the synapse that connects the peripheral neuron to the spinal cord neuron. This mechanism allows pain to be modulated by a number of other parameters – mood, circumstances, temperature, attention, and so on. That is why the wounded soldier feels nothing until he is out of danger: a more urgent need keeps closed a "gate" that, if opened, would give a green light to the sensation of pain. If the soldiers entrusted to Beecher's care did not even suffer once they were rescued, the explanation might lie in the significance of the wounded condition: it was a free pass to go home, perhaps battered, but alive. There are many factors that can inhibit pain by preventing the gate from opening: first of all, tactile sensations such as heat, cold, or a simple massage. This is precisely the reason why when a body part hurts, we have the instinct to rub it. And then there are the signals that come from the brain in a descending phase: for example, if we are laughing the brain releases endorphins that will help close the gate. When Melzack and Wall published their idea, illustrating the gate theory with a diagram reproducing the journey of the electrical signal with all its joints and gates, there were no diagnostic tools that could prove or disprove the theory. Is it still valid today? I have asked this question to many of my interlocutors – physicians, historians, neuroscientists. They are unanimous in considering it a milestone of the history of pain science, but there are some buts.

"It is a splendid theory but it has never been fully demonstrated," someone replied to me, or even, "It has been discredited in so many details." What is certain is that it was a Copernican revolution in the field of pain study. Wall and Melzack also retired the idea that a "pain center" exists in the brain, which annoys me in no small part because I was looking for just that. "Such an idea is pure fantasy unless one considers virtually the entire brain as the

pain center, because the thalamus, the hypothalamus, the reticular formation of the medulla oblongata, the limbic system, the parietal cortex, and the frontal cortex are all implicated in pain perception⁸.” Starting from this consideration Wall and Melzack began to speak of the “neuromatrix” to designate the entire branching system co-involved in the phenomenon.

A full 20 years after the first publication of the gate theory, the two, referring to the specificity theory, complained a great deal about one fact: the scientific community continued to confuse *physiological specialization*, that is, that there could be fibers specialized in conveying pain, and *psychological specificity*, that is, that stimulating those fibers implied the experience of pain. The first had already been demonstrated. The second had not, and the fact that pain was not an automatic consequence of certain stimuli is at the heart of their work. “If we get clarity on this,” they write, “we will have eliminated a major source of unnecessary discussion.”⁹ “What about phantom limb syndrome? How do we explain, today, the fact that I can feel pain in a body part that isn’t there? Fabrizio Benedetti writes:

Modern bioimaging techniques now allow us to understand that phantom limb sensation occurs entirely in the brain, which reorganizes itself after amputation giving rise to abnormal perceptions. For example, it may happen that the part of the brain where information from the face arrives invades the part of the brain that previously received information from the amputated limb. And so it happens that touching a lip generates a tactile sensation on a finger, and flicking the nose gives rise to a sensation on the palm of the hand.¹⁰

That is why the poor patients of the past who went to the doctor for phantom limb pain and went home with the anesthetized stump were disappointed: that was not where the signal came from. The syndrome is tangible evidence of a non-obvious circumstance, namely that pain can exist without there being any nociceptive stimulus (the reverse is also true, but this is easier: any anesthesia proves it). At one time pain without a manifest cause was dismissed as imaginary, but today that pain exists without nociception is evident in many cases of chronic pain.

While most laymen ascribe to the expression *acute* pain the meaning of “intense pain,” for the medical profession it is more a matter of timing. Acute pain lasts for hours, days, or weeks, while chronic pain can be a matter of months or even years. In the case of trauma, for example, the initial tissue damage may heal, but the triggered pain may remain, perhaps in a different form. In recent decades there is a lot of research on what distinguishes the two forms of pain. We are witnessing a paradigm shift: “To say that chronic

⁸ Ronald Melzack, *The Puzzle of Pain*, Penguin Books, Londra 1973, p. 93.

⁹ Ronald Melzack and Patrick Wall, *The Challenge of Pain*, Penguin Books, London 1982, p. 164.

¹⁰ Benedetti, *Il dolore. Dieci punti chiave*, cit., p. 28.

pain is the extended version of acute pain is like saying that an elephant is an unusually long-lived dog that does not eat meat,¹¹” writes medical ethicist Laura Kolbe.

48Chapter 2

The signature of pain

It was Valentine’s Day 1994. Myles Allen, a future star climatologist at Oxford University, was on his way to Boston to visit his girlfriend Irene Tracey, a neuroscientist. He smiled. The two were planning a trip to New York City: there, he would propose to her.

At least, that was the plan. On that very day in Boston, the reservation for using one of the first MRI machines, a sophisticated technique for the time, was unexpectedly canceled by the research group that made the request. Usually, a long waiting list was required to access the machine, but providently, that evening, it would be free for a few hours. Irene was not the type to pass up the opportunity: instead of the romantic night in New York, Myles Allen found himself spending hours in a frigid hospital, lying in the machine tube, shivering with cold, while his fiancée watched rapturously in the monitor dozens of shots of his sliced-up brain. For that time there, no marriage proposal.

