EVALUATION OF ANALGESIC DRUGS WITH SPECIAL REFERENCE TO SUBJECTIVE RESPONSES*

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INTRODUCTION

THE EXPERIENCE of pain, like other sensations, is a composite phenomenon. It must involve at least the stimulation of receptors, the transmission of this stimulation to the control nervous system, and the integration of the pain impulses in the CNS with other impulses to produce the response of the organism. Clearly, then, there are several places at which one might interfere with the pain experience. One might prevent the stimulation of receptors by avoiding the stimulus or preventing the response of the receptors, or one might interfere with the transmission of pain or its integration at various levels. Such measures as local anaesthesia, nerve or cord sections, or frontal lobotomies (9) have been used to remove an unbearable pain experience.

Furthermore, as every anaesthetist knows, the total experience of pain is affected by the past experience and training of the organism. Some patients report little or no pain with procedures identical with those producing an unbearable experience in others. In a study of unnarcotized wounded in the last war, Beecher *et al.* (1) could find no correlation between pain and the severity of the wound.

Hill and co-workers (15-18) in a series of papers have shown that, both in man and in animals, anxiety over the anticipation of pain is an important part of the pain experience and leads to disruption of organized behaviour. Furthermore, it is well known that emotion can obviate or intensify the reaction to pain. For example, Isbell (19) has shown that emotional disturbance of post-addicts at Lexington (produced by unexpected searches etc.) prevented or even reversed in some cases the usual action of morphine on pain threshold.

Clearly then, the pain experience may be modified by training or conditioning of the organism in the past or by social or environmental events in the present.

Therefore, when one comes to analyse the action of drugs which modify the pain experience, it is necessary to consider possible effects on many sites: on the pain receptors, on the transmission paths, on the integration of pain with impulses set up by other stimuli at various levels of the central nervous system, on the process of stimulation of other impulses by agents in the internal or external environment, on the past training of the organism in integrating such sensations.

EVALUATION OF ANALGESICS USING EXPERIMENTAL PAIN THRESHOLDS AND PROPOSED MECHANISM OF DRUG ACTION

The situation seems to have become confused owing to rigid adherence to an artificial classification of the possible sites of drug action. Hardy, Wolff and

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their co-workers (13, 14, 30) proposed that analgesic drugs (e.g., acetyl salicylic acid) act primarily by raising the "pain threshold" while others (e.g., opiates) act not only by this mechanism, but also by decreasing pain intensity and by decreasing the "reaction to pain." In the case of opiates, they add "the promotion of sleep" as part of their analgesic action Beecher (3) in studies on clinical pain has emphasized the dichotomy between pain sensation and responses to pain to an even greater degree, though he denies that Hardy *et al* (7) have succeeded in separating threshold for sensation from reaction.

When one attempts to give a material meaning to these proposed mechanisms, some difficulties arise. What threshold is elevated—that of the pain receptors, or of some synapse along the transmission path or of some integrating centre? Further, where does the sensation of pain cease and the reaction to pain begin? (In other words, are our reactions to pain, such as reflex withdrawal or muscle spasm or vocalization, a part of the painful experience?) Is there any interaction between the "sensation" and the "response" or the "anticipation"? (Judging from Isbell's work, repeated painful responses lead to anxiety and to alteration in subsequent painful experiences) What does sleep do? Does it raise the pain threshold or alter response to pain? Despite this lack of precision as to the meaning of the dichotomy, Hardy *et al* (12) have claimed that their radiant heat technique yields effects on the sensation of pain more or less independent of the reaction to it Beecher *et al.* (2, 3) on the other hand, believe that their studies on clinical pain are mainly concerned with reaction to pain

To begin to straighten out the existing confusion, it seems necessary to go back and re-examine briefly the experimental evidence on which the separation of the sensation of pain from the response to it was based

Hardy, Wolff and collaborators developed a system using radiant heat to produce repeatable physical changes on the forehead, leading to pain They showed, using themselves as subjects, that a threshold to this pain could be repeatedly determined with minimal variation on the same day There was considerable variation from subject to subject and in the same subject from day to day. However, they found that using a more or less standardized procedure acetyl salicylic acid derivatives raised the "pain threshold" some 30–60 per cent, and that narcotics like morphine could elevate the "threshold" over 100 per cent.

