

## PAIN AND ANALGESIC DRUGS

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Pain is often an issue of utmost importance in medical practice both to the physician and to the patient. Most quantitative work on the effectiveness of drugs in altering sensation has been done on pain. Before proceeding to discuss the clinical role of analgesic drugs it is necessary to define the term "pain" and to examine the underlying mechanisms that give rise to this sensation.

Few investigators have questioned the assumption that pain is the same, whatever its origin, or that the only characteristics of interest are the intensity and the duration of the pain. These ideas need revision, as it recently has become clear that the significance of pain can be of dominating importance.

**Definition of Pain.** Pain refers to an experience or a perception and not to the behavior produced by that experience. Pain is defined introspectively by every man. The difficulty comes in verbalizing this well known experience, that is, to say what it is - not merely to indicate its presence. This operational definition is somewhat unsatisfactory but the problem remains one of semantics.

**Types of Pain.** Von Frey demonstrated the existence of pain spots in the skin. This led to the demonstration of pain as a special sensation, served by its own receptor apparatus. The anatomical receptors for pain are naked nerve endings found in almost every tissue of the body. Pain impulses are transmitted to the Central Nervous System by two fiber systems. One system is composed of small myelinated A-delta fibers which conduct at rates of 12 - 30 m/sec. The other system consists of unmyelinated C fibers that conduct at the slow rate of 0.5 - 2 m/sec. Both fiber groups end on the lateral spinothalamic tract neurons and join impulses ascending via this tract and the vertical post-

eromedial and posterolateral nuclei of the thalamus to the post central gyri of the cerebral cortex.

It has been pointed out that 1) no sensation is experienced in the skin, only in the cortex and thalamus; (2) some components of sensation are irrepressibly carried into consciousness, some are registered by attention, while others are not capable of reaching consciousness; (3) the state of the skin modified the action of its sensory endings, chiefly by altering thresholds. The importance of differentiating between pricking and burning pain, delta and C fiber pain has also been emphasized. Most pain in pathology is probably C whereas most testing of analgesic drugs in humans has been done in delta.

Pain can be evoked by many kinds of stimuli: thermal, electrical, mechanical or chemical. If in a controlled laboratory situation these stimuli are applied to the skin, naked nerve endings or other tissue in which pain receptors exist, the resulting sensation may be termed experimental pain. Pain is also evoked by tissue damage or trauma, in which case it is referred to as Pathological Pain.

### MEASUREMENT AND CHARACTERISTICS OF EXPERIMENTAL PAIN IN ANIMALS AND MAN

Pain is measured in terms of its relief. This system is common throughout pharmacology where for example induced nausea is sometimes appraised through the power of a given anti-emetic agent to suppress it, and induced cough by the power of a given anti-tussive agent to check it.

The experimental conditions under which pain threshold and suspected analgesic agents should be tested in animals and man have been summarized as follows:

1. The painful stimulus must be applicable to an area not significantly different in different individuals.

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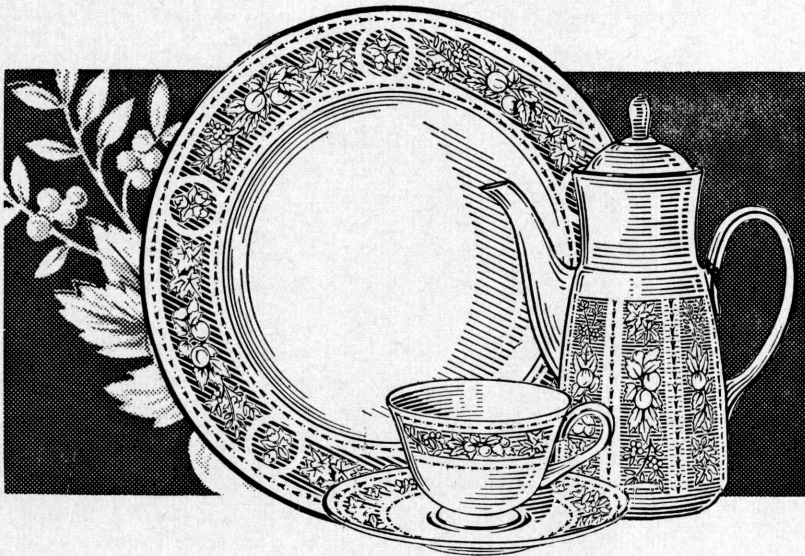
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2. The investigator must be able to obtain quantitative data without tissue damage due to the stimulus

