THE MEASUREMENT OF PAIN

Prototype for the Quantitative Study of Subjective Responses

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Table of Contents

"I often say that when you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind; it may be the beginning of knowledge, but you have scarcely, in your thoughts, advanced to the stage of *Science* whatever the matter may be."

Lord Kelvin

I. INTRODUCTION

Most of the quantitative work on the effectiveness of drugs in altering sensation has been done on pain. This is easily understood in the light of the practical advantages to accrue from such work. Just as pain was doubtless the first reason for the development of the physician, pain and its control remain one of his principal interests. Notwithstanding the fact that the limelight in therapeutics has for some time been focused on the great advances made in chemotherapy, it is nonetheless true (433) that much of medicine is still concerned with the treatment of symptoms, and of these the most important is pain; there is an instant need for the relief of pain. The scientist has a compelling interest in pain, in its anatomical apparatus, in its mechanisms of production and in the chemical and neurological processes involved not only in its production but also in its relief. There is an abundance of good reasons for work on pain; there is, however, still another reason for study: In work in this area over the past decade, the measurement of pain has never seemed to the writer to be only an end in itself, valuable as this end might be, but rather an area where he could learn how to attack other subjective responses, where points of view and insight into technical approaches to other subjective responses and to the controls essential for such work could be gained. Here is a comparatively neglected area of pharmacology as far as quantitative work goes. When one considers how many of the agents in the Pharmacopoeia are designed to alter subjective responses, the need for quantitative work is evident. The extensive work on pain merits re-examination.

The plan of this review has required the separation of parts of the material so that approaches to it can be made in several ways: Work on (a) man and (b) animals will be considered. The material involved will be separated further into

sections (a) on pain experimentally produced and (b) on pain of pathological origin. The principal techniques of experimental production of pain involve several types of stimuli: Thermal, electrical, mechanical, and chemical. The organs chiefly involved are: Skin (used in all four techniques), teeth (used principally with electrical, rarely with thermal and mechanical techniques), muscles (used with mechanical techniques), and viscera (used with mechanical techniques). The pathological pain studied has come chiefly from operative wounds or from malignant growths.

The chief purpose of this review is to examine, as thoroughly as the data permit, the pain techniques employed, their applications, and the results obtained therefrom. It seems rather remarkable that in all of the scores of studies that have been made, few investigators seem to have questioned the assumption that pain is the same whatever its origin and useful for all purposes to which it has been put, that the only characteristics of interest are intensity and duration. But it has recently become clear that the *significance* of pain (57) can be of dominating importance, and with the recognition of a fresh approach to pain, to its relief, and to studies of the mechanisms involved is required.

Prior to the last decade and a half, work on pain was not adequately controlled in most cases. Controls have been improving, and with this improvement the rôle played by bias in the interpretation of the results has lessened. One surprising consequence of this has been to question the validity of the use of experimentally contrived pain in man for the purpose to which it has chiefly been put, namely, the evaluation of analgesic agents. This question must be examined searchingly, yet the reviewer hastens to add that he has no intention of challenging all possible uses of experimental pain. Experimental pain has been essential for the work of those who have established the anatomy involved in pain impulse transmission. To mention a few: von Frey, von Helmholtz, Bishop, Gasser, Erlanger, Lorente de Nó, Adrian. It seems likely that ultimate understanding of the importance and relationship of the two parts of the dichotomy, original sensation and reaction to sensation, may be achieved by further use of experimental pain. Adequate experiments to do this in any complete sense have not yet been devised, although a good start has been made (316, 317, 318, 319, 384, 439, 440). Many other uses of experimental pain must be discussed. The limits of usefulness of pain of both origins, experimental and pathological, will be examined and compared.

II. DEFINITION OF PAIN

". . . let a sufferer try to describe a pain in the head to a doctor and language runs at once dry . . ." Virginia Woolf

Unfortunately pain is a universal experience of mankind and everybody knows what is meant by it; so this review will concern itself only briefly with past unsatisfactory attempts to define pain. Pain is, it must be admitted, uncommonly difficult to define. But attempts at definition are useful in that they throw light on the process and on the nature of the difficulties encountered.