How did they know that this was a change in the sensation of rather than the response to pain? They took as a measure of the reaction to pain, the electrodermal response to the pain (a change in skin resistance) This, in contrast to the pain threshold, they found to be variable and affected by emotional states, fatigue, etc This response was much reduced by opiates, but not by salicylates, even though these also elevated the pain threshold

Several questions immediately come to mind

1. Since the determination of pain threshold was subjective, what role does suggestion play? In other words, what is the response if the subject does not know the nature of the drug? In other studies, conducted by techniques which permit evaluation of the role of suggestion (use of placebos, double blind technique), no consistent elevation of pain thresholds by ASA type analgesics compared to placebos could be demonstrated (26) while elevations produced by opiates (26, 19) were much less marked. Subjective responses therefore are

influenced by suggestions (e.g. from taking of a drug) that pain will be reduced and the occurrence of marked pain relief or elevation of threshold in response to placebos bears this out

Hardy, Wolff and collaborators (14, 32) answered this objection by the claim that only trained subjects can determine thresholds and discriminate between drugs and placebos. In our own laboratory, using two different methods of determining pain threshold (deep pain from a pressure cuff on the lower leg and periosteal pain by point pressure on the forehead (8)), we have confirmed previous failures to find consistent differences between drugs and placebo effects on "threshold" with ASA type compounds and found a significant but minor elevation of 15 per cent only in the case of meperidine. Furthermore, training of some of the subjects over an entire summer did not improve their ability to discriminate between drug and placebo or did not reduce remarkably the variation from various sources in their threshold determinations. Such results leave doubt as to how the relief of pain by drugs clinically in a wide variety of individuals is related to a situation in which change in the pain sensation cannot be consistently demonstrated in the trained subject. Are we to conclude that the only effect of acetyl salicylic acid is that of a more or less expensive placebo, or that our methods are as yet inadequate? Even in the case of narcotics, where significant elevations over placebo thresholds have been found (8, 26), though not invariably (7), there is no proof that the subjects may not have learned to distinguish drug from placebo by some action other than that of pain sensation. For example, in our study a large fraction of the students receiving meperidine reported feeling nausea, or drowsiness, or some other drug effect, not reported with ASA compounds or placebos. In a careful study of this problem, Lasagna *et al* (21) have shown that narcotics do produce marked subjective dysphoria (not euphoria) in normal healthy individuals. There seems to be a distinct possibility that a subject might learn to recognize mood changes or other effects from opiates and by suggestion and conditioning respond by elevating their pain threshold. Lasagna showed that individuals with such training, post-addicts, could recognize quite small doses of opiates.

2 To what extent is it permissible to compare drug effects in the test situation to conditions under which pain is actually experienced? In most methods of measuring pain threshold, there is no anxiety or fear of consequences. The subject knows that the pain will produce no permanent damage, that it is not the harbinger of medical bills or of postoperative complications, and further that it will be over shortly or can be terminated at will. Furthermore, as previously mentioned, Hill and co-workers (18, 15) have shown that anxiety about anticipated pain can be conditioned in men and animals and become so strong as to disrupt purposeful behaviour. Opiates markedly reduced this response to anticipated pain. These same workers have also shown (17) that painful electric shocks are overestimated when compared to standard shocks by anxious individuals, and that morphine eliminates this effect of anxiety. In reassured individuals such errors are not made, and morphine has no effect. Since emotional and environmental factors certainly influence the pain experience, it seems doubtful that results from experimental study can be transferred to clinical pain.

3. Is the electrodermal response an adequate index of the "response to pain"? Hardy *et al.* (12) have maintained that prevention of changes in skin resistance after narcotics was evidence of the marked action of narcotics in the "response to pain." Wikler (27) has summarized evidence which casts doubt on this view: the electrodermal response is markedly affected by barbiturates which are not analgesics, after hypnosis or frontal lobotomy, which relieve pain, various "responses to pain" may be unaffected or intensified. Wikler states (p. 443) "that neither effects on pain threshold, nor effects on measurable physiologic responses to painful stimuli are highly reliable indicators of analgesia."

As a result of these divergent results and opinions it is not possible at the present time to give any accurate statement as to the mechanism or site of action of analgesic effects of opiates or other agents such as that proposed by Hardy *et al.* (30). A useful postulate might be that analgesics interfere with the conditioned responses to anticipated pain and relieve many of the anxieties and responses associated with pain as a result of direct actions on the CNS or on conditioned responses. In any case, it seems unwarranted at this time to dissociate the pain experience into cognition of the sensation and reaction to that cognition, and attempts to do so without recognizing the possibility of their mutual interaction seem to oversimplify the experience.