3. There should exist a relation between the intensity of the stimulus and the intensity of the pain response

4. Qualitative information as to the difference between slight stimuli must be distinguishable

5. The test must be repeatable without interference by previous testing.

6. The method should be able to show responses to agents of low analgesic activity.

7. The method must be able to differentiate graded doses of the test drug, i.e., a dose response relation should exist.

In general, the test should be applicable both to man and animals. The methods in use are not ideal. A few of the laboratory methods that have been widely used for the determination of thresholds and the screening of analgesics will now be enumerated:

#### 1. Thermal Methods

##### (a) Direct Heat Application.

Early attempts were made to get at pain threshold values by direct application of hot bodies to the skin. The difficulty with all contact methods was that sensations of touch and pressure were evoked by them as well as pain. This method is no longer used.

(b) **Radiant Heat Methods.** The method devised by Harvey, Wolff, and Godell has been widely used for the determination of pain thresholds and their alteration by analgesic drugs in both humans and animals.

The light and heat from a 500 or 1000 watt projection lamp is focused for precisely 3 sec. on 3.5 cm<sup>2</sup> of blackened skin, usually the forehead of the subject. The current applied to the lamp is increased in a stepwise fashion during the one-minute interval between exposure; hence the stimulus is of fixed duration and variable intensity. Finally, the subject experiences, and reports verbally, a sharp jab of pain at exactly the end of the 3 second exposure. Pain threshold may be determined before and then following administration of a test drug. Various modifications of this procedure have been used.

This method has several disadvantages :

(i) the intensity of the stimulus cannot be measured exactly as the skin temperature is determined by the heat applied to it, and the circulation through the area.

(ii) The stimulus cannot be repeated without some damage to the skin

surface.

(iii) The heat is not applied to pain receptors alone.

(iv) There is an effect due to species variation when any thermal method is applied to animals. Morphine, for example lowers temperature in birds and many mammals while it elevates it in horse, cow and rats; consequently, conflicting results may be obtained from different species.

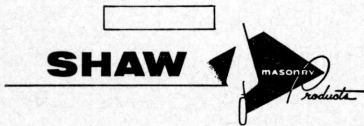
In both man and animals a slight heat stimulus may lead to release of histamine, bradykinin or similar substances and this in turn leads to hyperalgesia and to threshold alteration. Furthermore, repeated high levels of heat stimuli leads to gross erythema which interferes with pain threshold.

The proponents of this method have shown that attitude and suggestion are important in modifying both the experimental pain threshold and the reaction to pain. They report that a change in threshold often equivalent to that produced by analgesic drugs can be effected by suggestion through placebos. Even greater rises than these although of shorter duration have been produced by distraction.

A modification of the previous method was introduced by D'Amour-Smith. The intensity of the heat source is fixed while the exposure to the stimulus is of variable duration. This method is more suited to experimental animals. The heat, for example, is focused on a rat's tail, which lies in a groove. When the current is turned on a stop watch is started. At threshold, the tail is flicked away and the watch stopped. Burns with severe tissue damage can easily occur with impairment of the accuracy of the method. The chief criticism of this method is that the end point is a reflex reaction threshold rather than a true pain threshold. Can data obtained in this way be extended from animal to man?

(c) **Hot Plate Method.** This is a method widely used in the drug industry for routine screening of chemical agents for analgesic activity. Ten mice are placed on a hot plate at 55° for 30 sec. intervals. The hot plate temperature is increased from 55° to 70°C in steps of 5°C. The end point is the raising or kicking of the hind legs. This procedure is repeated before and after the administration of the test drugs. Because of the low temperatures involved, the experiment can be easily repeated many times without

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physical damage to the animals. The method is a general, convenient, rapid, rough, screening test for analgesic agents.

## 2. Electrical Stimulation

(a) The application of electrical currents to the skin or back of rats and rabbits has been used to test analgesic drugs. The end point was a visible muscular twitch. Again, one should not equate this reflex response with the pain threshold.

(b) The tooth pulp has been stimulated in both men and animals through amalgam fillings. The most interesting results to come out of human investigations is that adrenaline injected subcutaneously has been said to have analgesic activity in excess of morphine. It is possible the intense local effect of adrenaline on the circulation could have impaired the tooth sensitivity.

