

PAIN AND SOME FACTORS THAT MODIFY IT * †

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Received for publication February 2, 1951

JUST as the existence of pain requires clinical anesthesia so also pain is the central reason for work in the field of anesthesia. But there is another less obvious reason for work in this field: The anesthesia process is bound up with irritability, one of the fundamental characteristics of living tissue. As Lillie pointed out years ago, the problem of the general nature of anesthesia is inseparable from the wider problem of the nature and conditions of irritability in general. The irritability of a cell, the response of a cell to a stimulus is the most elemental form of "consciousness."

The problem of pain and some factors that modify it are considered for various reasons: first, in awareness to pain we have a factor that can be measured, not, however, as it has widely been measured; second, there is an abundance of material ready at hand for study. Surely one of the greatest problems in the study of pain is the discovery and control of dependable yardsticks.

Agents which will relieve pain often have other interesting (and possibly related) qualities. These other aspects of the effects of the barbiturates are relevant to our general theme: doses of small size, hypnotic doses, can be used not only to relieve pain (1), to suppress consciousness of pain, but doses of little greater magnitude can be used to draw up into the consciousness distressing events that have been pressed down below the level of consciousness (2).

The problem of pain, of suffering, is very complex and yet many papers appear on this subject, some from good laboratories, without the slightest attempt at setting up controls. It must be understood that easy generalization cannot be made.

To illustrate this complexity, I have sometimes told the stories (3) of a Christian martyr and an individual of opposite character, an Italian nobleman, who worked with the Fascists until caught and tortured for his trickery. Neither of the individuals suffered much, if any, from the blows they received from their tormenters.

It may be said that these individuals were abnormal, and perhaps they were. Some surprising things, however, are found in healthy,

* Presented at the Annual Meeting of The American Society of Anesthesiologists, Houston, Texas, November 9, 1950.

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normal, young wounded men (1). The common belief that wounds are inevitably associated with pain and that the more extensive the wound the worse the pain was not supported by observations made as carefully as possible in the combat zone. There, only one-quarter of grievously wounded men, not in shock, had enough pain to want anything done about it as they arrived at the most forward hospital, even though they had had little if any morphine, and that several hours previously. The question reminded them that they could have medication for pain if they wanted it.† Three-quarters of the seriously wounded did not need medication for pain. Others of the seriously wounded obtained relief from a cigarette, the smoothing of a pillow or a light sleeping pill.

Evidently then, pain, suffering (and these terms will be used synonymously), is an experience that can be modified by many complex factors. Wounds received during strenuous exercise or during the excitement of games often go unnoticed. This is true of injuries received during fighting and during anger. Strong emotion can block pain, mental distress as well as physical; that is common experience.

In martyrs and in hysterical individuals pain is sometimes abnormally blunted. The opposite also occurs and pain may be called forth when no organic cause can be found. Suffering may strengthen the character but chronic pain or even the perverted development of pain and suffering without adequate physical cause can lead to an illegitimate escape from physical obligation or spiritual responsibility, with destruction of the moral self. We can see how, because of abnormal immunity to pain, as in the case of the martyrs, some individuals allowed their bodies to be injured without suffering. Perversion of the sensibilities can be developed in either direction, but the end in each case is disaster, moral disaster when "pain" as an escape is conjured up out of nothing, physical disaster when pain is abnormally blunted. Then, too, drugs taken to relieve physical pain can lead to addiction and moral disintegration. Conversely, the thirst for alcohol that arises in mental distress can lead to destruction of the body. The relationships of pain to the individual are indeed complex.

Pain is a capricious disability. It is difficult to define it. Everybody knows what is meant by pain and suffering. There is no need to labor over an academic definition of what we all understand. The great problem in studies in this field is to obtain controlled data, data so well controlled that we can trust our own observations.

The best known, or perhaps the most widely used, method of measuring pain in man, the Wolf-Hardy method, failed completely in our hands when morphine and saline were compared as "unknowns," and failed, too, even when an observer with years of experience with the method tried to use it on our subjects. Inspection of our data (4) on

† The refusal of proffered medication for pain relief is evidence that the tolerance for pain of these men was not merely a living up to a half-tradition that the Anglo-Saxon wounded do not cry. The astonishing "pain" relief obtained through barbiturate medication is further evidence along this line.

pain thresholds determined by the Wolff-Hardy technic revealed such gross inconsistencies that a detailed statistical analysis was not justified. Some thresholds were higher after the injection of a placebo, normal saline solution, and some were lower after the use of morphine, and these discrepancies were common. Our apparatus was accurately calibrated. The subjects were intelligent, cooperative college men who had been drilled in the technic before the study began. They were not trained technicians, but since the technic was applied to 29 men 11 times each over a five-week period, these subjects became rather experienced observers.