This, of course, raises the question of the validity of all results based on such an attempted dissociation. Wikler (28) in an attempt to resolve conceptual difficulties stresses the operational approach in which effects of analgesic drugs have meaning only in relation to the method of measurement used. He points out that the process of measurement necessarily involves modification of that which is to be explained for purposes of control and quantification. For example, one must bring the subject into a test situation in either the laboratory or the hospital to evaluate analgesics, but the apparatus or questioning may alter the response of the subject. However, Wikler does not draw what seem the obvious conclusions, namely, that the effects of various factors in the method of evaluation should be studied, and that until such study is complete the most reliable method would be that most closely corresponding to the conditions under which analgesics will be used.

EVALUATION OF ANALGESICS USING CLINICAL PAIN

With these as well as the previous considerations in mind, Beecher and his group in Boston (3, 25) developed a method for the evaluation of analgesics under the actual conditions in which most postoperative pain occurs in patients.

They have laid down careful methods for guaranteeing that such evaluations will show clearly the pain-relieving effects of drugs under clinical conditions. Their methods involve the administration of drugs to patients, and the evaluation by the patient, as well as an objective valuation of their effect in relieving pain. The following were features to guarantee correct evaluation.

- (a) the use of postoperative patients who fulfilled the following conditions:
 - (1) had sufficient trauma to warrant persistent postoperative pain,
 - (2) showed no contra-indications to morphine;

- (3) could give reliable information as to pain relief,
- (4) were not in precarious condition, so that there was no risk from placebos, etc.
- (b) the use of the double-blind technique in determining drug effects, by which
 - (1) the placebos were made similar in every possible way to the drug(s) studied,
 - (2) neither the patient nor the recording technician knew the agent administered,
 - (3) neither the patient nor technicians had the opportunity to learn to identify drugs by other effects;
- (c) the use of the method of concurrent comparison in which
 - (1) agents (drugs, placebos) to be compared are given to the same patient, in so far as possible, in order to control variation between patients,
 - (2) agents to be compared are given in random order so that variation in pain intensity between patients and between various intervals in the same patient can be controlled.

They have used this method extensively to study the curve for the dose effect of sub-cutaneous morphine (7, 25) With a placebo, 50 per cent of patients are relieved With 5 mgm of morphine 61 per cent; 8 mgm. 74 per cent; 10 mgm 74 per cent, 12 mgm. 71 per cent; 15 mgm 83 per cent In subsequent studies (20) they have not always found the effect of 15 mgm. ($\frac{1}{4}$ grain) to be significantly better than that of 8-10 mgm. and present evidence that the higher dose causes more disagreeable side effects, at least in normal individuals (Side effects cannot be evaluated in postoperative patients because of difficulty in differentiating them from effects of surgery and anaesthesia.) The dose effect curve of morphine requires further study, but results so far indicate that a maximal effect may be achieved at 10-15 mgm of morphine, but that some patients will not be relieved by these doses.

They have been unable to demonstrate any greater effect from oral codeine (60 mgm.) or morphine (10 mgm.) than from a placebo (6) Large doses of acetyl salicylic acid (600 mgm.) did produce slight but significant effects. Elimination of placebo reactors from the data gave some indication that oral codeine and morphine were analgesic

They have studied the placebo response and report that patients who consistently respond to placebo can be characterized by psychological tests, especially the Rorschach test, and by their reaction to the hospital situation They tended to minimize their pain and when questioned thought that their care was excellent. They tended to be talkers, to be less educated and more religious. According to the authors, Rorschach tests indicated that placebo reactors were more responsive, anxious, self-centred and preoccupied with internal body processes, and more emotionally labile. They were more dependent on outside sources of stimulant than on their own mental processes, which were less mature. They had greater instinctual needs and had less developed regulation of the social ex-

pression of these instincts. They relieved their greater anxiety through their lability and outward orientation (e.g., talking).

However, it should be pointed out that there was a larger group of patients who sometimes responded to a placebo. This group also occurred in our own series of medical students. No attempt has yet been made to elucidate the nature of the factors controlling occasional placebo responses.

