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9. PAIN MEASUREMENT

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Pain is the perception of noxious sensation. Its measurement is confounded, therefore, by the act of perception. In the manner of love, hate, or anger, it is an intensely personal experience that defies ready communication. As a cognitive process, pain may be described by language, and a sophisticated lexicon has been developed to achieve this. Such description does not measure pain, however, only the opinion one has regarding its perception. The map is not the territory.

The definition of *pain* according to the International Association for the Study of Pain (IASP) is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage and described in terms of such damage." This comes close to providing the rules for such language, but falls short of providing the operational rules for pain's measurement.

As a "perception," pain does not bear a direct relationship to the intensity of the noxious stimulus that elicits it. The individual perceiving the pain does so from within a psychological set that incorporates the experiential background and contextual emotionality of the perception.

Both set and setting influence the act of perception. It is reasonable to suppose that perception of an acute pain administered to a healthy experimental research subject differs in terms of imputed "meaning" from that perceived as a result of injury in an otherwise healthy individual, which also differs from that experienced by the chronic pain sufferer. The emotional import of the pain is inextricably woven into the fabric of the overall perception. As a per-

ception, then, pain cannot be separated from its experiential matrix. In the mind's eye, it is viewed through the lens of experience, projected onto a screen composed of our judgement of its significance.

In attempting to measure pain in humans, the clinical scientist must first decide from which viewpoint he or she will observe the phenomenon. As in the case of the blind men describing the elephant, no one viewpoint can provide a complete view of the phenomenon, yet it is necessary to select a viewpoint in order to avoid syncretism.

The phenomenology of pain resides exclusively within the domain of the nervous system. On the afferent arm of the phenomenon lies *nociception*, the sensory detection of dangerously intense stimuli. It is generally agreed by biologists that nonverbal, infrahuman, species experience nociception. Nociception engenders reflex *behaviors*, and these are measurable: They can be observed. The unicellular paramecia experience nociception; they move away from a noxious stimulus — we call this phobotaxis. Paramecia do not call it anything. In humans, and only in humans, is the *perception* of nociception called pain. This is the behaviorist's dilemma. We cannot *know* whether nonverbal species experience pain as we do. We cannot know, that is, whether they "perceive."

This chapter is about the measurement of pain. It deals, therefore, with the human experience.

In common with nonverbal species, the human pain sufferer, in detecting the nociceptive stimulus, undergoes *physiological* changes, both on the afferent arm of the sensory detection experience and within the central nervous system (CNS) and its efferent limbs. These changes occur at the spinal and autonomic levels of nervous system organization. They manifest as *reflex behaviors*, and they can be observed and measured.

In attempting to measure this phenomenon in our fellow humans, however, we naturally rely on language. This is reasonable: Language is the operational difference between nociception and pain. Underlying the outward manifestations of behavior lie the neurophysiological correlates of perception. Underlying these are the biochemical bases of nerve function. Each is accessible to measurement.

BEHAVIOR

At the behavioral level, pain is manifest to the observer through the *voluntary* behaviors of language and of motor activity, and through the *involuntary* behaviors that are both specific to pain and general to suffering. These are the characteristic guarding, facial expression, and body postures of the pain-suffering individual. The expression of organized locomotor activity is affected also, with guarded gait, restriction of movement, and both the acquisition of certain pain-related behaviors (such as taking medication) and the extinction of normal movements. Such behaviors may represent strategies for both *pain relief* and *analgesia*, but a distinction between these must be made [1–3].

Pain relief is the process by which the perceived intensity of an ongoing pain is attenuated. Analgesia (more correctly, hypalgesia, but we shall follow the convention and use the term *analgesia*) is the state whereby sensibility to noxious stimulation is diminished. Analgesia can only be measured by the application of an external noxious stimulus, and it makes its presence known by a reduction in perceived noxiousness [4]. In the context of the modification of movements by the pain state, then, these modifications may serve the purpose of relieving the perceived intensity of a pain or of avoiding nociceptive stimulation.

BEHAVIORAL ASSESSMENT INSTRUMENTS

Behavioral assessment of pain is conducted at the verbal and nonverbal levels. At the verbal level, the information that is captured is the patient's self-report of the applicable language of pain. Instruments for its capture range from simple unidimensional measures to complex instruments that attempt to capture opinions of (or poll) more than one dimension of the pain experience. So much reliance is placed on these instruments, and their veracity, accuracy, reproducibility, and internal and external validity — described below — that it is sobering to remember that they are no more veridical than the patient's own descriptive choice of language. To make this obvious point more forcefully, if the patient were lying we could not detect this.

UNIDIMENSIONAL VERBAL DESCRIPTOR AND CATEGORY SCALES

Verbal rating scales

The simplest method of obtaining information on the patient's perceived pain intensity is to ask. Typically, the patient is asked to choose a number between zero and 100 that "best describes the intensity of their pain." This method, which has been termed the *101 point numerical rating scale* or NRS-101, is fraught with difficulty. The voice, tone, facial expression, and demeanor of the questioner are inevitably communicated to patients and influences their opinions. This face-to-face method is so capable of engendering bias that it has been used by investigators studying the placebo response as a means of provoking the subliminal expectation of pain relief [5].