In the past, many ingenious procedures have been devised for producing experimental pain so that its relief could be measured, not only heat to the forehead as in the Wolff-Hardy method which we used, but pricks of the skin, tourniquets to arms, heat and electric shocks to teeth and so on. These methods of experimentally producing pain have often led to divergent results and confusion when utilized to appraise analgesic power. We have had to conclude that they are without usefulness, in man, at least.

The question arose as to the validity of these methods for the purpose of measuring pain relief in man not only by our own unsatisfactory experience but by the general confusion to be found in the literature on the subject, the failure of one method to support the findings from another method and the failure of different observers to check each other when they used the same methods of producing experimental pain.

So Denton and I came to the conclusion that these methods which depend upon experimental pain are not suitable to the purpose put and that appraisal of real analgesic power must be based upon the capacity of the agent to relieve "natural" pain, pain that is a consequence of disease or trauma. This is so because the pain experience of man consists of perception of painful stimuli and the psychic modification of these stimuli. This concept will be considered in a practical way. The precisely inflicted trauma of the surgeon provides in surgical patients a large group of subjects suitable for study.

The criteria for rigidly standardizing the groups of patients in pain to be studied have previously been published (5). Groups of 25 or so postoperative patients in pain are suitable for study during a limited period (the twenty-fourth to the thirty-fourth hour) following surgical procedures. In this ten-hour period two or three agents can be studied in the same patient, one agent sandwiched between two doses of another, and so on. The order of administration of agents must be carefully controlled. The effectiveness of the method is recorded as the percentage of the group obtaining relief.

In the past three years more than a thousand patients have been utilized in developing our method of measuring pain relief. Six members of the methadone series, morphine, pentobarbital sodium and nor-

mal saline solution have been utilized in developing the method. All of these agents were administered as "unknowns" to the patient and, equally important, as unknowns to the observers. I believe that failure to maintain the agent under study as an unknown to the observer accounts for much of the confusion in this field.

The accumulated data show that a variation in sensitivity to analgesic effects of morphine, for example, exists among groups of patients, and the distribution of this is approximately normal. With the guidance of a mathematician, Professor Mosteller, mathematical models have been constructed from the data which provide for a single or point estimate of the proportion of patients helped by a drug, when more than one was administered to the same patient. From selected portions of the data curves have been constructed relating the probability of being helped to the difficulty of being helped.

The work of Denton, Keats and Professor Mosteller has been essential to the gradual evolution of this method, and the latter two have made essential contributions, also; to the work on barbiturates, to be described below.

The application (6) of this method to a study of the analgesic power of barbiturates in small hypnotic dose will be discussed and then an hypothesis built up of how these agents can be effective in relieving pain.

Several independent observers have reported the failure of barbiturates to protect against the perception of pain produced experimentally (7, 8, 9, 10, 11). Their findings provide the basis for the current teaching that barbiturates in small dose have little or no analgesic power. This view stands in contrast to our experience with barbiturates in the treatment of *existing* pain, both acute and chronic. By existing pain is meant pathologically occurring pain.

As early as the Coconut Grove disaster I observed that hypnotic doses of barbiturates appeared to be useful in relieving the pain of badly injured patients (12). These random observations were confirmed on wounded men during the recent war (1). These necessarily uncontrolled war-time findings led to our more recent controlled study. The data obtained demonstrate the analgesic power of a small (hypnotic) dose of pentobarbital sodium when used in treating pain from natural causes. In this work it has been necessary to evaluate statistically the influence of time and of previous medications on the production of analgesia.

Early in these observations it appeared probable that there is an effect of barbiturates on "pathologic" pain which does not become apparent in studies of experimentally produced pain (5). This concept suggested interesting implications as to the factors involved in pain of human beings as well as to the mode of action of barbiturates.

When postoperative patients developed steady (that is, constantly present) wound pain of severe degree or great intensity, they were used

as test subjects (5). Pain on motion, so frequent in postoperative patients, was not used since the barbiturate to be used might produce decreased body activity and apparent relief for this reason. "Gas pains" and other intermittent pains were not suitable for use because they often subsided spontaneously. In 40 per cent of the patients followed, pain of the proper type and degree developed and thus they became eligible for use as subjects. The mode of obtaining results, and the controls have been described in full in a previously published paper.

The three drugs used in this part of the work were saline, pentobarbital sodium and morphine sulfate. All were given on the basis of milligrams per 70 kg. of body weight, except saline which was constantly given as 1.0 cc. All drugs were administered intravenously.