In line with their findings on the variation in subjective response to placebos, this group has studied the effects of morphine, heroin, amphetamine etc. on mood in normal students, in a group of clinically ill patients, and in post-addicts at Lexington. According to their findings it is only in post-addicts that opiates produce euphoria regularly. In the other groups, they most frequently caused dysphoria and unpleasant side effects. A minority of individuals experienced euphoria, but again these could be characterized by psychological testing as deviants.

PRACTICAL IMPLICATIONS FOR ANAESTHESIA

Beecher believes (3) that the effects he finds are primarily on reaction to pain. Actually if elevation of pain threshold in experimental studies is made equivalent with pain relief clinically, there is little disagreement as to qualities of drug effect provided only adequately controlled studies are considered. Both studies yield evidence of marked analgesia independent of suggestion only if opiates and related synthetic drugs are used. The magnitude of the effects seems greater under clinical conditions and some experimental methods do not distinguish them regularly (7). Irrespective of one's opinion as to whether it was the effects of drugs on pain sensation, pain response, or on the whole experience which were studied by Beecher's group, these results have practical implications.

Postoperative Pain

1 *The dose of morphine* Beecher's groups have presented evidence that 8–10 mgm of morphine provides pain relief equal or nearly equal to that of 15 mgm. (ca $\frac{1}{4}$ grain) of morphine, with a smaller incidence of disagreeable side effects.

Tradition has established $\frac{1}{4}$ grain of morphine for the first trial at pain relief. No doubt it is effective in most cases, but would it not be worthwhile to try to determine precisely if equal therapeutic effects can be achieved with a smaller dose? The question requires further study and cannot be answered by dogmatic statement. However, if a large number of patients are effectively relieved by 8–10 mgm. of morphine, then there are good reasons for trying it. The incidence of addiction is dependent on and directly related to the total dose injected. The incidence of side effects is similarly related to the dose injected. At the present time it would seem reasonable to try 10 mgm of morphine initially. In most cases, it should be effective.

2. *The dose effect curve of morphine.* Beecher's group (20) has presented evidence that among postoperative patients there are some who are not relieved by 10 mgm of morphine or any larger dose. This raises the practical question:

Is there a plateau in the dose response curve so that beyond a given dose no further therapeutic effect can be achieved and the possibility of severe depression is enhanced? Clearly this would not completely agree with the old dictum that the dose must be titrated to the patient. The character of the dose effect curve needs further elucidation in patients being treated for pathological pain

3 *The placebo reactor* Lasagna (22) claims there is such a thing as the small minority of consistent placebo reactors with a definite psychological make-up. If so, lacking a simple means of identifying the reactor in advance, there seems to be little possibility of practical utilization of the fact. If, however, as our data as well as theirs tend to indicate, placebo reaction is an inconsistent response of many individuals to drug therapy, then the environmental factors which tend to promote a favourable placebo reaction should be further studied. Placebo reaction might be used to support the actual therapeutic effect of drugs if conditions for its occurrence were properly understood

In any case, the fact that placebo reactions do occur should serve as a further reminder that pharmacological effects of drugs per se are not responsible for many of the effects observed in clinical practice. Sir Thomas Lewis (23) has already pointed out that often medical practitioners tend to delude themselves in this regard. He states: "Every student [and he should include us all] should be convinced through both precept and example of the fallacy of the post ergo propter typē of argument" "It is unreasonable," he continues, "that any medical graduate should be ready to believe that any improvement witnessed in a patient under their care is necessarily the result of remedies given. Such men become too easily the dupes of those who trade in proprietary remedies, or of their own too quickly gathering confidence. If, after a remedy is prescribed, one patient improves and another becomes worse, there is on this evidence no more reason to ascribe the first than the second change to the remedy, but exceedingly few qualified men know this"

What placebo reaction implies is that it is not permissible to ascribe automatically the beneficial effects of a remedy to its pharmacological prowess, since suggestion (a placebo) can often produce the same effects. The occurrence of marked effects from placebos, especially when subjective effects are sought, should serve to remind us again that, in every therapeutic effort, the response of the organism is an important, more or less independent element in any effect that may be obtained in the conscious patient. The study and rational use of this response may be of great value in the relief of pain or the treatment of disease and certainly will aid in dispelling faith in quacks and their remedies