Visual analog scales

In an attempt to place distance between the conscious or unconscious expectations of the questioner and the response of the patient, printed questionnaires are commonly preferred. A printed form of the NRS-101 has, for instance, been used. The visual analog scale (VAS) is another simple questionnaire method. A 10 cm line is printed having two extreme descriptors at either end, thus:

NO PAIN ——————————————————— MAXIMUM POSSIBLE PAIN

The VAS may also be interrupted by index lines, thus:

NO PAIN ---+---+---+---+---+---+---+---+--- MAXIMUM POSSIBLE PAIN

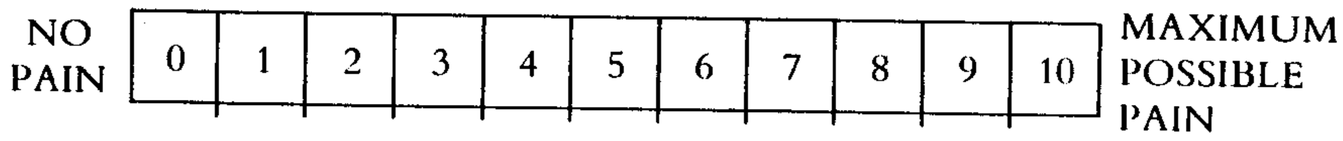
The subject is asked to rate the intensity of his or her pain by marking the line at some appropriate distance along its length. The marked line is then removed from the patient's sight so that it does not influence the scoring of subsequent presentations of the VAS, which may be at hourly or shorter intervals. For simplicity, some investigators use measurements of the reciprocal of the VAS for "pain intensity" as a "pain relief" scale in the assessment of pain-relieving and analgesic effects of drugs. Within certain limitations, the VAS is a reliable way of polling opinion on a unidimensional axis, and it has the advantage of being quick and easy to do, is easily understood by the patient, is readily scored by measuring the distance of the patient's mark along the line, and has been validated against other polling methods [6–10].

Limitations of analog methods

Apart from the obvious limitation that pain is not an unidimensional experience, and from the consequences of representing the pain experience as an ordinal continuum when it is not, the VAS methods suffer from peculiar disadvantages. Patients vary in their predilection toward "clumping" and "splitting" of their responses. Chronic pain patients tend to use only the right-hand side of the VAS, whereas cancer patients may use both ends and make relatively little use of the middle. The instructions given to the patient are also critical. There are additional problems with the way in which the VAS may be analyzed. One patient's "7.5 cm" may be another patient's "4.0 cm." These scores are not ordinal numbers, each patient's pain dimension is his or her own, and it is incorrect to treat different patients' scores as co-ordinal, by, for instance, averaging them. The precision with which the line can be measured also tends to give a false impression of precision to the VAS's meaning. There is, in addition, a tendency among investigators to treat the data so acquired as an ordinal scale subject to analysis by parametric statistics. This is clearly wrong. A more honest, and yet still uncertain, method of treating such data is to normalize it relative to each patient's own response range. The data are thus trnasformed to a ratio scale that can be analyzed by nonparametric methods.

Category scales

Whereas the NRS-101 and the VAS methods purport to represent pain as an undivided continuum, category scales seek to limit the patient's response to one of several predetermined choices in a single dimension. A numerical category scale is the simplest form, such as the category version of the VAS called the 11 point box scale (BS-11) [8]:



The majority of category scales permit the patient to choose from among a ranked list of verbal descriptors, the accepted meanings of which punctuate the range of the dimension that they describe and delimit. Category scales are used to poll patients' reports of pain relief (having elements of: NONE, A LITTLE, SOME, A LOT, COMPLETE), of pain intensity (e.g., NONE, A LITTLE, SOME, A LOT, TERRIBLE), or of the emotional aspects of pain [11].

Category scales have entered widespread use in the assessment of pain and pain-relief therapies. In use, the patient marks the category that best describes his or her opinion of the dimension being measured. This rating is repeated at intervals of time. Each category is assigned a numerical value by the investigator (e.g., NONE = 0, A LITTLE = 1, etc.), and the numerical sum of each time interval's category score is obtained for the entire measuring period. When used with a "pain relief" scale, this has been called the total pain relief (TOTPAR) score. Such a method, using a five-category pain relief scale (NONE, SLEIGHT, MODERATE, LOTS, and COMPLETE) has been used by Wallenstein, et al. [12] to compare the analgesic efficacy of Zomepirac® and morphine. These same investigators report that in a large population of cancer patients, this category scale is sensitive enough to detect dosage, age, and ethnic differences in response to morphine administration.

Category scales do not necessarily have to be limited to ranked scales of words or numbers. Frank et al. [13] used eight "cartoon faces" drawn to represent a ranked continuum of facial expressions representing the range extending from tears and misery to smiles and laughter. They found good correlation between patients' cartoon choices and their VAS and verbal descriptor scale responses.

Limitations of category methods

As with the analog scales described above, problems surround the validity of quantified category scales. The assignment of equally spaced integers to a rank order of verbal descriptors gives the appearance of an ordinal distribution that is, in fact, not real. Since the numerical assignments are ranked, they are perhaps more ordinal than nominal, yet the ordinal distribution is unknown. The "distances," that is, between the word-values, are unknown. Consider, for instance, the series of pain intensity scores such as 4,2,2,1,0, which may represent the opinion of a patient who starts out with "terrible" pain and who responds to the administration of morphine by recording "some," "some," "a little," and then "none" at 15-minute intervals. It is invalid to state that the patient's average pain intensity is "1.8," there is no such rank as 1.8. Heft and Parker [14] have shown experimentally that commonly used pain descriptors

are unequally spaced along the intensity continuum. They propose that category scale quantification should reflect this with a weighting scale that corrects for unequal spacing. This argument has merit.

MULTIDIMENSIONAL REPORT SCALES

Insofar as unidimensional pain scales represent the overall intensity of pain as existing on a single axis, these methods fail to describe its qualities.

A number of questionnaires have been devised that attempt to give respondents a range of qualitative dimensions over which to describe their perceived pain. Such instruments are particularly useful in polling the opinions of the chronic pain patient over time and in response to treatment. In substance, multidimensional questionnaires are made up of batteries of analog and category scales, completed at a single time. Several of these instruments have been reviewed recently by Chapman and Syrjala [15], the most well known of which are perhaps the McGill Pain Questionnaire (MPQ) devised by Melzack [16] and the Wisconsin Brief Pain Inventory [17].

