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TEXTBOOK OF PAIN

FOURTH EDITION

疼痛学

（第4版）

Patrick D. Wall
Ronald Melzack

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第 4 版 ● Fourth Edition

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Ronald Melzack OC FRSC PhD

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Textbook of Pain

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Introduction to the fourth edition

PATRICK D. WALL

The chapters in this book express the independent views of the selected authors. Everyone writing on pain has in mind a plan of how pain mechanisms operate. There are many different plans and some are complementary rather than contradictory. The editors have made no attempt to unify these concepts because we would rather leave the reader with the opportunity to select between the various widely held views. There are those who still believe pain can be adequately described as the result of activity in a dedicated pathway originating in peripheral nociceptors. Others propose a more complex approach which takes into account the plasticity of all the conduction pathways and the nature of pattern detection by parallel processing and the active participation of the brain in perception. The traditional scheme starts with a stimulus and follows the consequences through to a sensory-emotional response. In this introduction, I propose a way to bring all the chapters together by a search beginning with the perception of pain.

ATTENTION

No conscious awareness of anything is possible until it has captured our attention. Our sense organs in the eyes, ears, nose and body are in continuous action, day and night, awake or asleep. The central nervous system is receiving steady reports of all the events these sense organs are capable of detecting. Obviously, it would be a disaster of excess if we were continuously aware of the entire mass of arriving information. We completely ignore most of the information most of the time. And yet any fraction of this inflow is capable of rivetting attention. For this to happen, there has to be a selective attention mechanism which must have a set of rules. Those rules are not arbitrary. Every species displays their rules which incorporate a selection of those events that are important to survival and well-being. Some rules seem to be built in. Large, sudden novel events have precedence in their attention-grabbing ability. And, I would propose, that the arrival in the nervous system of messages signalling tissue damage is another of these built-in high-priority events.

There is a learned component of our selective attention mechanism. The bored radar operator sits staring at the screen which is a snow storm of random blinking dots. Let one of these dots begin to move in a consistent line and attention locks onto that dot to the exclusion of all the others. Let the classical migraine sufferer detect a small twinkling area in the visual field and his attention is rivetted on this trivial event because he has learned that the aura on his oncoming migraine attack begins with just such a scintillating area.

In social animals, subtle triggers of attention can be shared. In West Africa, two species of monkeys feed together in flocks but eat different fruits. Their main enemy is the monkey eagle and one species is quicker to spot arriving eagles so that both species benefit from the alarm of one. In Australia, a grouse selects her ground nest close to a tree containing a hawk nest, because the hawk's superior height and eyesight detects distant predators long before the earth-bound grouse. And so it is with humans, where attention is infectious.

The attention mechanism must be continuously scanning the available information in the incoming messages and assigning a priority to the biological importance of the message. There are examples of 'thoughtless' decision, as in the switch of attention in the car driver in conversation with a passenger while engaged in 'unconscious' skilled driving

until some fool cuts in front of her, whereupon attention promptly switches from conversation to avoidance. This brings out the second rule of selective attention, which is that only one target at a time is permitted. Obviously it is possible to switch attention back and forth quite rapidly. However, at any one instant, only one collection of information is available for conscious sensory analysis. This one object can itself be preset. An example is the detection of the mention of your name in the random buzz of cocktail party conversation. It is possible to scan a long list of names and detect the one you seek with no recall of any of the other names.

It is not intuitively obvious that attention can only be directed to one subject at any one time. It would seem a rather ridiculous limitation in a mental process which clearly has freedom to rove over vast areas; 'shoes and ships and sealing-wax, cabbages and kings'. An explanation for this strict limit on attention could be that sensory events are analysed in terms of the action which might be appropriate to the event. If the aim of attention relates to appropriate action, then it follows that a fundamental requirement of nature is that only one action at a time is permitted. It is not possible to move forwards and backwards simultaneously. You must 'make up your mind'. The explanation for the singleness of momentary attention would then derive from the purpose of attention, which is to assemble and highlight those aspects of the sensory input that would be relevant to carrying out one act.