In partial consolation to Allen, the evening marked the beginning of a formidable career for his future wife that earned her the nickname Queen of Pain. Her Majesty now works at Oxford University, where she has at her disposal a small room she laughingly calls “my torture room.” It is there that Irene Tracey carries out her experiments on the brain related of pain: she searches for the signature that pain leaves in the encephalon, assuming there is one. Participating in her studies usually means experiencing the effects of the same capsaicin that Letizia Marsili will never again be able to forget. Never underestimate capsaicin: it can cause pain equivalent to that of a second-degree burn. For as long as MRI has existed, attempts to trace pain through blood flow in the brain have been numerous, but the most optimistic neuroscientists have been disappointed: there is no brain area that can be associated with pain the way the visual cortex can be associated with vision or Broca’s area to language. A lot of things happen in the brain of a person undergoing pain, different and distant areas are activated, but none of them are the exclusive preserve of pain. Tracey argues that we have very little knowledge of the biology of pain¹², and she is working precisely in this direction. The beginning of the breakthrough for her research came in 1998, when a well-conceived experiment on a group of college students (field hockey players most boastful about how much pain they would be able to

¹¹ Laura Kolbe, *Where Does It Hurt? Three New Books Attempt to Locate the Origin of Pain and Its Vocabulary*, “The New York Review of Books”, June 23, 2022.

¹² Nicola Twilley, *The Neuroscience of Pain*, “The New Yorker”, June 25, 2018.

endure) allowed Tracey and her doctoral student Alexander Ploghaus to observe something interesting¹³.

The study participants were subjected to pleasant and painful stimuli that alternated in a seemingly random manner, accompanied by light signals of different colors. Within minutes, the volunteers became aware of a well-defined pattern: the green light always preceded a pleasant warmth, the red light, on the other hand, presaged a prickly pain arriving. Well, the moment the students grasped that correlation, their brain response changed. Tracey and Ploghaus were able to map an activation that manifested at the sight of the red light, before the pain began: it was thus related not to pain, but to the expectation of pain. Studies like this show how complicated it is to assign meaning to an experiment, no matter how controlled, about what is happening in our brains: the colorful images on MRIs are the result of a multitude of stimuli that are difficult to unravel. In the case of pain, experiments of this kind are still charting the path to better understand whether and how the experience of pain is mapped in the encephalon in a way that is intelligible to us.

The new Ice Bucket Challenge

Apart from making them the object of study and teaching them to be much more careful about various accidents and their own health conditions, the outcome of the research involving Letizia Marsili and her blood relatives has not changed their lives much. The most glaring consequence was being overwhelmed by global media attention.

Letizia had already appeared on TV or gave interviews in her role as a researcher, but for the rest of her family it was all new: “For my mom to be interviewed by Japanese television, or English television, or Austrian television, or to go on *La vita in diretta*¹⁴, were all situations that were a little out of the norm. Sometimes people would look at us and recognize us,” she tells me. There was even a script broadcast in Japan with actors playing the various members of the family, not to mention when a camera crew arrived at Letizia’s house to film her holding a hand dipped in a bucket full of ice. By her side the journalist was doing the same, surrendering well beforehand. “Then she may be exhausted, screaming, a crazy thing. I, on the other hand, with my hand in the ice was there more than three minutes.” Three minutes with one hand dipped in ice is a lot?

How long would I last?

If nothing else, I finally found the motivation to defrost the freezer. One evening in February, together with six very generous friends who in return settled for nothing more than a pumpkin and mushroom *risotto*, we did the test: standing with one hand submerged in a container full of crushed ice does indeed hurt. We lasted between 27 seconds

¹³ Alexander Ploghaus *et al*, *Dissociating Pain from Its Anticipation in the Human Brain*, “Science,” 284, 5422, June 1999, pp. 1979-1981; doi: 10.1126/science.284.5422.1979.

¹⁴ One of the most popular daytime TV shows in Italy [ed.].

and 3:42 minutes. All seven of us felt pain, sharp, starting on average about twenty seconds from the beginning. Pins on the fingertips, numb or numb hands, pain going up the arm, fingers that felt like they were burning; everyone responded in their own way. That Letizia stayed three minutes, therefore, is not strange; that she felt nothing is. I think everyone of us could have lasted longer if there had been a good reason to do so. I gave up at 2:30 minutes, more out of fear of freezing my fingers than the pain itself. But is a pain over which you have full control, which you know you can stop at any time, then real pain? For those who design experiments this is quite a problem, I will find out later.

From one extreme to the other

Letizia Marsili is more than happy to be able to offer research insights that one day, who knows, might prove useful in pain therapy. She is also very aware of the uniqueness of her family's situation, and considers being the object of study a potentially useful resource for all her loved ones. Chatting with her, however, she also seems to glimpse a hint of disappointment: "It turns out it's related to our genes... but I used to think I was almost a superwoman. I thought the point was that I didn't feel the pain because I didn't want to feel it."

Here, now I am ready to *ask the question*, "What is, for you, pain?"

"Pain for me is something you can live with well. It's not scary, because when one feels it the way we feel it, even going to the dentist is not that traumatic... I very often don't get anesthesia, because I know I can go up to a certain point of tolerance. But the pain is a thing that is important to feel, because it makes you realize the severity of what you have. At first it makes you cry, grit your eyes and grit your teeth, but then it passes. It's hard for me to tell you in a different way, because if I burn myself, that is, I take a pan from the oven because I forget, I feel the pain but then I wait a moment and I don't feel anything anymore."

Letizia Marsili, however, is clearly thinking about the pain she experiences for a few moments when she gets burned or hurt. But there are cases when she also feels pain for a long time.

How do you describe that kind of pain? That of back pain or cystitis? The answer surprises me not a little.

"It's something that... it's a good thing I live on the ground floor because I would jump out the window!" he exclaims. He is laughing; it is clear that in the overall balance of his life, pain is not a concern. She uses challenging words to describe it, though: "It is an unbearable feeling. If it lasts long it could lead to unconscionable acts." Impossible not to wonder if such a strong position might depend on her not being used to experience pain. Do those who suffer rarely, when they suffer, suffer more? Does one "get used" to pain? Is there a kind of habituation? Letizia does not

know, and in fact when she talks about pain she says: “What
I call pain.”
But how do you measure pain?