The Memorial Pain Assessment Card

The Memorial Pain Assessment Card (MPAC) [18] is the simplest of the multidimensional assessment tools. It is a single sheet of paper containing a battery of three visual analog scales (for pain intensity, pain relief, and mood), and a set of eight adjectives describing pain intensity (no pain, just noticeable, mild, severe, etc.), which the respondents mark to indicate their perceived pain status at the moment of completing the test. The test takes seconds to complete and the questionnaire is arranged in such a way that it can be folded, so that respondents can see only one scale at a time. The MPAC — and similar scales of this type — are ideal for the assessment of pain relief following analgesic drug administration or other therapies. It has the advantages of the unidimensional VAS methods, including simplicity and ease of use, with the added benefit that more than one dimension is polled.

The McGill Pain Questionnaire (MPQ)

This questionnaire attempts to poll the report of three dimensions of the pain experience: sensory, affective, and evaluative [16]. There are four parts to the MPQ. In the first part, the patient is asked to mark a picture of the human form so as to indicate the location of pain and whether it is external or internal. In the second part, the patient is presented with 20 sets of adjectives, each set composed of a ranked list of words in increasing order of severity (e.g., pinching, pressing, gnawing, cramping, crushing). The most appropriate single word in each set is to be circled. Ten of the sets describe sensory qualities of the pain, and five describe affective qualities. One set, referred to as "evaluative," lists "annoying, troublesome, miserable, intense, and unbearable." Four additional sets described as "miscellaneous" are primarily sensorial in nature. The third part of the MPQ polls the patient's opinion regarding what

factors exacerbate or relieve his or her pain. Three sets of related words are provided from which the patient chooses to describe the temporal qualities of his or her pain (continuous, rhythmic, transient, etc.). The fourth part of the MPQ provides the patient with a ranked list of five pain intensity descriptors, category choices from which to answer six questions regarding his or her pain history.

Arising from the work of Melzack and Torgerson [11], the MPQ has been subjected to widespread application and testing in a variety of clinical pain states. To quantify its responses, the investigator scores the ranked adjectives and computes the total rank of chosen words, either as a global total or as a total within each dimension. Factor analysis studies of the responses to the MPQ tend to support the dimensional assignments of descriptors [19,20] and for the grouping of words into semantically homogenous sets [21], although there is evidence that the scaling of ranks within sets might differ across different groups of pain patients [19].

Unique patterns of MPQ responses have been associated with different types of chronic pain state, including those of arthritis, cancer pain, and low back pain [21–23]. Despite its widespread application in chronic pain assessment and of pain relief, the MPQ is time consuming to perform (about 15 minutes) and does not readily lend itself to the assessment of analgesic drug effects, where measurements must be polled at 10- or 15-minute intervals. Perhaps its most serious drawback is its requirement that the respondent possess a fairly sophisticated vocabulary.

The Wisconsin Brief Pain Inventory

The Wisconsin Brief Pain Inventory (BPI) is a multidimensional pain measure, the reliability and validity of which has been demonstrated in the assessment of pain of various types. These include the pain of cancer, chronic orthopedic pain, and arthritis pain [17,24]. It has also been used to assess procedural pain [25]. Using a scale of 0–10, patients report on the intensity of their pain as they perceived it at its worst, least, and average during the preceding week, as well as at the time they are filling out the questionnaire. They report on analgesic medications and pain relief obtained, qualitative descriptions of pain, location of pain, and areas of interference with quality of life. When the questionnaires were applied cross-culturally, cancer patients in Wisconsin and (using a Vietnamese translation) in Vietnam demonstrated comparable factor loadings in their patterns of response in the "pain severity" and "pain interference" scales of this instrument. The utility of the BPI thus appears to generalize across cultural and linguistic barriers [26].

West Haven-Yale Multidimensional Pain Inventory (WHYMPI)

Introduced by Kerns, Turk, and Rudy [27] as a briefer alternative to the MPQ, the WHYMPI is more well founded in classical psychological theory, with a strong cognitive-behavioral orientation. It is principally designed to assess

self-reported behaviors relevant to the chronic pain population. It is a 52-item questionnaire, and is arranged in three parts comprised of 12 scales. The first assesses the impact of pain on the patient's life, the second assesses the patient's opinions regarding the responses of others to the patient's communications of pain. The third scale polls the opinion of the patient regarding the extent to which he or she participates in the activities of daily living.

Because of its cognitive-behavioral orientation, the WHYMPI may be considered a form of behavioral activity self-report, the general limitations of which are considered more fully below. It does not lend itself to the assessment of pain relief or analgesic effects in the acute setting.

ASSESSMENT OF BEHAVIORAL ACTIVITIES

The rather clumsy term *behavioral activities* is used here to denote those nonverbal activities associated with everyday life, such as eating, walking, sleeping, and social interaction, that may be affected by the pain state. The modification of behavioral activities is seen by many investigators as being "more objective" than verbal self-estimates of pain intensity and quality. It is the experience of most investigators in the field, for instance, that many chronic pain patients, unlike acute pain patients [26], misjudge their own pain intensity in relation to its history [28]. In an attempt to capture this report of behavioral activity, investigators either solicit it from the patient themselves (self-report) or rely on external observers. The disadvantage of the former is that self-reports of activity suffer the same inaccuracies and misestimations as do those of pain intensity [29,30]. Despite this major limitation, many investigators poll this information as an estimate of the patient's own opinion of his or her physical disability.

Self-report of behavioral activity

Several of the multidimensional assessment tools cited above, including the WHYMPT and the BPI, include a behavioral dimension by which the patient may score — as a category scale — the extent to which his or her pain state interferes with activity. Thus, on the BPI, patients are asked on the "pain interference" axis the extent to which their pain has influenced their general activity: walking, work, relations with others, and sleep.