Pain is a subjective matter clearly "known to us by experience and described by illustration" (414). There seems little point for the present purposes to labor a definition of what all understand. Lexicographers, philosophers and scientists have none of them succeeded in defining pain. Having said that it is the opposite of pleasure, or that it is different from other sensations (touch, pressure, heat, cold), or how it is mediated (through separate nerve structures), or what the kinds of it are (bright, dull, aching, pricking, cutting, burning) or what kinds of things will produce it (trauma to nerve endings, or to nerves, electric shocks, intense stimulation of the sensations of touch, pressure, heat, cold) or what it comes from (injury, bodily derangements, or disease), or that certain types of mild stimulation can probably be stepped up to a painful level through conditioning, or what some reaction patterns to it are (escape or avoidance), none of these individual statements, nor indeed their sum total, provides a definition of pain.

Sir Thomas Lewis said (414), ". . . I am so far from being able satisfactorily to define pain . . . that the attempt could serve no useful purpose." Burke said, "Pain and pleasure are simple ideas incapable of definition."

Bishop's and Gasser's and Adrian's intensive and productive work on pain covering many years has given them abundant reasons to understand the difficulties here. Gasser (237) has commented, on request, as follows: "I am almost sure that I have never attempted to formulate a definition of pain. If I had I would be more successful in trying it now. Can we not look at it this way? The word pain serves as an inter-personal signal. Whatever it denotes to a particular individual is only something that he himself knows. That it must mean much the same to one individual as to another, is inferred because the signal can be used in inter-personal communication, with the communication still making sense. In other words, the signal passes a pragmatic test for everyday life.

"If I remember right Lewis described pain sensations having three different qualities. I think I identified two but not the third. Whether or not any of my recollection be correct, is unimportant. The point is that I had to perform the operations in order to see if I could make any differentiations in the qualities of my private experience."

Bishop (85) has, on request, made a valiant effort to define what seems to be patently undefinable: "Pain is what the subject says hurts. You can't get behind that. It consists however of two phenomena. A. Pain as a subjective experience, reported as a *sensation* when referred specifically to some part of the body and sufficiently unpleasant to be designated as painful by the subject. End definition A.

"This unpleasant sensation will of course vary with emotional state, anxiety, anticipation of disaster, etc., and is almost impossible to deal with quantitatively since it has such a large component of what is referred to as reaction to sensation. It may be due to activation of any modality of sense, and I suspect, to none. I know of people who can throw a sick headache, and so do you, as a protest, and I can't say they don't have one. I once knew a man who could raise gooseflesh on his arm by thinking of a war experience.

"B. Pain as a physiological process, with a subjective evaluation in addition to perception is a result of stimuli to sensory endings or pathways of two types of fibers; certain small myelinated fibers causing pricking pain on adequate stimulation, and unmyelinated fibers causing burning pain.[1] Both pass up the lateral columns of the cord after synapse in the substantia gelatinosa. End definition B.

[1] First and second pains have been separated (256) by determining the conduction times of the two. Interference with the alpha rhythm of the electroencephalogram marked the cortical arrival of the fast impulses. After the fast pain had been eliminated by tourniquet

"As far as I know, no other endings will cause pain as a report from normal subjects relaxed and unapprehensive. This pain is also a subjective experience as all sensation must be but with less emphasis on reaction, and more on immediate perception and discrimination. I wish there could be two names for these two, both types of experience, the first including the second, but I am not a philologist and to coin new names for so conventional an experience doesn't persuade anybody as to what hurts and what doesn't.

"I am not sure this will do *you* any good, but when I have to test a patient as to what operation is to be performed, if any, the second definition seems to be a practical one. It does require some 'training' of the subject including a relief of anxiety etc., and some repeated tests for learning to discriminate. But it usually differentiates between pain B and anything else if done carefully, even in anxious patients.

"Pain could also be tied to the physiological reactions like sweating, blood pressure etc. but I don't think that differentiates adequately, like the man who can raise gooseflesh any subject can go through the motions of being hurt. So while these tests have some value, I wouldn't make a definition depend on them. I am afraid I wouldn't make it depend on the effects of analgesics either, especially after your own work with them.

