The Treatment of

Chronic Pain

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MTP
Medical and Technical Publishing Co Ltd

Published by

MTP
MEDICAL AND TECHNICAL
PUBLISHING CO LTD
PO Box 55, St Leonard's House,
St Leonardgate,
Lancaster, Lancs

ISBN 0 85200082 0

First Published 1974

Filmset by Technical Filmsetters Europe Ltd,
and
Printed by The Garden City Press Limited,
Letchworth, Hertfordshire SG6 1JS

Foreword

Despite the fact that pain is the central theme running through all branches of medicine and surgery and is the main reason for our patients coming to see us, relatively little has been written of its long-term control. Of all pain it is the chronic unremitting variety that is the most difficult to ease effectively and to control adequately. To relieve what has been called 'the long pain' has been the aim of the six authors in this book. In such a huge subject we have not tried to cover all aspects of therapy, but have merely aimed to discuss how we, the authors, set out to control chronic pain in some of its more common forms by drugs and by surgery and other methods. We have not attempted to discuss pain control by other means, such as manipulation or acupuncture. The authors are Physicians (two), Surgeons (two), anesthetist (one) and Psychiatrist (one). Each chapter is individual and complete in itself and therefore there is some, though relatively little, overlap. We hope that medical students as well as General Practitioners and Medical and Surgical specialists may find something of interest in these pages, though they are written essentially for the General Practitioner and final year medical students. And, finally, the Editor is immensely grateful to his Collaborators for their magnificent co-operation and to the Publishers for their ready help at all times.

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Pain: Mechanisms and Measurement

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Pain is an everyday experience, a feature of psychological as well as physical illness, an advantage in health and a disadvantage in disease; few can ignore it. For doctors it is the complaint of their patients; two of every three patients seeking medical help have pain (Suchman, 1965; Devine and Merskey, 1965). For patients it is the complaint from which relief is desired; most are unconcerned with laboratory tests and measure the success of treatment only in terms of the symptom, pain. For these reasons, pain has attracted the interest of doctors, who wanted to know the mechanism of its production in the hope of interfering with the process. The ability to measure pain is essential for scientific study of the phenomenon as well as for accurate evaluation of treatment designed to relieve it.

Pain is a sensation which we all recognize even if we cannot define it. As such it has aroused interest from earliest times. Keele (1962) has reviewed historical concepts attempting to explain the localization and mechanism of pain sensation. For Aristotle, the heart situated in the center of the body was the seat of sensation, receiving ripples from the periphery and transmitting them in the blood vessels. Plato suggested that pain was the result of the violent actions of the four elements, earth, air, fire and water, on the soul. Though the central nervous system was discovered in about 300 BC, it was not until the nineteenth century AD that further progress was made as a result of careful observation and experiment. Since that time, knowledge of pain mechanisms has developed in two separate ways, one concerned with the physiological mechanisms, the anatomical, physical and chemical requirements for the production of the sensation of pain, the other

concerned with psychological mechanisms. The beginning of progress was the discovery by Bell that the posterior nerve root was a specific organ of sensation; this led Muller to postulate that individual nervous pathways carried particular sensations, the beginning of the search for the 'pain pathway'. Later the surgeon was able to study the effects of dividing pathways and the physiologist to demonstrate the electrical activity of individual nerve fibers.

The mechanism of pain; anatomical, physiological and biochemical considerations

THE RECEPTOR

Von Frey (1895) described specific nerve endings for each of four cutaneous modalities, including pain for which the receptor was a free nerve ending. He showed that pain spots could be identified, and at these spots, other modalities such as touch were not perceived. Woollard *et al.* (1940) studied nerve endings in the rabbit ear and showed that responses interpreted as indicating that the animals felt pain were produced by stimulation of free endings of non-medullated and finer medullated nerve fibers in the deeper layers of the epidermis. Though the free nerve endings are capable of responding to noxious stimuli, though not necessarily exclusively so, combined clinical and histological studies have failed to support the assignation of the other modalities such as temperature to a specific end-organ. Iggo (1972) argues that specific pain receptors must exist since some isolated nerve fibers respond only to certain types of noxious stimuli.