Perhaps the simplest category scale for behavioral self-report is the six-item behavior rating scale of Budzynski et al. [31], termed the *BRS-6* by Jensen et al. [32]. It has the elements of:

( ) No pain
( ) Pain present, but can easily be ignored
( ) Pain present, cannot be ignored, but does not interfere with everyday activities
( ) Pain present, cannot be ignored, interferes with concentration

( ) Pain present, cannot be ignored, interferes with all tasks except taking care of basic needs such as toileting and eating
( ) Pain present, cannot be ignored, rest or bedrest required

A major reason for seeking nonverbal assessment of pain behavioral activity is to ascertain the extent of the patient's incapacity when not in the clinic. There is a well-known class of chronic pain patients — many without obvious organic pathology — who tend to overemphasize their reported pain and disability. Measures such as the BPI detect this easily, yet their measurement is compromised thereby [26].

The pain diary

To the extent that such overemphasis is a characteristic of the poor historian rather than the dissimulator, more accurate self-reports can be obtained by the use of a contemporary pain diary. A pain diary is a log of daily activities in which the respondent records, at intervals of 1 hour or less, every day, the amount of time spent sitting, standing, walking, or reclining. It may also be used to record contemporaneously the subjective pain intensity at those times and the medication consumed. The pain diary is extremely useful in chronic pain assessment, yet it will not overcome the problem of dissimulation. Ready et al. [33] have found, for instance, that certain chronic pain patients report medication consumption that is 50–60% below actual consumption. Similarly Kremer [29], who compared patient self-report records with staff observations, found major discrepancies. For this reason, many investigators have sought "objectivity" in behavioral activity assessment by the use of standardized observer reports and automatic motion detection.

OBSERVATIONAL ASSESSMENT OF BEHAVIOR

Immune to self-reporting errors, observational assessment by trained observers detects the objective impact of pain behavior — and to an extent the underlying disease state engendering the pain — on controlled and free responding of the patient.

Controlled behavior

As recently reviewed by Keefe [34], the "specific" behaviors that elicit pain and the behavioral modifications that the pain patient enacts in order to avoid pain, differ among the different pain syndromes. For this reason, several investigators have instituted standardized test situations to exert control over the pain behaviors emitted. These tests have certain common features. Richards [35], who developed the University of Alabama at Birmingham (UAB) Pain Behavior Scale, uses the following simple method: The patient is asked to walk a short distance, stand for a brief time, then transfer to a sitting, and again to a standing position. Trained observers estimate the severity of ten

behaviors characteristic of pain by using a three-point rating scale. Inter-observer reliability is high, 95%, and scores correlate well with self-assessed pain rating at discharge, though not with the MPQ score. A recently revised version of the scale using eight categories has been found to correlate better with the MPQ [36]. Keefe and Block [37] have also used a standardized test situation to elicit controlled behavioral responding. These authors recommend that the sequence in which the tests are carried out be randomized, with the duration of each task held constant to prevent order effects in the study of populations [34]. They report that quantitative indices of pain behaviors in their test subjects (guarding, grimacing, rubbing the painful area, etc.), scored at regular 30-second intervals, provides an accurate measure of low back pain. To the observational measurements of Keefe and Block [37] have been added four additional behavioral categories by Follick, Ahern, and Aberger [38]. These authors report that the four behavioral categories: partial movement, limitation statements, sounds, and position shifts, correctly classified 94% of the patients and 95% of the controls.

Free behavioral responding

Behavioral observations in the natural setting have significant advantages over controlled responding in formal test situations. In general, such methods use the same or similar checklist items to which is added a pain-diary type of dimension, often called the activities of dialy living (ADL). Appropriate only to the in-patient setting, these observations may be conducted by the nursing staff during the course of their daily duties [39]. An earlier study by Cinciripini and Floreen [40] used trained observers to observe patients for 5 minutes in each half-hour throughout a 12- to 15-hour day. The behavioral elements that they scored included nonverbal pain behavior, pain talk, nonpain complaints, pro-health talk, and assertion. They found, as might be expected or hoped, dramatic increases in "well behavior" and reduction in "pain behavior" over the course of treatment.

Particularly in the chronic pain patient population, time spent walking and moving about ("up time") is considered an index of therapeutic progress. It is generally realized, as found by Linton [41], that there is no relationship between activity level and pain intensity report, yet increased "up time", even with no reduction in pain intensity, is a behaviorally desirable therapeutic goal. Since the use of trained observers in an outpatient setting is impractical, several investigators have examined the use of automatic activity monitors to capture this information. Such electromechanical and electronic devices are of various degrees of sophistication. Keefe and Hill [42] have found that chronic pain patients differ from normals in terms of gait parameters as measured by pressure transducers placed in the heels of their shoes. Patients are found to take smaller steps and to have asymmetrical gait. Their method could even distinguish patients receiving disability payments from those not so blessed! The former had a longer stride length. Some success has been obtained with

simpler devices that indiscriminately record "up time" by means of inertial measurement or orientation sensors. In the manner of Keefe and Hills' pressure transducers [42], they are relatively expensive and unsuitable for general outpatient use, however [30,43]. Cheaper methods such as the "actometer," which is a pedometerlike instrument modified from a mechanical watch [44], appear to fail in reliability over time when used in the general pain population, possibly as a result of gait constraints [45]. Automated procedures for gross monitoring of behavioral activity may thus show future promise, but do not currently appear to be applicable to the chronic pain patient — the population in which such measurements are most needed.