"If you ever get a good psychologist to tell you what pain is, please let me know. I haven't had any luck."

Adrian (6), on being asked if he would attempt a definition, said "When I was an undergraduate the inner circle based their views on George Moore. His book was called 'Principia Ethica' and it set out to analyse all the definitions of 'good' and to show where they all went wrong. He did this so effectively that I should never dare to risk formal definitions of anything. I suppose when we think of mental pain we mean the reverse of pleasure and when we think of physical pain we mean something much simpler. But I don't see how one can define the particular quality of physical pain. A chapter about its definition would be well worth having, for it would remind the reader of all the characteristics and consequences, etc.—but I think it would be like Moore's book on 'good' and would have to end up the same way by saying that when we say a thing is good we mean that it is good and not something else."

A so-called operational definition of pain (197), where criteria such as the subject's statement, a cry, skeletal withdrawal, or other reflex are employed to denote the presence or absence of pain is still not a *definition* in any satisfactory sense, even though such signs perhaps adequately indicate the probable presence of pain. As Edwards points out (197), pain refers to an experience, not to the behavior produced by that experience. He concludes that no operational definition of pain has so far been formulated: "The word pain is now used to refer to a perception, like a tone or a color, rather than an affective state or a performance in a choice situation." It is not far-fetched to consider the subject's report as "operationism."

It seems paradoxical to speak, as we shall in this review, of measuring something which cannot be satisfactorily defined, and if this were true it would be paradox or nonsense or both. The fact is, pain is defined introspectively by every man. The difficulty comes in verbalizing this well known experience, not very difficult in terms of statements of its presence or absence in various degrees or kinds but in saying *what* it is.

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asphyxia, the arrival time of the slow pain was determined in the same way. Thus it was possible to demonstrate in an *objective* way the conduction velocities of the two types of pain.

Wikler (641a) and his associates have set themselves the formidable task of defining operationally "anxiety associated with the anticipation of pain." This is done "in terms of disruption of adaptive behavior, not in terms of 'avoidance' or 'escape' responses. There may or may not be significant differences among the kinds of 'anxieties' reflected in these three different measures, but what we have been aiming at, is the experimental investigation of 'giving a damn about pain', and our hypothesis is that how much 'gives a damn' about pain can be inferred from observation of the extent to which signals heralding nociceptive stimuli *which the subject cannot escape or avoid*, disrupt previously learned responses that are 'adaptive'. After all, is that not actually the basis on which we proceed in assessing 'clinical' pain for purposes of deciding whether or not to intervene? Perhaps we are getting closer to an operational definition of that sort of pain for which analgesics are prescribed. But this is a problem about which there can be many opinions, and on the basis of the limited evidence presently available, I cannot successfully refute your conclusion that 'Pain cannot be satisfactorily defined, except as every man defines it introspectively for himself'—yet!" In view of the Lexington group's superb achievements to the present, it would take a much hardier soul than the present reviewer to aver that they will never succeed.

III. PAIN APPARATUS; PAIN AS A SPECIFIC SENSATION

The scientific study of pain is more than a hundred years old; one can place its beginning at 1846[2] with Ernst Heinrich Weber's interest in the pain apparatus, specifically, with his separation of pain from the sense of touch. "It was plain to him that pressure, warmth, and cold are true sensations," as Boring (99) puts it, "because they have their proper stimuli .... Pain, on the other hand, seemed to him to have no proper stimulus but to represent a bodily need, like hunger or nausea. In recognizing this difference, Weber rendered science a service, but his contribution was negative ...."

It was only a little while later, 1850, that Fechner saw in Weber's studies on intensity of sensory experience, "... a way for writing the quantitative relations between mind and body, or, more particularly, between sensation and its stimulus. Out of this inspiration grew the whole of psychophysical research and, thus, in a way, of the new experimental psychology" (Boring, 99).