Pentobarbital sodium was selected as the barbiturate for use in this study primarily because it is short lasting, is representative of most barbiturates in action and has been widely used in neurophysiologic experimentation. Eight milligrams of morphine per 70 kg. was chosen because it is a small intravenous dose which would relieve postoperative pain in about 90 per cent of unselected trials. Five groups of subjects were studied in this manner, differing from each other in the dose and order of administration.

Soon after initiation of this study it was observed that in a sizable number of subjects following doses of morphine and more especially pentobarbital, the decision as to the presence or absence of pain relief was exceedingly difficult. Two types of puzzling reactions were observed. One was in those subjects who claimed that their pain had not, or only slightly, changed and yet who did not want further medication. They appeared perfectly comfortable, content and divorced from any "painful" experience in contrast to their predose state. Despite the fact that their pain was said to be still present, we could not believe that further medication was indicated. The converse was found in those subjects who claimed that the pain was "quite a bit better," and yet who continued to be restless, tense, unhappy, bothered greatly by minor ailments (position, tubes) and generally uncomfortable. It was impossible to believe that the medication had been successful in these subjects despite the relief of pain. The patient was not content. Therefore, all doses were evaluated both for pain relief and for comfort. Thus four categories of response were observed: (1) no comfort, no pain relief, (2) no comfort, pain relief, (3) comfort, no pain relief and (4) comfort, pain relief. The latter two categories of response were considered to represent the therapeutic or desired effect, both from the physician's and the patient's viewpoint. Further justification for the use of these criteria will shortly become apparent.

Pain relief was judged present when "all" or "most" or "more than half" of the pain was gone at thirty minutes. "Slightly better," "a little better" or "less than half gone" were judged as no pain relief. The presence or absence of comfort can best be described as an

estimation of the over-all status of the subject following medication and by his satisfaction with the results of the medication. Since before the drug was given, all subjects were uncomfortable by reason of their pain at least, this evaluation was not difficult. Primary emphasis in evaluation was placed on the subjective responses, but objective evidence was also considered. Whatever difficulties of criteria were encountered in any single subject, the errors made were consistent with all three drugs by reason of our experimental design.

The doses of pentobarbital used intravenously might be expected to produce such sleep as to suppress all complaints and preclude any reliable evaluation. This was rarely the case. Whereas wide variations among subjects were seen in the hypnotic effects of these dose levels, many did not sleep and almost all could readily be aroused. At thirty minutes they could give intelligent responses to the questions put to them. Sleep occurred more frequently after morphine than after pentobarbital (although not so deep), presumably the result in part of relief of their discomfort. Sleep in itself was not considered to indicate necessarily either comfort or pain relief and all subjects were awakened for interviews. In this way evaluation of effects of both morphine and pentobarbital were made *during* almost peak action of the drug and the errors of retrospective opinions (unreliable in our experience) were eliminated. Sleep did not necessarily accompany relief since often pentobarbital produced deep sleep without either comfort or pain relief, according to the subjects' statements.

When a large volume of data was obtained with adequate controls, it was evident that the placebo, saline, produced satisfactory pain relief in 20 per cent of our patients, 60 mg. of pentobarbital per 70 kg. satisfactory pain relief in 40 per cent, 90 mg. in 50 per cent and 8 mg. of morphine per 70 kg. in 80 per cent of the patients.

Some factors that may help to explain how these agents act can now be considered. Impulses resulting from painful peripheral stimuli or reaching the thalamic nuclei are projected to the cortex by way of pathways still not well defined (13). It is probable that in this projection these impulses or their spread is modified by reinforcing or inhibiting impulses from other areas of the nervous system, ultimately effected through the subcortical internuncials. We are focusing our studies at present on these internuncials, measuring their depression. The resultant modified impulses appear at the cortex and in consciousness as the complex symptom of pain.

Some of the complexities in studying and treating pain in man can be resolved by an appreciation of the contribution of both the original stimulus and the modification of this stimulus in making up the total picture of pain. Lacking more specific information, we have categorically labeled these modifying influences as psychic and assume a wide range in the degree to which the psychic factor can operate in any individual.