CHEMOSENSITIVITY

Keele and Armstrong (1964) showed that there were chemosensitive pain receptors. They applied a cantharidin plaster to human skin producing a blister, the top of which could be removed leaving an exposed area thought to contain pain receptors. It was then possible to demonstrate that some naturally occurring substances such as bradykinin, which is involved in the process of acute inflammation, were capable of inducing pain at very low concentrations. Pain could also be produced by hydrogen or potassium ions, histamine,

5-hydroxytryptamine, acetylcholine and various peptides, but not adrenalin or nor-adrenalin. Recent evidence suggests that prostaglandin E_1 is able to sensitize the pain receptor to the action of chemical mediators and other stimuli such as pressure, though it is not itself a pain-producing substance except in very high concentrations. Ferreira (1972) infused prostaglandin E_1 subdermally in human volunteers and showed that this increased sensitivity to bradykinin or histamine; pain was also elicited by slight pressure over the infusion site. This effect of prostaglandin E_1 also suggests a mechanism of action for peripherally-acting analgesics such as aspirin; Vane (1971) showed that aspirin inhibits prostaglandin synthetase, preventing the formation of prostaglandins. Relief of pain may be produced by the absence of the sensitizing effect of prostaglandin E_1 on pain receptors.

NERVE FIBERS

Bishop (1946) produced evidence that each sensory modality was associated with activity in sensory fibers within size ranges whose maxima at least were characteristic; for pain, peak activity was found in large rapidly-conducting myelinated A delta fibers and the small slow-conducting unmyelinated C fibers. These fibers are not specific for the sensation of pain; Douglas and Ritchie (1957) showed that C fibers could respond to non-noxious mechanical stimuli such as light touch. Hensel *et al.* (1960) studied isolated single C fiber preparations and showed that though some fibers may be specific for one mode of stimulation, others can respond to different types of stimuli.

TRACTS AND COLUMNS

The pathways of pain fibers inside the spinal cord and central nervous system have been mapped largely as a result of surgical experience in the relief of pain, aided by the effects of accidental injuries. McCarty and Drake (1956) summarize surgical experience; structures apparently involved in pain transmission or perception include the dorsal root, the lateral spino-thalamic tract, the thalamus and the prefrontal cortex. Surgical lesions of these structures modify pain but do not necessarily abolish it; in fact such lesions may cause pain. Other structures are involved indirectly, for example the sympathetic nervous system.

GATE THEORY

Melzack and Wall (1965) proposed a unifying theory of pain mechanism, the gate theory. The gate is situated anatomically in cells of the substantia gelatinosa, which are found in dorsal horns throughout the spinal cord. The first central transmission or T cells send sensory information to higher centers after it has passed through the gate. Sensory information is also transmitted centrally in the dorsal columns and, after processing, can influence the gate by way of descending tracts; this constitutes the central control mechanism.

The gate theory sets out to explain a number of observations concerning pain mechanisms. Pain is mediated by a group of large fibers and a group of small fibers. Volleys of nerve impulses in large fibers are initially effective in activating groups of T cells in the spinal cord of the cat; later this effect is reduced by an inhibitory mechanism. Volleys in small fibers activate an excitatory mechanism which exaggerates the effect of sensory input. There is a continuous barrage of activity from incoming nerve fibers on the spinal cord in the absence of stimulation and this is carried mainly in small fibers. Stimulation of higher centers can activate descending efferent fibers which influence conduction at spinal cord synapses; this mechanism provides a convenient explanation for the effect of central nervous system effects such as emotion and conditioning on pain.

How the gate works

The gate is normally kept open by tonic activity in small fibers which continues even in the absence of a noxious stimulus. This keeps the system in a state of readiness but it is easy to see how pain could be produced without noxious stimulation or disease, for example by the influence of central factors such as anxiety or depression on the gate.

Large and small fibers act on the T cells but also send communicating branches to the substantia gelatinosa cells; those from the large fibers being excitatory, those from the small fibers inhibitory. The cells of the substantia gelatinosa inhibit the efferent fiber terminals on the T cells; this inhibition is increased by activity in large fibers and decreased by activity

in small fibers. The final discharge of the T cells is therefore controlled by the relative activity in large and small fibers. If a stimulus activates mainly large fibers, it will fire T cells and cause pain but also partially close the gate by increasing the inhibitory activity of the substantia gelatinosa cells on the T cell, cutting short the T cell discharge and the pain. It is thought that maneuvers such as vibration, rubbing and scratching may increase large fiber discharge and thereby diminish pain.

The firing of T cells, when it reaches a critical threshold, is believed to activate an action system which includes the sensory awareness of pain as well as rubbing and scratching, avoidance behavior such as withdrawal, and various reflex phenomena such as crying out, turning of the head and eyes to inspect the damage and autonomic reactions such as those of fight and flight.