A generation later, 1880, the theory of specific nerve energies presented the concept that separate nerve fibers served each quality of sensation. It was believed that thus nerve fibers had their own beginnings in receptor organs and their own endings in the brain. This view had the powerful support of Johannes Müller and of von Helmholtz (99). Before long this generally correct belief was

[2] Presumably it was sheer coincidence that scientific attack on the pain problem and the clinical interest in pain and conquest of one segment of the problem, through the general introduction of anesthesia, took place in the same year, 1846. And yet, one can speculate that there may have been a common tide of interest at that time in the pain problem that led to such great results. In any case the scientific interest in pain stemmed directly from the fact of clinical pain. If the two developments just mentioned arose from a common atmosphere of interest, then 1846 can be said to mark the modern beginning of what has become in recent years a recognition that the origin of some kinds of basic (the term is used in its classical sense) scientific advance is to be found only in the sick room, only in the presence of disease. This view has lately been notably exemplified by the advances made in the physiology of the endocrine glands, basic advances that could not have been made until triggered by the problems presented by deranged endocrine glands.

confused by the work of Goldscheider who, because he had difficulty eliciting pain alone from the skin, concluded erroneously that pain arose from intense stimulation of any sense. It remained for von Frey to set investigation again in the right direction. In 1894 he demonstrated pain spots in the skin. This led to the demonstration of pain as a special sensation, served by its own apparatus. The anatomical basis for this has been clarified and supported by the work of many (7, 235, 303, 423, 427).

Specific references to the papers of Weber, Fechner, Müller, von Helmholtz and to the numerous papers presenting the long controversy between Goldscheider and von Frey have been omitted since these as well as the papers describing the more recent developments concerning the pain apparatus, while interesting and relevant to the subject of this review cannot be dealt with here for reasons of space, and need not be, for thorough reviews are easily obtainable (5, 80, 197, 235, 236, 289, 574, 617, 636).

IV. PAIN STIMULUS

Pain can be evoked by many kinds of stimuli: thermal, electrical, mechanical, chemical. Pain originating in the skin has been more thoroughly studied experimentally because of the greater accessibility of its receptor organs than has visceral pain. Few if any divergent views or conflicts of opinion have arisen from studies in the two areas. Pain is also evoked by disease or trauma. Formidable controversies have arisen as a consequence of the assumption that all pain of a given intensity and duration is alike whatever its origin. A major purpose in planning this review was to examine the assumption that pain is always the same, varying only in intensity and duration, and if this view be found incorrect, to show why this is so. It can be said at once, however, that there is much evidence that a serious error is made when it is assumed, as was nearly universally the case only a few years ago, that all pain from any origin is equally useful for study of all problems. This is demonstrably not the case and the reason is that while all pain apparently has two components, original sensation and the reaction thereto, variations of great degree in the reaction part are determined by the significance of the cause of the pain, as has been shown (57). The significance of the pain controls the field of usefulness for study of pain of a given origin. This will be discussed in detail below.

It has often been stated that "the adequate stimulus for pain sensation is the damaging of tissue" (289). This seems unlikely. Light pressure on a sensory nerve can be exquisitely painful. It seems improbable that this produces tissue damage. The view concerning tissue damage as the adequate stimulus is not accepted by Bishop (86a), nor by Beecher (57).

Much evidence is available to indicate that the reaction component usually differs widely in the two types of pain and is responsible for the differences encountered. Wikler (639) said, "A 'stimulus' cannot be defined in terms of its own properties alone, since its capacity to evoke responses is determined in part by antecedent events, and by particular experimental arrangements." In other words, conditioning plays a part and so does all of the elaborate mechanism of

the reaction component. Attention will later be given to the view that pain thresholds are not pure perception but include reaction and that this is why they are so far from constant. The difficult but soluble problem is to introduce quantification into this complicated field. Most successes have resulted from the careful design of experiments whereby otherwise uncontrollable complexities are kept constant and made to cancel out. For example, just as the life history and pain experience are comparable for no two individuals, so error is introduced if this conditioning is not represented essentially unchanged throughout a given experiment, hence the importance of the use of correlated data, that is, the study of the same drugs under the same circumstances in the same subjects.