## 3. Mechanical Stimulation

(a) VonFrey Hairs. Several investigators have applied this old method in modern times to sensitive areas of skin such as the lips and upper eyelids. Horse hairs of various diameters and lengths were attached to a lever and the weights required to bend the hairs to produce pain in the epithelium were determined. Pain threshold was found to be variable.

(b) Gross Mechanical Pressure. Several methods of applying mechanical pressure to the tail of different animal species have been widely used to screen suspected analgesics. The method widely used in industry consists of applying an artery clip to a rats tail for 30 sec. and recording the animals behavioral responses. The test drug is then given and after 30 minutes the clamp is re-applied. The results are expressed as per cent of rats responding to the clip after 30 sec.

(c) Tourniquet Method. Ischaemic pain produced by a tourniquet has been used by several investigators to determine the time of appearance of pain threshold in humans.

## 4. Chemical Stimulation

One of the most common methods used for analgesic assessment under this category has been the formation of a blister on the skin by application of catharidin. The separated epidermis was removed and the base of the blister used for testing. This method has several advantages.

(1) The exposed nerve endings permit immediate contact with the test solution,

(2) The same nerve endings can be exposed to various test solutions or drugs.

(3) Standard pain producing solutions of potassium chloride or acetyl choline can be used as controls for indicating fluctuations in sensitivity of the blister.

(4) Spontaneous pain in the lesion goes away within 10 - 15 minutes. The pain threshold response to a given chemical was found to be constant for a given individual.

In summary, to indicate the pain threshold in man, a verbal end point has proved useful although not always dependable. This verbal end point should not be confused with muscle twitching, blinking, withdrawal or any form of reflex determines the end point of nearly all animal experiments. This is a reaction threshold, not a pain threshold.

## PAIN THRESHOLD

The pain threshold can be determined and studied only in conscious and co-operative man. The pain threshold is defined as the first barely perceptible pain to appear in an instructed subject under given conditions of noxious stimulation. Evidence suggests that the pain threshold is not constant from individual to individual, and may vary from time to time within the same subject. The fact that the pain threshold has not been shown to be constant speaks for contamination of pain perception by a reaction component.

A myriad of factors other than analgesic drugs can produce changes in pain threshold. Many of these factors are probably operative during the testing of analgesic compounds in humans. The following list will serve to illustrate the difficulties an investigator encounters in dealing with human subjects:

1. Race. Negroes and Southern Europeans perceive pain at a lower level than peoples of North European extraction. The North European's spread between perception and reaction is distinguishable whereas the negro reacts to pain at or near his pain *perception* level.

2. Sex. Women are said to be more sensitive to pain than men. This has been denied.

3. Aging. Pain perception is reported to decrease with age. This statement has also been challenged.

4. Circulatory Change. Pain itself can cause peripheral vasoconstriction resulting in

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increased pain threshold. The effect of adrenaline in elevating pain threshold is probably due to the action of the catecholamine on the blood vessels.

5. Skin temperature  
6. Sweating  
7. Elevation of CO<sub>2</sub> tension. Elevation of CO<sub>2</sub> tension increases pain threshold 13 - 28% by means of a central effect similar to the action of N<sub>2</sub>O.

8. Hyperalgesia - e.g. Sunburn, raises the skin's sensitivity to heat. This lowers the pain threshold.

9. Other Forms of Trauma. Skin lesions, traumatic deformation of the tissues, callouses, or tissue injury near the nerve endings can alter pain threshold.

10. Nausea. The pain threshold is elevated during nausea due to palor (vasoconstriction), distraction and emotion.

11. Fatigue. Fatigue may elevate or may lower the pain threshold.

12. Anxiety and Fear. In these states subjects tend to overestimate the intensity of painful stimuli; hence, the pain threshold is lower.

13. Bias. Bias on the part of both subject and investigator can influence the determination of the pain threshold.

14. Adaption. Adaption to pain does occur and this adaption is more pronounced in experimental pain situations.

15. Distraction, inattention, lethargy, etc.

16. Suggestion and emotion. When subjects are under drug effects it is possible that suggestion carried by the tone and inflection of the investigators voice has produced pain threshold elevation especially in a highly drug experienced group. Suggestability was apparently a learning process on the part of the subjects. This difficulty could be avoided by the double-blind technique.