Pre-Anaesthetic Medication

Another point that seems to require re-examination is the basis for the use of narcotic analgesics in pre-anaesthetic medication. Lasagna (21) has shown that in normal individuals, i.e. not in pain and not post-addicts, morphine, heroin, etc. cause dysphoria rather than euphoria. What essential role, then, does morphine fill in pre-anaesthetic medication? Beecher (5), on the basis of Lasagna's work, has suggested that nothing desirable is added to pre-anaesthetic medication by morphine, and that there may be a greater risk of CO₂ accumulation and other

effects of its depressant actions. He summarizes, but has not yet reported fully, evidence that, using the double blind technique in 558 patients, experienced anaesthetists could tell when a narcotic had been given with the usual pre-anaesthetic medication only about 54 per cent of the time. Guessing should have done as well. He also states that there is little valid evidence for claims that a pre-anaesthetic narcotic reduces the dose of anaesthetic required to produce a given level of anaesthesia.

Certainly this problem requires careful direct examination by the methods permitting correct evaluation of subjective effects which have been previously mentioned. However, it does not seem scientifically correct to extrapolate from Lasagna's students to the anxious patient facing operation. Therefore, before any conclusions can be drawn, a study must be made of the effects in such patients of morphine vs. a placebo on the mood, on the ease of induction, on the dose of anaesthetic required for a given plane of anaesthesia, on respiratory exchange in the patient, etc.

The work of Hill and co-workers (18) has already clearly shown that morphine prevents the behaviour-disrupting effect of anxiety in post-addicts. If anxiety does affect any of the significant variables influencing rapidity, ease, and safety of anaesthesia, then morphine might be expected to remove this effect. Whether the prevention of anxiety by morphine is entirely beneficial or whether it can be provided equally well by adequate sedation with a barbiturate is a question requiring study rather than speculation.

CONCLUSION

Some of our cherished concepts may be modified as our understanding of the mechanisms whereby drugs alter subjective phenomena grows. However, cherished concepts are less valuable than the knowledge which permits maximum use of all possible therapeutic tools. We seem to be approaching a day when the study of some drug responses in patients, though difficult, will be widely recognized as necessary, wherever it is possible, because such study provides information which cannot be obtained in any other way. Significantly it is an anaesthetist who is showing that studies in human patients do yield reliable and new information. Furthermore, if this field is like others, re-examination of concepts because of their inadequacy in practice will have value beyond the immediate range of the practical problems which initiated the reappraisal.

RÉSUMÉ

On a mentionné les endroits où les drogues peuvent influencer la conduction de la douleur. À part l'effet bien connu des drogues sur les récepteurs, sur les voies de transmission, sur l'intégration à différents niveaux, on a insisté sur la possibilité des effets sur le conditionnement antérieur et l'intégration des stimuli environnants.

On a fait chez des humains des études sur la douleur expérimentale, puis devant des conclusions contradictoires et prêtant à confusion, on a repris l'étude du concept voulant que les opiacés agissent en élevant le seuil de la douleur, en diminuant les réponses à la douleur et en produisant le sommeil. On a mis en

évidence le rôle de la suggestion et de l'aptitude à identifier les analgésiques par leurs autres effets pharmacologiques causant une élévation de seuil de la douleur expérimentale. On a cité des expériences où, à l'aide de contrôles personnels, on a démontré que des analgésiques puissants n'avaient que peu ou pas d'effet sur le seuil de la douleur. On a pu démontrer, en plus, que les études expérimentales sont incapables de renseigner sur les effets possibles d'une drogue sur l'anxiété et/ou sur plusieurs réponses à une expérience clinique sur la douleur.

On a résumé le travail de Beecher, Lasagna et leurs associés de Boston; pour étudier les effets analgésiques, ces auteurs ont employé le soulagement de la douleur clinique, pathologique. On a décrit les modes de contrôle employés par ce groupe (les placebos, la technique doublement aveugle, la comparaison concomitante, etc.) On a mentionné et discuté quelques-uns de leurs résultats dont les suivants, à savoir.

- (a) que la dose optima pour la morphine est 8-10 mgm. plutôt que 15 mgm
- (b) que les malades non soulagés par de petites doses de morphine pourraient bien ne pas l'être par de plus fortes doses
- (c) que les placebos sont des analgésiques puissants mais que leur efficacité en cette matière dépend de l'état psychique du patient et de certains autres facteurs inconnus
- (d) que les narcotiques pourraient ne jouer aucun rôle essentiel dans la médication préanesthésique

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