Of course, rival sensory events may compete for attention. The myth of the ass who starves to death when placed equidistant between two bales of hay is indeed a myth which would never happen. There may be many events occurring simultaneously each demanding attention. They are rank ordered into a hierarchy in terms of biological importance. The practical consequence of this ordering is the apparent paradox of the painless injury. Each of these victims was involved in a situation where some action, other than attending to their wound, had top priority. Getting out of a burning aircraft is more urgent than attending to a broken leg. The attention does not oscillate between the two demands. One is assigned complete domination until safety is achieved. Only then is the alternate assigned the top position, attention shifts and pain occurs. The workman in the course of a skilled task and the tackled footballer about to score a goal carry on to complete the task with engrossed attention in spite of the conflicting demands of their coincidental injury. Only when the conditions of the top priority fade, there is a reassessment of the next most urgent priority. In conditions of complete 'emergency analgesia', pain emerges as the dominant fact when the emergency is over. The priority ranking of importance of what deserves attention is partly built in and partly learned from personal experience and partly a component of culture.

From the first positron emission tomographic (PET) images of people in pain, intense activity was detected in the anterior cingulate. It is even apparent in patients with very chronic pain associated with a single nerve neuropathy and, even more surprising, it is only present on the right side irrespective of which side the pain is on. However, this general area is also active in many other situations, including directed visual or auditory attention, precise eye and hand movements, and even during complex speech. The suggestion that this zone is involved in attention mechanisms fits with the results of surgical destruction of the area as a treatment of obsessional melancholic depression which I take to be a disorder of attention.

Therapy based on a moulding of attention is effective. It is called distraction. When a toddler trips, smacks into the pavement and howls, what does a parent do? Pick it up, dance about, coo, oo and ah, kiss it better. These are distractions. Because you can only attend to one thing at a time, it follows that you can only have one pain at a time. This fact led to many excellent folk remedies; hot poultices, horse linaments and mustard plasters. They are called counterstimulants. When pain really sets in, attention is utterly monopolized and nothing else exists in the world but the pain. Many therapies attempt to intrude on this fixation. The distraction that is effective may be simple but it will depend on established priorities. A game of cards, letting the cat out or the sight of a hated neighbour can provide a brief interlude in pain. Some victims discover this for themselves and prolong their brief holidays from pain by inventing distractions, while others get professional help in occupational therapy. In another distraction therapy given the pretentious title of cognitive therapy, the victim learns to day dream where they play out an internal fantasy. It may be that they are on a warm sunny beach or at a football match or in their favourite bar. Some people can become very skilled at these distractions and give themselves longer and longer respites from their miserable pain.

ALERTING, ORIENTATION AND EXPLORATION

As attention shifts to pain, alertness appears. There is something wrong. Alarm bells. Action stations. Muscles tense and the body stiffens to a ramrod. Unknown to the victim, these overt changes are part of a massive reorganization of many parts of the body. The heart and vascular system get ready for action. The hormone system mobilizes sugar and

alerts the immune system. The gut becomes stationary. Sleep as an option is cancelled.

The eyes, head and neck turn to inspect where the pain seems located. The hands explore the area. Muscles are contracted to learn what makes the pain worse and what eases it and to seek a comfortable position and then hold it. The end result is a body fixed in an overall pain posture. Muscles are in steady contraction and, as time goes by, some muscles grow while joints and tendons deteriorate because this frozen posture itself sets off local changes. The vascular and endocrine systems hold their emergency state if pain is prolonged and these systems are not evolved to cope with this prolonged stress state. The quiet gut demonstrates its inactivity as constipation. Perhaps worst of all, sleep is impossible and chronic pain patients become completely exhausted. Even intermittent sleep deprivation drives the strongest of us into pretty peculiar ways of thinking, as any doctor on night duty knows and as any parent with a new baby knows. Chronic pain patients get to their wits end as their grim experience is prolonged.