17. Placebos. A subject who is aware of the fact that he has been given an analgesic will demonstrate more pain threshold - elevating effects than does the subject who, receiving the same drug is convinced that he has not received an analgesic. A subject who can perceive he has been given an analgesic agent is often referred to as a drug-wise subject.

## THE PRODUCTION OF ANALGESIA

The term *analgesia* comes from two Greek

words meaning absence of pain. The definition of an analgesic agent is one that brings about relief of pain without significantly dulling consciousness. It is customary to exclude agents which act by removing the cause of pain, and agents which block pain impulses peripherally.

A characteristic of a sense organ in which pain *receptors* are found is that a single brief stimulus sets up a repetitive series of nerve impulses which are probably responsible for the *original* sensation component of pain. Perception of this *original* sensation requires in addition to the receptor organs themselves the presence of conducting pathways and intervening synapses all the way up the central nervous system until awareness of sensation is achieved. No systemically administered analgesic is known that will abolish function in pain receptors or the conducting nerves. Synapses are vulnerable to a number of agents but there is no evidence that the customary doses of analgesica used systemically in man can influence them.

Several investigators believe that clinical analgesia is a result of one or more of the following effects: (1) interruption or reduction of afferent pain sensations in the midbrain or thalamic area, (2) altered reaction component, (3) increased threshold to pain at the periphery. This last one appears to be of lesser importance as far as analgesia in pathology is concerned.

There is considerable evidence both for and against a relationship between dependable analgesic action and experimental pain threshold in man.

The reaction threshold changes produced in animals have often been more useful and reliable in appraising analgesic powers than the pain threshold in man. The usual failure to detect affects in animals with weaker analgesics like acetylsalicylic acid is a point to be considered, so also is the failure of the powerful narcotic N-allylnormorphine to alter reaction threshold. To an animal pain is pain - hence all pain is serious and significant. Threshold changes in animals are very different things from those in man. In animals these changes are indicated by reflex activity, usually spinal reflexes. In man, however, they are based upon cortical activity. Just how misleading work with experimental pain as opposed to pathological pain can be, was shown by the fact that several workers re

ported that acetylsalicylic acid was a more potent analgesic in guinea pigs than was meperidine, and total failure to detect the narcotic action of N-allylnormorphine. Approximate ceiling effectiveness of analgesic drugs are demonstrated fact in man. Little increase of the pain threshold occurs with doses of morphine above 15 mg. or of codeine above 60 mg. The ceiling effect is less well defined in animals but this may be due to the fact that reaction threshold does not truly measure pain threshold.

### REACTION FACTORS OF THE PAIN EXPERIENCE

There are many kinds of reaction to noxious stimulation. These reactions generally fall into one of three groups: (1) skeletal muscle responses, (2) reactions mediated by the autonomic nervous system, and finally, (3) the processing by the central nervous system of the original stimulation. The latter is the most important factor as it determines the presence or absence of suffering - an intimate part of the pain experience. The other factors are not a component of pain but a consequence of it.

**A. Psychic Reaction** In discussing pain it is important to appreciate as exactly as possible what is meant by the terms *original sensation* and reaction. The output produced by stimulation of sensory receptors is the primary phenomenon. The resulting afferent nerve impulses emerge in the central nervous system and become a recognized sensation or perception. Presumably in all normal individuals the mechanism of the events is the same for a given stimulus. There can be little doubt that the secondary response, the reaction to, or the processing of the primary events is different for each individual.

The existence of sensation and its recognition are the factors which precipitate the important psychic reaction or processing. This latter process is influenced by the subject's concept of sensation, by its significance, by its importance, and degree of seriousness. The meaning of sensation depends upon, and is governed in large part by experience as well as by present consideration; thus discrimination, memory and judgment enter into the process of reaction. For example, an ache beneath the sternum, in connoting the possibility of sudden death from heart failure, can be an upsetting experience, where as the same intensity and duration of ache in a

finger is trivial. Physically, *association pathways, long circuiting* or reverberation of nerve impulses involving internuncial neurons may be involved. By extension, it is possible that one can perhaps eliminate subjective response with drugs by: (a) lessening or blocking original sensation (b) by reducing or impeding the process of recognition, or (c) by altering the process of discrimination, memory and judgment which follow recognition.