Evidence for and against the gate

Evidence in support of the theory comes from electrical stimulation of nerves and from observation in post-herpetic neuralgia. Wall and Sweet (1967) found that threshold stimulation of peripheral nerves, which is assumed to activate only large fibers, abolished the ability of local pressure to cause pain. This is interpreted as 'gate closure' by reducing the effectiveness of afferent impulses on T cells and it offers a method by which control of various otherwise intractable pains might be achieved. Noordenbos (1968) studied nerves from patients after infection with *Herpes zoster* and found a disproportionate loss of large fibers; this leaves the unopposed action of small fibers on T cells, a wide open gate, and pain which may be caused by non-noxious stimuli such as light touch. The theory has been questioned by Schmidt (1972) and Iggo (1972) who point to conflicting evidence concerning the effects of small fiber stimulation on dorsal root potentials and question the evidence for continuous afferent small fiber activity. The gate theory remains a useful working hypothesis and provides an anatomical framework within which modification of stimuli by central and peripheral factors could explain the variability of the sensation we know as pain.

The mechanism of pain: psychological considerations

PERCEPTION AND REACTION

Marshall (1894) and Strong (1895) were the first to make a distinction between two components of pain, perception and reaction. Pain is not produced simply by a stimulus sufficiently noxious to activate the pain receptor and send a message on its way to the sensory cortex, a process which may be called the perception component of pain. The modification which this message undergoes so that its effect—the sensation of pain, which is not necessarily proportional to the stimulus—is termed the reaction component. Beecher (1962) advanced the following evidence in favor of the existence of the reaction component.

1. Great wounds may be painless and small wounds painful. Guthrie (1827) noted this in the Peninsular War and Beecher (1946) in the Second World War; it was a curious finding that patients with great wounds but no pain could still feel the effects of clumsy venepuncture, suggesting that the pain mechanism or perception component is intact and implying that it is the reaction to or interpretation of the noxious stimulus that has been modified. For perhaps the same reason, sportsmen become aware of their injury after the game.

2. Emotion, suggestion, hypnosis and placebo therapy can block pain and such block is presumably on the reaction component; one would not imagine for example that a placebo could affect the pain-producing mechanism or perception component in any way.

3. Lobotomy and sometimes drugs may make a patient comfortable even though he continues to be aware of pain and his pain mechanism is presumably intact; lobotomy has been regarded as a surgical lesion of the reaction component.

4. Beecher (1962) argues that narcotic analgesics are effective only when pain is judged significant; they have no effect on transient experimental pains which are without significance and in which the reaction component is presumably minimal; in other words narcotic analgesics also act on the reaction component of pain.

MECHANISMS OF PAIN

It is clear that pain does not depend simply on the peripheral stimulus, and experience in clinical medicine supports this view. Many clinical writers have noted that pain is not necessarily the result of local disease; Sir Benjamin Brodie (1837) for example, was consulted concerning a young lady with severe pain and tenderness of the knee which was not accompanied by local signs of disease; later the patient manifested other hysterical features. Brodie concluded that it was not uncommon for a joint to be painful so that it was thought to be the seat of some serious disease, although no such disease in reality existed. Devine and Merskey (1965) found that no less than 53 of 137 patients attending a general medical clinic with pain had no organic lesion to explain it. Pain may be produced in a number of ways and the scheme which follows is based on that of Hill (1970).

1. Pain may be caused by disease.

2. Pain may be normal; Trotter (1921) argues that though pain in disease serves no obviously useful purpose, it seems to have a protective function in normal people; absence of pain in congenital indifference to pain is a disadvantage and leads to severe trauma. Pain is an everyday experience which is felt in the same way as heat and cold, but not usually remembered.

3. Pain is sometimes caused by disorders of the pain-producing mechanism, for example by lesions of peripheral nerves or the thalamus.

4. Psychosomatic pain occurs when a painful physical disorder results from a psychological state, for example occipital muscle spasm in anxiety.

5. Psychogenic pain is the direct result of psychological disorders, such as anxiety and depression, which are common in patients whose pain cannot be explained by organic disease. Conversely pain is common in patients with such psychological disorders (Merskey and Spear, 1967). It is perhaps unfortunate that patients do not complain of psychogenic pain; Szasz (1957) emphasizes that the differentiation of organic and psychogenic pain is not based on any difference between the pains but on the judgement of the observer.