As recently reviewed by Keefe [34], specific facial expressions are highly characteristic of the pain experience. Insofar as these are largely unconscious primitive nociceptive primate reflexes, they hold promise for objective quantification of pain's behavioral correlates. A facial action coding system (FACS), developed by Ekman and Friesen [46], has been characterized with normal volunteers undergoing painful electric shock [47]. The original FACS requires that 44 separate action units be extracted from filmed behaviors observed frame by frame. Unsuitable for routine use, a practical alternative may prove to be the Global Rating Method developed by LeResche and Dworkin [48]. Such methods have not yet found their way into clinical pain research.

Pain assessment by monitoring medication requirement

The philosophical differences between *pain relief* and *analgesia* become critical when the medication requirement is used as an index of the underlying pain state. To recapitulate, pain relief is the diminution in perceived intensity of an endogenous pain state, whereas analgesia is the reduction in sensibility to an applied — external or incident — nociceptive stimulus. The measurement of analgesia *requires* the use of an applied nociceptive stimulus. The measurement of pain relief does not; one merely polls the opinion of perceived endogenous pain intensity. Medications can be pain relieving without being analgesic; aspirin in the treatment of inflammatory pain or anticonvulsant drugs used in treatment of the pain of tic douloureux and tabes dorsalis being examples, or tricyclic antidepressants in chronic pain [4,49]. Since the perception of pain is phenomenologically a psychic event, and since the biological substrate of this psychic event is, we believe, neurochemically mediated by endorphinergic and other neurochemical systems [50,51], the mechanism of pain relief engendered by analgesic opiate drugs is quite complex. Indeed, the opiate-abusing addict who is not a pain sufferer — the "street user" — experiences a painful hyperesthesia on drug withdrawal, accompanied by affective changes that can only be described as "psychic pain." Despite the widespread clinical belief that the same does not occur in pain patients, it is biologically impossible to separate the pain-relieving and affective actions of opiate analgesics using the pharmacological agents currently available. One can, however, measure the analgesic effect by means of a nociceptive stimulus and

compare the results so obtained with the patient's subjective report of pain relief. In our own laboratory, we have used a radiant heat stimulus to measure the analgesic effect of standard doses of intravenous and intrathecal morphine on cutaneous pain tolerance in the pain patient [52]. We find major differences in the correlation between pain relief (assessed by VAS) and analgesia (assessed by elevated pain tolerance), depending upon the route of administration of the drug. Intrathecal administration engenders pain relief with, initially, no analgesia (no change in pain tolerance to the radiant heat-beam stimulus), and intravenous administration engenders both simultaneously.

Such measurement has unfortunately not yet become common practice in the clinic. Monitoring of the pain patient's demand for pain-relieving (and analgesic) medications is nevertheless common practice and is used as an index of the severity of the underlying pain state. Despite the limitations of this procedure — drug demand may outlast resolution of the organic basis of the pain and may reflect the avoidance of withdrawal hyperaesthesia — there is a certain usefulness in such measurement.

The advent of the patient-controlled "analgesia" (PCA) pump facilitates the collection of this data. The PCA pump is an automated intravenous infusion device capable of being programmed to deliver a limited quantity of drug (the prescribed maximum) per unit time. Individual doses are administered on a *pro re nata* basis by the patients themselves using a push-button control. There are various types of pumps available. Some emit a tone whenever the patient demands medication, whether or not medication is delivered, some emit a tone only when the delivery takes place. The time of each demand by the patient is recorded, and such records of demand, delivery rate, and cumulative dose form the overall estimate of the patient's perceived need for pain relief and — by reciprocal inference — of his or her underlying pain status.

Given the limitations of such data in the absence of an independent measure of analgesia, the PCA pump has restricted utility in pain research. Clinically it is, however, well tolerated by the patient and, needless to say, by the nursing staff. It is reported that patients using these pumps achieve better pain relief while requiring less pain medication than patients treated in the traditional p.r.n. fashion [53,54]. Clearly the placebo effect engendered by the greater sensation of self-control that is inherent in the use of these pumps is measurable thereby.

PSYCHOPHYSICAL AND PHYSIOLOGICAL METHODS OF ASSESSMENT

Psychophysical methods

As described earlier, and as recently phrased by Gracely [55], "due to an almost universal distrust of nonphysical — subjective — reports, the physical measures of behavior and physiology enjoy at least equality, if not presumed superiority, over verbal judgments . . . however . . . pain exists only in consciousness."

Psychophysical procedures attempt to establish the link between the external physical environment and its internal psychological representation. There are various depths to which the psychophysical researcher may delve in investigating this relationship. A simple stimulus-dependent psychophysical test, for example, forms the basis of the clinical audiometry examination. Sounds of various frequencies and amplitudes are directed to the human ear, and respondents indicate the range and acuity of their hearing by signalling their ability to detect these frequencies and amplitudes. The psychophysical relationship between stimulus intensity and perceptual quality is readily calculable. A portion of the audiometry examination entails a test of the subject's ability to understand spoken words against a background of various types and intensities of sound interference. The comprehension of such content comes also within the purpview of the audiometry test, even though the perception of content is a complex product of education and gestalt. The test does not purport to measure the cognitive psychological basis of the comprehension of speech and language, yet without such basis the test could not be conducted. Clearly more is involved than the sensitivity of the ear. The subject's comprehension is inherent to the test.

Psychophysical methods thus rely on the subjective report of the test subject, and they attempt to control for bias and sensitivity to stimulation by means of sophisticated experimental designs.

Psychophysical principles originated with the work of Fechner [56], who argued that sensation is proportional to the logarithm of stimulus intensity. More recently, Stephens [57] has introduced a simplified form of the relationship that has come to be called "Stephen's power law." It states:

$$\text{Reported sensation intensity} = C \times S \times B,$$

where C is a constant, S is the stimulus intensity, and B is the proportionality constant that maximizes the fit of reported sensation intensity to stimulus intensity.