Clearly this state of affairs needs therapeutic attack. The key word is relaxation and much ingenuity has been used. The problem is to override a natural defense mechanism which has a protective role in brief emergencies but which becomes maladaptive when prolonged. Drugs to inhibit the overactive muscle are commonly prescribed but they are sedative and intellectually flattening. After a while, patients refuse them or become zombies. Physiotherapists have many ways of relaxing muscles and of re-establishing movement in frozen zones. First they have to overcome the patient's natural fear that movement which produces pain does not necessarily increase the injury and that lack of movement which seemed at first to prevent pain eventually plays a role in prolonging the pain. Yoga and the Alexander technique are examples of posture training. Relaxation is not easy and training methods are needed. One successful version, 'bio-feedback' training, provides the patient with an electronic indicator of the amount of contraction in a muscle and allows the patient to judge second by second his success in relaxation. The patient has to learn how to relax and how to prolong the effect into real life outside the training sessions. Sleep follows relaxation but it may need additional help until the patient can sleep on his own.

THE SENSATION OF PAIN ITSELF

We are used to discussing sensation as the consequence of stimulation in a series of boxes: firstly injury generates an announcement of its presence in sensory nerves; secondly the attention mechanism selects the incoming message as worthy of entry; thirdly the brain generates the sensation of pain. Now the question is 'how does the brain interpret the input?' The classical theory is that the brain analyses the sensory input to determine what has happened and presents the answer as a pure sensation. I propose an alternate theory that the brain analyses the input in terms of what action would be appropriate.

Let us explore the alternate theory as it has practical consequences for pain. If the classical theory were true, the first action of the brain is to identify the nature of the events which generated the sensory input. This should produce the first sensation of injury as pure pain. The next stage of the classical theory is that different parts of the brain perceive the pure sensation and generate an assessment of affect, that is to say 'is the pure pain miserable, dangerous, frightening and so on?' My first reaction, on introspection, is that I have never felt a pure pain. Pain for me arrives as a complete package. A particular pain is at the same time painful and miserable and disturbing and so on. I have never heard a patient speak of pain isolated from its companion affect. Because classical theory assigns different parts of the brain to the task of the primary sensory analysis and others for the task of adding affect, one would expect some disease to separate pain from misery. No such disease is known. During neurosurgical operations, very small areas of brain can be stimulated and some cause pain. There has never been a report of pain evoked which was not accompanied by fear or misery or other strong affects. Finally there are parts of brain, the primary sensory cortex, which have been classically assigned the role of primary sensory analysis and yet, in the imaging studies, these areas are often reported as silent while the subject reports pain. Even for the sympathetic pain on hearing of the death of a friend, the sensation is inseparable from the sadness and loneliness.

Therefore let us explore the alternative, which is that the brain analyses its sensory input in terms of the possible action which would be appropriate to the event which triggered the whole process. There is in this absolutely no suggestion that any action need actually take place. Trained subjects and stoics may receive a clearly painful stimulus with no overt movement even though they can later report the nature of the pain they felt. There are elaborate and extensive areas of our brain concerned with motor planning as distinct from motor movement itself. It is precisely these areas that are most obviously active when the brain is imaged in subjects who are in pain but who are quite stationary with no movement. Chapter 8 by Ingvar describes the areas found to be active while the subjects feel

pain. The first area of surprise to be reported was the anterior cingulate which becomes active in any act of attention and this is exactly what is expected given the evidence that attention is a prerequisite of pain. The other areas consistently reported as active by many investigators are the premotor cortex, the frontal lobes, basal ganglia and cerebellum. All of the last hundred years of neurology have assigned these areas a role in the preparation for skilled planned movement.