Pain, as seen in the medical clinic, is a complex phenomenon of which the noxious stimulus is only a part; processing of the message plays a large part in determining the final sensation and it appears that pain may arise in the processing mechanism which may include the gate of Melzack and Wall (1965).

The measurement of experimental pain

PAIN THRESHOLD

Pain threshold is defined as "the first barely perceptible pain to appear in an instructed subject under given conditions of noxious stimulation" (Beecher, 1957). It is measured in terms of the stimulus as the lowest intensity which will cause pain. The perception of pain is usually revealed by a verbal statement and Beecher (1957) points out that it can therefore be measured only in conscious and co-operative man. Pain threshold is an experimental concept and opinion has held at one extreme that it is a physiological phenomenon akin to the electrical threshold of isolated nerve fibers, and at the other that it doesn't exist. The former view is untenable since it fails to take account of the processing which a noxious stimulus undergoes. That pain threshold is a valid measurement is supported firstly by the reasonable constancy of pain threshold in an individual which distinguishes him from others, and secondly by the relationships shown between pain threshold and various aspects of pathological pain (Keele, 1968; Huskisson and Hart, 1972). Though Hardy, Woolf and Goodell (1940), using themselves as subjects, found a remarkable constancy of pain threshold, Chapman and Jones (1944) using the same method in 200 subjects, found much wider variations and later authors agree. There is strikingly more variation between subjects than between different measurements in the same subject (Gaensler, 1951) suggesting that pain threshold is a distinct individual characteristic. Seevers and Pfeiffer (1936) using von Frey hairs, showed wide individual variation in pain threshold and though measurements were fairly constant over the course of hours, there was much greater variation from week to week. Many external factors vary from week to week and one would expect these variations to be reflected in the processing of pain.

THE IDEAL METHOD OF MEASURING PAIN THRESHOLD

A wide variety of experimental procedures has been used to produce pain in man either to study the phenomenon or to measure the effects of drugs upon it. Hardy *et al.* (1952) suggested six requirements of an adequate method of measuring pain threshold:

1. Measurability of stimulus with reproducibility,
2. Controllability,
3. Adequate range from threshold to ceiling,
4. Production of minimal damage to tissue,
5. Convenience,
6. Production of clear-cut perception of pain.

Beecher (1957) adds:

7. Applicability to a body part where neuro-histological factors are at a minimum,
8. Possibility of carrying out repeated stimulation without interfering with subsequent determinations,
9. Sensitivity to analgesics.

Mechanical methods

Mechanical methods of producing pain have often been used because they are simple and acceptable to patients. Von Frey pressed horse hairs of various sizes on the skin and measured the hardness of the hair required to produce pain; this method was used by Seevers and Pfeiffer (1936) to test analgesics. Libman (1934) pressed on the styloid process with his thumb and graded the response; Pelner (1941) tried to eliminate the variability of the pressure applied by using a mechanical gauge pressed on the proximal phalanx of the thumb until it became unbearable. Hollander (1939) used a cheese grater concealed inside a sphygmomanometer cuff, which was inflated until the patient winced, changed expression or cried out. Algometers have apparently been used since Victorian times; McDougall used one to measure the pain threshold of Polynesians in 1903 (Merskey and Spear, 1969). More recently the method has been used by Hardy *et al.* (1952) who called it a coiled spring esthesiometer, Keele (1954), Clutton Brock (1964) and Huskisson and Hart (1972). The appâratus described by Keele (1954) consisted of a blunt-ended rod, one end of which was

applied to the forehead of the patient. The other end was attached to a coiled spring; a scale measured the displacement of the rod and could be calibrated in kilograms. The pressure was increased at the rate of 1 kg per second and the end-point taken as the verbal statement of pain. Burn (1968) used a device which delivered a measurable blow to the soft tissues in front of the Achilles tendon, a site favored by clinicians for testing deep pain sensation.