Psychophysical methods have been used to investigate the phenomenon of pain sensibility in the experimental subject and, more recently, in the patient suffering endogenous pain.

Pain assessment in the experimental subject

Pain-free human volunteers are used for the most part in psychophysical procedures to investigate the relationship between the intensity of noxious stimulation and perceived pain intensity. Gracely [55] has elegantly reviewed and compared the psychophysical methods designed to assess this relationship and broadly divides them into two types: stimulus dependent and response dependent. In stimulus-dependent methods, the subject's predetermined responses constitute the fixed, independent variable and the intensity of stimulation required to evoke these responses is the dependent variable. Response-dependent

methods present a series of fixed stimulus intensities to which the response judgement varies.

Stimulus-dependent methods have been used to investigate the features of the pain sensitivity range described by Stephen's psychophysical power law. A lower region of stimulus intensity, evoking a sensation termed *prepain*, has been recognized, particularly with electrical methods of stimulation [58]. The term *pain threshold* is used to describe the region of stimulus intensity where sensory judgement is "just noticeably" of pain, where prepain turns into pain. Suprathreshold stimuli, more intense than that required to elicit the pain threshold sensation, occupy what is commonly referred to as the *pain sensitivity range* or more properly, the *pain sensibility range*. At the upper limit of subjective pain sensation lies the *pain tolerance level*, defined as the stimulus intensity above which the volunteer is unwilling to endure — or incapable of enduring — further stimulation [59]. Scaling of subjective pain intensity along the pain sensitivity range is possible with both stimulus-dependent and response-dependent methods. The principal concern of the investigator engaged in such tasks is to measure and control response bias, and various test procedures have been designed to achieve this [55]. As with all psychophysical research, it is the judgement of the subject that forms the basis of the response. This judgement is subject to manipulation by various factors and thus may these factors be studied. Theoretically, the effect of an analgesic may be detected by its ability to modify the perceived intensity of any portion of the pain sensitivity range. In practice, most studies have been carried out on the boundary extremes — the threshold or tolerance levels.

Pain thresholds have been studied using a variety of noxious stimuli, including electrical stimulation [58], radiant heat [60], and pressure [61]. Pain tolerance levels are usually assessed by the use of a continuous, rather than a discrete, noxious stimulus. The elapsed time to the limit of endurance, or the total stimulus energy of this, is the measure of the pain tolerance level. The starting point of the measurement can be taken as the pain threshold or the start of the stimulus. Pain tolerance has been measured by a variety of means, including that of the "cold pressor test," in which the hand or limb is immersed in ice water until unendurable pain results [62], focal pressure [63], tourniquet ischemia [64], and radiant heat [65]. Of the types of noxious stimulation available, certain modalities have been criticized for their lack of "physiological" relevance. The sensation of electric shock, for instance, does not resemble any of the common clinical pain sensations. Electrical stimulation, moreover, indiscriminately engenders generalized neuronal barrages in both afferent and efferent circuits. The sensations of the tolerance level engendered by cold pressor, tourniquet ischemia, and radiant heat methods more closely resemble the clinical report of pain sensation in their quality. Tolerance methods using these techniques, unlike threshold methods, also evoke some not inconsiderable anxiety and apprehension on the part of the subject, which may loosely resemble the anxiety of the pain-suffering patient. Tolerance methods may

possess a peculiar usefulness in that they are ideal for the detection of analgesic effects due to analgesic drugs [52,64].

Pain psychophysics in pain patients

For reasons that are not entirely clear, a schism has developed over the years between the work of those investigators who study pain sensory phenomena in normal volunteers and the work of those who seek to quantify pain in the clinical situation. In part this may represent ideological differences — turf battles — or, as suggested by Naliboff and Cohen [66] in their recent review, it may have arisen as a result of the finding by Beecher in 1959 [67] that pain *thresholds* to radiant heat are unaffected by various analgesics in doses known to relieve clinical pain in humans. This has led to a widely held view that clinical and experimental pain studies are inimicable. Recent evidence suggests that they are not.

Improvement in our understanding of pain has given new impetus to the reexamination of the use of laboratory methods to assess clinical pain in pain patients [66,68,69]. It is hypothesized that the state of suffering an endogenous pain influences the perceived intensity of an applied, experimental, pain; that is, the pain patients differ from pain-free normals in their judgment of the painfulness of a nociceptive stimulus.

The evidence to date is admittedly confusing at this early stage of the investigation. There are fundamentally two theories of how the clinical pain patient will judge the intensity of an incident — applied — pain. One theory, the *hypervigilance theory*, holds that the clinical pain patient will be more sensitive to an applied painful stimulus and will judge it to be more painful than would a pain-free individual. The second, opposing, *adaptation-level theory* holds that the pain patient judges the intensity of an applied pain stimulus in the context of his or her own pain and so will be less sensitive to an applied painful stimulus and will judge it to be less painful. Rollman's studies [68,70] in normal volunteers support the existence of an adaptation theory. Our own work, in chronic pain patients suffering from medical conditions permitting neurosurgical resolution, also supports the adaptation level theory. We have found that while these patients are in pain, before treatment, their pain tolerance to a radiant heat stimulus is elevated over that of normal pain-free volunteers. When their pain is relieved by surgical treatment of their pathological condition, their pain tolerance is reduced, and it is comparable to that of normal volunteers [65].