In discussing skin sensation Bishop (81) points out that 1) no sensation is experienced in the skin, for sensation is a function of the brain cortex and thalamus; the skin contains certain mechanisms for changing environmental energy into nerve impulses. 2) Some of the activities of sensation are "irrepressibly" carried into consciousness; some are registered in consciousness by attention; some are not capable of reaching consciousness. 3) The state of the skin modifies the action of its sensory endings, chiefly by altering thresholds. Thus temperature thresholds depend on the temperature of the skin. Touch and pain thresholds depend on the skin's flexibility, *i.e.*, moisture content. Various irritative and inflammatory processes increase the excitability of the sensory endings in the skin. Bishop (86a) emphasizes the importance of differentiating between pricking and burning pain, delta- and C-fiber pain. He says, "most pathological pain is probably C whereas most testing is done in delta."

Pain can be separated from other sensations: Spatial summation of pain does not occur, but summation does occur for warmth (temperature sensation) (289). The wounded soldier may first be made aware of his wound by the blood flowing over his skin (150). Whether this is due to warmth or touch is not entirely clear; warmth seems to be the sensation first observed, in the absence of pain. The thresholds for sensations other than pain (touch, vibration, two-point discrimination, smell and hearing) were not raised by morphine, codeine, ethyl alcohol, a barbiturate or acetylsalicylic acid in ordinary dosage (642). The pain threshold appears to be separable from the threshold for other modalities. A "marked dissociation" was observed between tactile and pain sensitivity when the pain threshold (von Frey hairs) was elevated with ingested alcohol (465).

A pain stimulus must be chosen which can be controlled and measured and which permits the establishment of a clearly perceived end point. The end point must not be altered by the necessary repetition of the experiment. This is a problem with all forms of stimulation; it is especially great with the radiant heat stimulus. Boring (99) describes "two notable contributions" made by Hardy, Wolff and Goodell: 1) They have provided a measurable stimulus for pain. He points out that Weber had no proper stimulus; von Frey used heavy forces applied to small surfaces with force distributed, or needles acting by destruction of tissue. In either case effectiveness is not properly measured by the force applied. While Hardy, Wolff and Goodell were not the first to use radiant heat as a painful stimulus, they were the first to make a systematic

study of it. 2) Boring considers that their next important advance was to measure the intensity of pain—the dol scale. This, ideally at least, permits the plotting of sensation against stimulus and is applicable to Fechner's century old "fundamental problem for psychophysics."

A verbal end point has been used successfully in studies of nearly all types of sensation. It is dependable in the study of pain. (See V, B, 2.) It is not to be confused with muscle twitches, blinking, withdrawal, or any form of reflex or glandular response (285). Differences between pain threshold and motor responses are well established (126, 128, 129, 132, 133, 519, 520, 521).

It is the reflex response which determines the end point of nearly all animal experimentation in this field. But this is a reaction threshold, not a pain threshold. The use of respiratory depression as the critical parameter is an exception (592). (See V, A, 8.)

V. METHODS FOR MEASURING PAIN

A. Pain for experimental procedures

A rather full list of references will be given to the methods of producing pain for experimental purposes and their modifications and applications to various problems. The procedure of each method will be stated, but for reasons of space, principal attention in this review will be given to an examination of the advantages and limitations of each method. It is remarkable how often the originators of "algesimetric" apparatus proceed on the assumption—indeed in most cases there does not appear to be awareness that an assumption has been made—that the only problem is to devise some ingenious means of inflicting pain which is quantifiable in mechanical, thermal, electrical or chemical units and which, preferably, differs from methods devised by others. Such investigators sometimes focus their inventive powers on the machine to be used and neglect the man to be tested.