Heat and cold

Extremes of heat and cold are painful and both have been used as noxious stimuli to produce experimental pain. Hardy *et al.* (1940) used radiant heat focused onto an area of blackened skin. A projection lamp is used as the heat source and a shutter exposes the subject to the stimulus for 3 seconds. The intensity of the stimulus can be raised and when the threshold is found, a measurement is made by introducing a radiometer into the path of the beam. Problems with the method, reviewed by Beecher (1957) include variations in blackness of the skin, changes in ambient temperature, effects of repeated stimulation particularly if there is tissue damage and technical problems such as changes in exposure time. Using this method, Hardy *et al.* (1952) produced a 'dol' scale of pain; they found that there were 21 just noticeable differences in intensity of pain between pain threshold and ceiling pain and called two such differences a dol. A modification of the method by D'Amour and Smith (1941) used a fixed intensity of heat and measured the time taken to produce pain. The method has been used in man by Lee and Pfeiffer (1951) who called their apparatus a warm-wire algesimeter and in animals by Woolfe and MacDonald (1944) who placed mice on a hot plate and measured the time taken to react. Wolff *et al.* (1969) used a modification of the cold pressor technique; the subject's hand was immersed in warm water then transferred to ice-water. Two end-points were measured, the subjects being asked to shout 'pain' when pain was felt and 'stop' when it became unbearable.

Electricity

The ease of controlling an electrical stimulus has contributed

to the popularity of this method of producing pain, which was first used by von Helmholtz in 1851 (Beecher, 1959). Later workers have applied electrical currents either to the skin or tooth pulp. The latter may have advantages over skin because it is less subject to external influences such as temperature and sweating. Brief shocks are applied to an amalgam filling in a tooth and threshold for pain determined. Because it is not possible to apply the method to a standard size filling in a standard position in a tooth, it is doubtful whether the method can be used to measure the pain threshold of an individual, though it has been used to follow changes after drug administration.

Vascular occlusion

Lewis *et al.* (1931) used a tourniquet applied to the upper arm in a patient who was contracting his hand muscles at a constant rate and measured the time taken to produce pain as the pain threshold. Hewer and Keele (1948) and later Smith and Beecher (1969) used the method to test analgesics.

Visceral and chemical methods

Methods of producing visceral pain are of great interest though their application is limited to very special situations such as surgical operations and the rather unusual volunteers found in American prisons. Gaensler (1951) distended the bile duct through a T tube and determined pain threshold. Chapman and Jones (1944) distended the esophagus by inflating a balloon introduced through the nose, the end-point being taken as a feeling of substernal fullness rather than pain. They were not able to produce a severe pain by this method, but pain threshold correlated with measurements using radiant heat. Lim and Guzman (1968) infused bradykinin into the peritoneum of volunteers, finding an optimum individual dose which caused pain. Armstrong *et al.* (1951) found that the concentration of pain-producing substances required to produce a certain intensity of pain was constant for a given individual and this is a measure of pain threshold.

End-points

Considerable confusion exists over the definition of end-points

in pain threshold studies. There are three quantities involved, pain threshold, severe pain threshold or pain reaction threshold, and pain tolerance.

If the intensity of a noxious stimulus is slowly increased, a point is reached at which pain is felt and this is the pain threshold. Because the patient is required to make a statement to this effect, Keele (1968) preferred to call it pain complaint threshold and other suggested terms include verbal report of pain (Hall and Stride, 1954), pain perception threshold (Merskey *et al.*, 1962; Chapman and Jones, 1944; Gelfand *et al.*, 1963) and lower pain threshold (Sternbach and Tursky, 1965).

If the intensity of the noxious stimulus continues to be increased after pain has been felt, another point is reached at which the patient says that the pain has become severe or 'hurts a lot' and this may be called the severe pain threshold (Merskey *et al.*, 1962). Some authors have taken this point as intolerable pain which causes confusion with pain tolerance, discussed below. Others have taken some reaction to pain as the end-point; this may be wincing, withdrawal (Chapman and Jones, 1944) or changes in pulse rate (Hazouri and Mueller, 1950), and is appropriately called the pain reaction threshold. Sternbach and Tursky (1965) called it upper pain threshold.

Pain tolerance, expressed as usual with experimental pain in terms of the stimulus, is the difference between pain threshold and severe pain threshold or pain reaction threshold; it is therefore the quantity of pain-producing stimulus which can be tolerated. Gelfand *et al.* (1963) used an ultrasonic generator to apply heat to the thumb and measured pain threshold as the time after application when pain was first perceived. The subject was then asked to keep his thumb in contact with the painful stimulus until pain became unbearable; the difference in seconds between this point and pain threshold was called pain tolerance. It is not surprising that there was a good correlation between pain threshold and pain reaction threshold, the point of withdrawal of the thumb; this is a statistical artifact arising because pain threshold is a major component of pain reaction threshold. There was no significant correlation between pain threshold and pain tolerance. Merskey and Spear (1964), whose findings were the same, called pain