This approach to the pain experience makes it unreasonable to conclude that patients obtaining pain relief from placebos or saline do not have "real pain." It is likely that in such patients the psychic modification of pain stimuli is very great and that suggestion of relief alone is sufficient to block the thalamocortical spread of impulses by a purely cortical mechanism. Such a psychic mechanism is possibly like that which operates in the blockage of the pain experience by hypnotism and similar to the suppression of pain from injury during athletic contests in which the excitement of the game has prevented awareness of the injury or its pain. The same holds during fighting, as pointed out previously (1). It would seem from this that cortical impulses alone can interrupt the perception of pain stimuli. We predict that the pain experience can be altered by any large quantity of afferent or sensory stimuli, however produced (mechanically, or by drugs, by environment and so forth). Indeed, the euphoria-producing action of morphine has been suggested as responsible for most of its pain-relieving properties (14) presumably by alterations in the psychic factors operating. It is probable that such drugs as dextro-amphetamine sulfate (15) and procaine intravenously (16) for which analgesic powers have been claimed, act through their abilities to produce psychic changes rather than any alteration in the actual pain stimulus. It is possible that any drug which will produce reasonably large changes in the psyche can be shown to possess some analgesic powers. These postulates are to be tested experimentally.

This approach also makes it understandable why different results can be obtained with the same drug when applied to existing pain on one hand and to the perception of experimentally inflicted pain on the other. The perception of inflicted pain represents the recognition of a threshold physical stimulus, whereas existing pain is the stimulus plus its associated psychic modification. It may be convenient and wise to consider the physical stimulus only as "pain" and the combination of physical and psychic modification as "suffering." In man we are concerned with "suffering"; in animals we are probably concerned primarily with "pain." Obviously, man is the animal of necessity for the study of pain (see Keats, Beecher, and Mosteller, loc cit.).

The recent experience with prefrontal lobotomy for the relief of intractable pain gives support to this concept of the pain experience. In this surgical procedure, no representative pain areas are excised, little cortex is destroyed, and yet by it many patients are divorced from their suffering, presumably by interruption of these same thalamocortical projections. Lobotomy patients sometimes admit that they still have their pain, but that "it does not bother" them (17). The concern, anxiety and significance have been detached from their pain present before lobotomy. This observation is akin to the experience of a large number of our subjects who, after receiving pentobarbital, were observed to be quite comfortable but without any diminution in their awareness of

pain (comfort without pain relief) and justifies the distinction between comfort and pain relief. The demonstration that lobotomized patients have no loss of ability to perceive pain and, in fact, are said to have a lowered skin threshold to inflicted painful stimuli (18) further emphasizes the importance of this separation of the pain stimulus and the psychic modification of the stimulus, and the separation of perception of inflicted pain stimuli and existing pain.

We believe that pentobarbital has relieved suffering in a way similar to that of lobotomy, by interruption of the previous spread of pain impulses from the thalamus to certain cortical areas, thus blocking or altering the psychic modification of these pain stimuli. There is some evidence that pentobarbital can prevent the spread of afferent impulses. Forbes (19), in 1922, proposed the now well-accepted explanation of the spinal cord after-discharge phenomenon as the consequence of reverberation or long circuiting in the central nervous system of an afferent impulse after the original stimulus had ceased. Forbes, Cobb and Cattell found that spinal cord transection resulted in a great reduction in after-discharge, presumably as a result of *physical* curtailment of the reflex circuits (20). In studying the effect of various anesthetic agents on after-discharge, McDonough, Forbes and I found that barbiturates, in contrast to ether, affected after-discharge like spinal cord transection (21). Barbiturates reduced after-discharge and, by inference, the internuncial spread of afferent stimuli by *pharmacologic* curtailment. That the action of barbiturates on the brain itself is in part a depression of the internuncial spread of impulses is suggested by other recent evidence (22, 23). The barbiturates can be thought of as producing a temporary reversible lobotomy, a sort of pharmacologic lobotomy, a reversible depression of the internuncial spread of pain impulses perhaps between the thalamus and the cortex. In 50 per cent of our subjects tested, pentobarbital would seem to have prevented or satisfactorily reduced the conscious perception of the psychic modification or emotional associations of pain stimuli, and prevented suffering. How do these observations of experimental pain fit into an effort to describe how consciousness of pain is produced? They offer a theory that pain depends on the functioning of association. We are testing this by determining whether one can generalize that these agents which cut down association paths also cut down pain.

It is not to be concluded from the observations made here that barbiturates alone can be substituted for morphine in the routine care of postoperative patients. Even when given intravenously to our selected groups, the degree, frequency and duration of analgesia were significantly less than with morphine, and the hypnosis was greater. Undoubtedly, in certain patients pentobarbital alone can be used to treat pain; in others it can be used advantageously as a supplement to a small dose of narcotic, and increased comfort achieved. The significant observation is that half of our subjects while under the effects of pento-

barbital either did not experience what is commonly called pain or were not made uncomfortable by it.

It is hoped that the implications of these observations on the mechanisms of pain and pain relief and the mode of action of barbiturates will stimulate further inquiry.

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