The reaction pattern in certain instances has been shown to be independent of perception and may be dissociated from it. Common examples of the dissociation of pain, perception from reaction pattern are the indifference to injury sustained during the excitement of games, combat or sexual arousal; during injury the absence of reactions to pain effected by suggestion or hypnosis, the apathy to injury during mystical religious rites, and painless childbirth. It should be observed that all these examples are derived, as far as the cause of the pain is specified, from pathological or traumatic situations.

The separation of the two pain components has been further demonstrated in humans by the dissociation of pain and comfort by barbiturates and by morphine. In the presence of persisting pain comfort can be established. The pain apparatus functions but the disturbing element is blocked. Frontal lobotomy produces a similar situation.

There is evidence that pain perception and attitude can be separated, that the reaction component is the most important from the patient's point of view, and that suffering is largely dependent on the reaction or attitude rather than on the original sensation.

In summary, it is an assumption that all pain experience in man consists of original sensation plus the reaction to the stimulus, and that in various situations there are great quantitative differences in the role of the two components.

**B. Experimental Versus Pathological Pain and the Psychic Reaction Component.** Because of the difficulty in reproducing in the laboratory pathological reaction to the original stimulus, the choice of a *real* pain situation for the final screening of analgesic drugs as opposed to contrived sensation has been advocated. It has been stated that if real progress is to be made in experimental situations, a way of separating pain sensation



from reaction pattern must be derived so that the role of each component can be understood in the pain situation. This separation has not been achieved.

The patient on a bed in pain, his happiness, security, indeed his very life threatened, provides a milieu and reaction entirely different from the laboratory. It is not likely that the contrived experimental situation can even approximate closely the real situation which arises in pathology or trauma.

One can successfully differentiate between powerful and weak analgesics and placebos using pathological pain in man, but not if experimental pain is used. The casual discomfort of experimental pain contrasts sharply with a pain that means or implies a disease or even impending death.

A large dose of morphine is not capable of consistently and significantly altering brief jabs of experimental pain, even in properly set up and controlled experiments in man. By contrast, large wounds with great significance and presumably great reaction are made painless by small doses of morphine. The difference in the two situations appear to be the significance of the two wounds. Morphine acts on the significant pain, not on the other. There is no simple direct relationship between the wound *per se* and the pain experienced. For example, the majority of severely wounded men removed from areas of intense action during World War II had their expected pain blocked. On arrival at hospital many were euphoric, their reaction one of satisfaction due to removal from an area of destruction and death. Many other factors of course determined the ultimate pain reaction in these men, but the fact remains that less than 5% requested or would accept any analgesic medication. This figure while not exact, certainly contrasts with the large percentage of post-operative cases which request analgesic or narcotic drugs to alleviate pain.

It has been agreed upon that experimental pain can be useful in appraising analgesics in animals. Experimental pain in man has proved relatively useless when compared to pathological pain testing. Presumably all pain is serious and significant to an animal. In man only pathological pain is serious and significant. Thus, in both instances, narcotics are effective, but probably chiefly effective in the presence of significant meaning of the pain involved. It appears that nar-

cotics are effective through their relationship to the meaning of pain or the reaction to it. Placebos can only effect reaction. The increased effectiveness of placebos with increased stress can seemingly be explained by the importance of the reaction (or processing) component of suffering.

Since gravely wounded men complain as vigorously as normal men at an inept vein puncture there is no total pain block. It can be concluded that their nervous system can transmit pain sensations but that somehow the reaction to them was altered when the wound occurred. That emotion can block pain is common experience. It is difficult to understand how emotion can affect the basic pain apparatus other than by affecting the reaction to the original sensation. This conclusion is strengthened by the observation that no dependable relationship has been observed between an experimental pain threshold in man and the effect of very powerful analgesics, yet the fact that these drugs were universally effective in testing pain of pathological origin indicates that there is a difference between experimental pain and pain of pathological origin.

It has been pointed out that pain is followed by slight adaptation, the less completely the stronger the stimulus. The cumulative central effect of pain summation is an important feature. This central factor of cumulation more than compensates for the slight degree of adaptation shown by the sense organs and becomes the factor of major importance in pathological states.

In conclusion, analgesic agents appear to exert their principal, if not entire effect on *reaction component* rather than on *original sensation* of the pain experience. This is the most surprising concept to come out of many investigations. It has profound significance for future therapeutics - if proven.

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