Pain is measured in terms of its relief. This system is common throughout pharmacology where induced nausea is sometimes appraised through the power of a given anti-emetic agent to suppress it, and induced cough by the power of a given antitussive agent to check it; antispasmodics in standardized doses reveal during relief the extent of induced smooth muscle spasm and antihistamines are compared on the basis of their power to relieve the effects of a given dose of histamine, and so on. One special problem with pain is that the "adequate stimulus" for it is said to produce tissue damage (289, p. 23) with possible error to ensue when subsequent measurements are made. (Bishop (86a) questions tissue damage as necessarily the adequate stimulus for pain production.)[3]

[3] Notwithstanding perfectly clear statements in the Hardy-Wolff-Goodell book (289), Hardy (276a) states his current view as follows (280): "The threshold of pain and reflex responses to noxious stimulation by heating is determined by the lowest rate of inactivation of tissue proteins which will cause tissue damage if the thermal stimulation is sufficiently prolonged." In an effort to be fair the reviewer has included this current view as affirmed by Hardy in a recent letter. But in this sentence as elsewhere Hardy has linked pain threshold and tissue damage, although *rate* is to be emphasized.

All of the common forms of stimuli used to elicit experimental pain (thermal, electrical, mechanical and chemical) have been observed (289) commonly to produce evidence of local tissue change, for example, a transient erythema. Unlike the consequences of arousal of other sensations, painful stimuli, if continued, invariably alter the tissue so much as to disrupt its function. Such observations led to the hypothesis that the adequate stimulus for pain is tissue damage (289). As will be discussed later, it is difficult to reconcile this view with Beecher's (57) demonstration that great wounds are under some circumstances painless and that significance of the wound appears to determine the presence or absence of pain.

Goetzl *et al.* (244), in common with most investigators in the field, start out with the assumption that there are experimental procedures that can be used to evaluate the analgesic power of drugs and among them a "best" one. This review will be concerned with the evidence that the methods "work" and if they work, whether they do, both in man and in animals, and under what circumstances and for what purposes.

Most of the early studies on pain were made on man (244); animals as subjects are more recent. Early investigators outlined (a) the pain receptive field, (b) physiology of the pain receptive organs (normal and pathological), (c) conduction of pain impulses, (d) responses to painful stimuli, (e) study of analgesic properties.

It is to be emphasized, reliability in algesimetry is determined by a number of factors: reproducibility of a known stimulus, stability of pathway between stimulator and receptor, stability of threshold of receptor and of perception and not only the power to duplicate findings in the same subjects but also in different subjects (292).

Miller (451) comments that pain being a subjective phenomenon should be more easily characterized by man than by an animal. Somewhat paradoxically the opposite seems to be the case as far as experimental pain is concerned. This will later be discussed in detail.

Either one of two approaches to determination of the pain threshold is acceptable: the painful stimulation can be delivered for a fixed time at increasing intensity, or a fixed intensity for increasing time. A reciprocal relationship between time and intensity should be established for a given method when time is used to determine threshold (289).

1. Ideal method. Several investigators (131, 244, 289, 451) have attempted to set down in general terms the requirements of an ideal method for producing painful stimuli. The aim has been to find which practical method comes nearest to the ideal. The requirements of the ideal method are as follows. It should provide: (a) stimulus which can be applied to a body part where neurohistological variations are at a minimum in different individuals, where it can be measured and closely associated with the changes which produce pain, (b) quantitative data in response to a given stimulus under given conditions, with little tissue damage at the pain threshold level and the hazard to the subject small at the highest intensities, (c) a relationship between the intensity of stimulus and the

intensity of the pain experienced, (d) quantitative information as to the least difference between the intensities of two stimuli throughout the range of useful intensities, (e) the possibility of carrying out several to many repetitions of the stimulation even above the pain threshold value without interfering with subsequent determinations, (f) easy application of the stimulus and clear identification of the pain end point, even though other sensations may be aroused by the stimulus (strictly speaking, in ideal terms no other sensations should be aroused by the stimulus), (g) quantitative determination of each pain quality when more than one are present, (h) sensitivity so that agents of low analgesic power can be detected, (i) differentiation among graded doses of an analgesic through their power to alter the effects of a standard pain stimulus, (j) applicability both to man and to animals.