Because I am proposing a quite new hypothesis here, one should explore widely to see if there are facts which support the possibility that sensory analysis is carried on in terms of motor action which would be appropriate to the input. Of the many imaging studies carried out on normal subjects or on patients in pain, some have shown no activation of the primary sensory cortex and even in those showing such activation, the area extends rostrally into the motor area in spite of the fact that no overt motor movement is detected. The marked activation of the cerebellum is a great surprise because classical opinion assigned no sensory role to the cerebellum. However, more recent work has clearly shown that the cerebellum plays a role in the analysis of sensory input in the course of establishing conditioned responses. Similarly the basal ganglia, putamen and globus pallidus were classically only given a function in overt movement and yet show marked activation in subjects in pain who show no signs of movement. However, muscle ache is a common prodromal sign of parkinsonism and responds to L-DOPA, which is reported to reduce neuropathic pain.

Sometimes the detection of a sensory input is demonstrated by motor movement. Mimicry is an example. The earliest sign that a baby is detecting complex visual stimuli is its mimicry of facial expression; opening the mouth, smiling, etc. Cells in monkey cortex in the inferior precental area have been detected which respond when the animal carries out a complex hand movement such as grasping but astonishingly these same cells also become active when the animal observes someone else making the same movement even though the animal makes no such movement. The acquisition of bird song has been studied in great detail in the zebra finch and necessarily involves the motor system during the learning phase. Even in human speech, Chomsky and Halle described a form of recognition which they termed analysis by synthesis. Here the correct detection of a sound pattern is confirmed by imitation. In these examples, the brain is showing and proving that it has detected a sensory input and checks the correctness of its analysis by producing an imitative movement. Now we ask if the movement is necessary. The nature of the stimulus must also be represented in the premotor system which preceded the movement of mimicry.

Evidence for this is seen in the firing of single cells in the posterior parietal areas when the animal is presented with visual targets on which it will fixate. In a classical sensory system, the target would first be located in a visual space after which the motor system would decide what would be the appropriate movement. What is found in fact is that the cells respond from the beginning in terms of the appropriate movement. Another example is observed in the best studied auditory cortex which is that of bats. The animal locates its prey by analysing return echoes. If this was a classical sensory system, the brain would analyse the echoes in order to locate the target's position when the sound bounced off the target. In fact the cortex also analyses the speed and vectors of target and the outcome is the collision course on where the target will be when the bat gets there. This is analogous to the display in modern aeroplanes on auto-pilot which show not primarily the position of the plane but the course to the chosen destination and at the same time the courses to all the alternate airports in range. The sensory information from the inertial navigation equipment is displayed in terms of appropriate action.

The most dramatic example in man is the unilateral neglect syndrome seen in patients with inferior parietal lobe destruction. If the lesion is on the right side, no visual or auditory or somatic stimuli on the left side are detected or identified. If such patients are asked to draw a clock face, they number correctly the hours 12–6 but fail completely on the left side. On classical theory, these patients have a hole smashed in their sensory map. Recently a new dimension of this large sensory deficit has been observed by a number of groups and has been imaged by PET scanning. If the vestibular system is stimulated by cooling one external ear canal, the patient has a nystagmus and experiences spinning in one direction. While this is going on, the neglect of the left sensory input disappears completely. There are three conclusions: (1) the sensory analysis mechanism had not been destroyed by the lesion; (2) sensory analysis is only possible in a predetermined frame of motor response; and (3) one of the factors determining the location of that sensory frame is the vestibular system. The vestibular system determines the posture of appropriate motor action and evidently of sensory analysis. I propose that these are one and the same mechanism.

What would be the consequences of following the hypothesis that sensory events are analysed in terms of the appropriate potential motor responses? It would provide a more satisfactory explanation of the paradoxes produced by the classical hypothesis and the beginning of understanding

of the facts just described. What are the appropriate motor responses to the arrival of injury signals? They attempt to: (1) remove the stimulus; (2) adopt a posture to limit further injury and optimize recovery; and (3) seek safety and relief and cure. The youngest most inexperienced animal may attempt a series of these responses triggered by built-in mechanisms. As the animal grows in experience, the reactions will become more subtle, elaborate and sophisticated. If the sequence is frustrated at any stage, the sensation-posture remain fixed.