As reviewed by Naliboff [66], there is good evidence for the truth of both theories. How can this be? It is possible that both are indeed true; there may be two different *types* of chronic pain patients: those who are stoical and those who are hypervigilant. It is possible also that future studies may find that the pain sufferer is hypervigilant to certain types of stimulus and stoical to others. It is also important to realize that the studies conducted thus far are a mixed bag; some measure the pain threshold, others — like ours — the pain tolerance

level. As stated by Rollman [70], "the method of pain induction is not an issue that can be examined in isolation . . . often the pain source is chosen on the basis of what apparatus is readily available rather than by an informed judgment regarding its capacity to mimic the sensory, affective or evaluative properties of particular clinical disorders". It is also possible that the normal psychophsical relationships of the pain sensitivity range are different in chronic pain patients, and indeed there is no certainty that they are comparable for the different modes of noxious stimulation, even in normal volunteers. The biological basis of different parts of the pain sensitivity range may not be the same. Thus morphine does not change the pain *threshold* to radiant heat [71], but it measurably increases the pain *tolerance* level [52]. This may indicate that endorphinergic processes are involved in the latter but not the former.

Studies that support the hypervigilance theory have largely used electrical stimulation or focal pressure to elicit the judgement of pain threshold. Even in trained normal subjects, the pain threshold, where prepain becomes just noticeably painful, is a composite of nuances and is difficult to judge. In the patient suffering excruciating endogenous clinical pain, the detection of such nuances may be overly difficult. Pain tolerance, in contrast, is a more easily recognized point. Defined as the limit of endurance, most subjects can readily identify this and reflexively signal when this level is reached.

It is to be hoped that future studies in algesiometry, as described above, will resolve the questions they have posed. It is possible, even probable, that the pain sufferer differs in reproducible and predictable ways from the individual not in pain, and thus may the pain state be measured. Since these studies are occurring in the arena of psychophysics, an arena well used to the experimental control of bias in subjective response, they hold out great hope for providing an "objective" method of pain "measurement" by using patients' own pain perceptive machinery to assess their pain status.

Physiological methods of assessment

The advantages of finding a physiological correlate of the "pain state" are manifold. To the clinician, it would represent an "objective" measure of this subjective condition. To the scientist, the pursuit of physiological correlates is doubly exciting, representing the search for the biological bases of pain perception and its physiological expression. In truth, the definition of pain is so inextricably bound up in the emotional context within which it is perceived that its biological separation from this context at the level of central neurochemical processing is probably neither desirable, possible, nor meaningful.

There are various levels at which physiological correlates are sought. On the efferent arm of the nervous system lies the autonomic response associated with pain. Measured at the central nervous system, we find the electrophysiological consequences of sensory detection and processing. These are both spinal and supraspinal. Within the neurochemistry of the brain reside the humoral mechanisms of synaptic action associated with neuronal function.

Autonomic correlates

Using galvanic skin response as a measure of autonomic sympathetic nervous system activation, Naifeh et al. [72] studied two patient groups. One group was surgically preoperative and was stressed, but not in pain. The other was surgically postoperative and considered to be in pain and stress. A group of normal volunteers acted as the control. All were subjected to a Valsalva maneuver and a mental arithmetic test. The pain patients gave smaller galvanic skin response changes to these tests, indicating decreased arousal of the sympathetic nervous system.

Nociceptive reflexes

Nociceptive reflexes occur in both nonverbal animals and humans, with the difference being that in humans a verbal report can be obtained on the perceived painfulness of the stimulus. In animal studies of analgesia, thermal or electrical stimuli [73,74], or other such methods, are used to evoke the nociceptive reflex that analgesics inhibit. Analgesia in humans is presumed to represent the antinociceptive effect in animal tests.

Electrical stimulation of the human sural nerve elicits such a reflex readily amenable to study [75,76]. Nociceptive rather than tactile stimulation of this nerve elicits a reflex withdrawal. Stimulated at the skin surface behind the external malleolar at the ankle, electromyelographic responses of the biceps femoris muscle are recorded at the posterior face of the thigh. Delivery of noeiceptive stimuli of different intensities can be subjectively scaled over the pain sensitivity range by standard psychophysical techniques and can be related to reflex recruitment by the muscle. No muscle movement occurs until very near the maximum stimulus intensity. In reviewing this technique, DeBroucker, Willer, and Bergeret [77] have demonstrated, in normal volunteers, that the pain threshold (by self-report) covaries with the reflex threshold, and that the pain tolerance level covaries with the maximum recruitment reflex threshold. The effect of morphine administration is to shift the stimulus-response curve to the right, with a minimal effect on threshold and a maximum effect on tolerance. It is naloxone reversible. Supraspinal influences also modify the relationship [76]. The stimulus-reflex relationship holds true even in paraplegics, however, in contradistinction to radiant heat methods of pain tolerance assessment, which require intact pain perception. This leads one to conclude that the sural nerve reflex may be useful in studies of spinal nociception processes but not in studies of pain perception per se. Its value may lie in the elucidation of diffuse noxious inhibitory controls and in the assessment of supraspinal influences on these controls.

Electroencephalographic (EEG) methods

Insofar as cortical arousal is manifest by changes in the frequency domain of the EEG, modern computer methods of analysis of the EEG signal are capable of capturing this information. Typically the data are digitized as they are

collected (in real time), or are stored as an analog magnetic tape signal for later (off-line) processing. Transposition of the original signal captured in the time domain into the frequency domain is usually accomplished by means of fast fourier transformation (FFT), and by this means the frequency spectrum may be numerically analyzed [78]. The transformed signal is then available in greatly simplified form and is amenable to statistical methods of computer analysis. Principal component analysis and discriminant function analysis, to name but two methods, have become quite common.

Curiously, the power of these computer methods to tell us which specific features of the EEG signal are associated with specific physiological states greatly exceeds our understanding of the physiological basis of the EEG itself. These techniques have nevertheless spawned the science of pharmacoelectroencephalography, a method and discipline that seeks to match the phenomenological features of the quantified EEG with the underlying psychic states associated with them, these latter engendered by psychoactive drugs of known action and mechanism [79]. Using principal component analysis, Bromm and Scharein [80] have derived a measure of arousal from the EEGs of volunteers undergoing evoked potential measurement. Similarly Bourne et al. [81] have used an expert system derived from discriminant function analysis features, which is sensitive to and correctly diagnoses the dementia of uremia in human subjects. Our own studies [82] have shown that these methods are applicable to the animal research laboratory.