Humans develop and elaborate the three-stage response from the moment of birth. Until about 10 years ago, pain in the newborn was neglected and even denied by professionals for two reasons. The first was that the human brain was seen as a hierarchy of levels – the spinal cord, the brainstem and the cortex. This view had been introduced by Hughlings Jackson in the nineteenth century. Each level was believed to dominate and control the level below. The hierarchy of levels was believed to be an evolutionary development and to be repeated in the development of each individual. The ability to feel pain, misery and suffering was assigned as a property unique to the cortex. All reactions to injury in the absence of cortex were called simple reflexes and thought to be mechanical and free of sensation or emotion. This view led Descartes to deny mind to lower creatures and was perpetuated in post-Darwinian neurology which assigned sensation and emotion to recently evolved structures such as the forebrain and cortex. It is true that we have a poorly developed cortex at birth. It takes 2 years for the major motor outflow from the cortex to establish control over the spinal cord. The second line of reasoning by professionals was that because babies could not feel pain, there was no point in giving them potentially dangerous analgesic drugs.

Fortunately, thinking has changed and pain in babies and children has become a major focus of attention. The chapters in this book by Fitzgerald and by Berde demonstrate the progress (see Chs 9 and 42). Turning away from endless inconsequential philosophy on whether a baby feels pain, they and others turned to practical objective measures. The first question was whether a baby who must be operated on soon after birth prospers better if treated with the full battery of analgesics which would be given an adult. The answer was a powerful yes and the result has been a marked change in neonatal anaesthesia and in survival. The second question was to ask if the injuries commonly suffered by babies, especially premature ones, produce a long-term shift of behaviour. Again the answer is yes. Fitzgerald showed that even the act of taking a blood sample without anaesthesia changed the motor behaviour of premature babies. This has focused new studies on long-term effects. Most surprising is a Swedish study confirmed in Canada where a large group of boys who had been circumcised soon after birth were compared with similar boys who were not circumcised. These children were observed 6 months later when they received their standard immunization injections. The circumcised boys struggled, shouted and cried far more than the others. Subtle controls showed that it was indeed the circumcision which had engendered the abnormal reaction to subsequent minor injury. In the child and the adult, there is a continuous development of the way in which the victim moves through the three stages of reaction. Experience teaches skills. Society adds its methods of help and its prohibitions. Expectation becomes tuned.

Finally, we need to re-examine the alternative either that pain signals the presence of a stimulus or that it signals the stage reached in a sequence of possible actions. Obviously the placebo phenomenon represents a profound challenge to these alternatives. The placebo by definition is not active and therefore cannot change the signal produced by the stimulus. It can hardly be categorized as a distraction of attention. Someone who has received placebo treatment for pain does not actively switch attention to some alternate target. On the contrary, they await passively the onset of the beneficial effect of the placebo while continuing the active monitoring of the level of pain. If, however, the sensation of pain is associated with a series of potential actions – remove the stimulus, change posture, seek safety and relief – eventually the appropriate action is to apply therapy. If the person's experience has taught them that a particular action is followed by relief, then they respond if they believe the action has occurred. In this scheme of thinking, the placebo is not a stimulus but an appropriate action. As such the placebo terminates and cancels the sense of pain by fulfilling the expectation that appropriate action has been taken.

WHEN PAIN PERSISTS

THE DISEASE DEVELOPS

In chapters in this book, repeated examples are given where damage to tissue is followed by inflammation. The quality of the pain and what to do about it changes. In postoperative pain, the initial acts of tissue damage were carried out under anaesthesia and the patient wakes up to sense only the later stages where the body attempts repair. In slow-onset diseases such as arthritis, pain escalates as the disease process extends. Pain may grow in sudden jumps as in some cancer pains where the tumour has expanded into new