Since the utility of the EEG is limited by our understanding of its physiological basis, and the linkage of this to cognitive and perceptual processes is poorly understood, researchers in the field do not hold out immediate hope that such methods will be successfully applied to pain measurement in the near future. The work is proceeding at a furious pace in both human and animal models, however, and may yet surprise us.

Evoked potential (EP) methods

Insofar as specific cortical arousal states may prove characteristic of the pain-perception process (as indexed by autonomic and electroencephalographic measures, see above), the evoked cortical potential arising from painful peripheral stimulation provides the most specific method for accessing brain signals associated with pain. Less general than EEG measurement, the EP signal is readily associated with the noxious signal evoking it. It provides a method, therefore, for examining psychophysical relationships at the level of their cortical processing.

Such psychophysical relationships have been examined in normal human volunteers using a variety of peripheral stimuli, including electrical tooth stimulation [83], ultrasonic stimulation of the joint [84], and laser stimulation [85]. As pointed out in recent reviews by Chapman and colleagues [23,49,83], waveform amplitude of the long-latency component measured from the vertex increases with the energy of peripheral stimulation. There is good corre-

lation between such amplitudes and the subjective pain report. As with the EEG itself, EP signals are usually transposed into the frequency domain by fast fourier transformation or other methods. Using a further data reduction algorithm called the maximum entropy method, Bromm [49] has revealed that power in the delta range (between 1 and 4 Hz) is highly correlated with subjective pain rating where this is evoked by painful electrical stimulation.

EP studies show exceptional promise in the study of pain psychophysics in the normal volunteer. Furthermore, because the pain patient may process the perception of an applied pain in a different way from the pain-free individual (reviewed above), EP methods may provide the ideal means for quantifying this phenomenon at the level of the electrophysiological processing of pain. The work of Bromm and Scharein [80] suggests that this value lies latent.

Biochemical correlates of pain

The humoral basis of neuronal endocrine communication and intercommunication provides an observational window through which these processes may be observed.

At the level of the periphery, sampling from blood, the phenomenon of the pain state is associated with increased levels of circulating stress-related chemical mediators, including ACTH, cortisol, catecholamines, and the longer lived endorphins, including beta-endorphin and its precursor beta-lipotropin.

As recently reviewed by Noel and Nemeroff [50], beta-endorphin and several other endorphins are potent analgesic substances when centrally administered in animals. The finding that there is a proportional relationship between circulating levels of peripheral beta-endorphin and pain report, as has been described in burned children by Szyfelbein, Osgood, and Carr [86], thus implicates this moiety in the mediation of pain and the stress associated with pain. Since beta-endorphin is believed to act as a neuroendocrine mediator in the periphery, since the molecule is not known to penetrate the blood-brain barrier intact, and since it seems to act in an entirely different manner (as a neuromodulator) in the brain itself, it is unlikely that peripheral beta-endorphin is directly mediating the presumed autoanalgesic response of the "pain limb" of the pain-stress complex.

In apparent confirmation of the more general role of peripheral beta-endorphin in states not specifically painful, it has been found to increase in concentration during pregnancy and to undergo further increase during labor and parturition [87,88], with no specific correlation to the (self-reported) painfulness of these conditions [89].

We must look within the brain itself for the neurochemical correlates of pain perception, and at this level also beta-endorphin concentrations have not been found in proportional association with the pain state per se. However, lower levels of met-enkephalinlike immunoreactivity have been found in the ventricular fluid of chronic pain patients than in pain-free individuals [90].

The vast majority of CSF endorphins have not been characterized to

identity, although their presence can be measured quantitatively in terms of their opiatelike effects [50,91]. It is amongst these uncharacterized endorphins that differences have been found between the pain patient and the pain-free individual. Terenius' group have found that a chromatographic region of the cerebrospinal fluid (CSF), which they term *fraction one* is present in lower concentration in the chronic pain patient with organic but not psychogenic pain [92,93]. In our own studies of this region of the chromatographically fractionated CSF, we have found that one of the components of fraction one, which we have termed *peak B* because it is the second of the many opioid fractions to elute from the system, is specifically associated with the chronic pain condition and the autoanalgesic processes of the placebo response. Peak B levels are reduced in chronic pain patients compared with normal volunteers. In those pain patients capable of engendering a placebo response, peak B levels are normalized after the patient has reported placebo-induced pain relief, but remain depressed in those patients that do not experience the autoanalgesic effect of the placebo [5]. Peak B is a potent analgesic in animals tests, and we have proposed, therefore, that it is the mediator of the autoanalgesic response engendered in the pain patient in response to the psychological cue of the placebo [94]. Peak B measurement may well prove to be useful in both clinical pain assessment and in furthering our understanding of the neurochemical processes of pain perception and its psychogenic control and modulation.

CONCLUSIONS

The aim of this review has been to bring together the established clinical methods used to assess both the self-report of pain and its externally observable signs. It has been attempted to illustrate the strengths and limitations of the methods historically used and the quite considerable advances that have been made at the cognitive-behavioral, psychophysical, physiological, and neurochemical frontiers on our understanding of these signs, and to explain how these relate to the elusive definition of "pain".

Pain research stands at a turning point in its development. Combined and concerted efforts of different scientific disciplines have been directed at the question of the biological basis of this perceptual phenomenon, and these efforts are beginning to bear fruit. Our future success in achieving a quantitative measure of the phenomenon of pain will be directly proportional to our understanding of its nature.

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