The abstraction, "the ideal method," can have some value in orienting one's interests and goals. The abstraction does more harm perhaps than good if it suggests that all of its "requirements" are worthy of a practical search. In fact, it is quite evident that most investigators working with experimental pain have tacitly assumed that the goals indicated above are legitimate and attainable. This is not the case in one or two important instances. For example, take the reasonable-sounding statement that the ideal method should show a quantitative relationship between the intensity of stimulus and the intensity of the pain experienced. It would be most convenient if it did. The fact is, there seem to be insuperable difficulties in achieving any such precise relationship. The reason for this does not emerge in the statements made so far in regard to the characteristics of the ideal method. The reason emerges only when it becomes plain that a dominating factor has been left out of consideration, the reaction component. It will be shown later on that this factor is at times of absolute importance, that is, it can determine, whatever the stimulus to the pain apparatus may be, whether pain will or will not be perceived. It will be made evident too that the reaction to pain of pathological origin is far greater than it is to experimental pain. Nonetheless, experimental pain appears to contain enough of the reaction component to destroy many a fine thesis. The evidence for this will be presented in detail later. Briefly, it is probable that the lack of constancy of the pain threshold, the failure of so many investigators to demonstrate a dependable relationship in man between the pain threshold and analgesic action, and the failure of pain threshold data in man to be borne out in experience with clinical pain, indicate the presence of an important reaction component in experimental pain.

It is difficult or impossible to state all of the requirements of an ideal experimental pain method in meaningful terms when the complications introduced by the reaction factor are taken into account, unless one clings to the view that it must be held constant, yet knowing full well that it is probably never the same for two individuals nor even for the same individual from one time to another. These are strong statements; strong evidence is available to support them.

Another difficulty with statement of the ideal experimental pain method lies in the problem of applicability both to man and to animals. Any statement of

the ideal should recognize what the parameters of decision are for the separate species and that they are very different. Even the ideal method, if it is to have helpful meaning, must take the species differences into account. It seems evident that any very useful statement of an ideal method for producing experimental pain has to be hedged about with so many qualifications as to give it only limited value.

2. Thermal methods in general. The following studies, indicated by number, refer to original methods, their development and their application in the categories specified.

Man: 15, 17, 19–22, 60, 64, 75, 106, 121, 129, 131, 132, 136, 142, 165, 168, 214, 216, 227, 264, 265, 277–280, 282, 283, 284, 286, 287, 288, 290, 301, 324, 352, 353, 376, 384, 402, 404, 405, 424, 469, 485, 493, 515, 519, 520, 525, 528, 531, 558, 561, 571, 591, 604, 610, 629, 630, 633, 642, 668, 669.

Animal: 23, 66, 120, 157, 194, 200, 212, 219, 264, 280, 297, 298, 315, 324, 338, 344, 451, 489, 490, 491, 531, 591, 647, 648, 649, 651, 675.

The highlights here are chiefly these: Goldscheider (249) introduced heat as a means of evoking pain experimentally (see also 289). In the beginning heat was transmitted by contact, either through hot water or hot objects (121, 523, 524, 525) generally applied to the skin. The sensations evoked by hot and cold water in the alimentary canal were studied (97). These methods were not concerned primarily with pain threshold studies (289); however attempts were made (199) to get at threshold values by direct application of hot bodies to the skin. The pain threshold value for cold water was determined as 18°C. (657).

A great difficulty with all contact methods is that sensations of touch and pressure are evoked by them as well as pain. Alrutz (13) suggested that this problem could be avoided by the use of radiant heat. This was accomplished by focusing the sun's rays on the skin (557, 610). Adaptation to pain will be considered in a separate section (X, 17) but it should be mentioned in passing that it does occur to heat (572).

One of the greatest advances in this area came about when Oppel and Hardy (474) showed that the heat radiation technique could be applied so as to permit study in quantitative terms of the temperature sense of man. The extensive series of papers by Hardy, Wolff and Goodell on the radiant heat method for producing experimental pain stem from this. They have summarized six advantages of the use of thermal stimulation:

> "1. The necessary apparatus is simple and easily constructed. 2. The intensity of the stimulating agent can be precisely measured. 3. The sensory threshold to pain as a result of this stimulus is a sharply defined experience so that thresholds may be determined with accuracy higher than that of other methods. 4. The method is flexible so that the time of exposure to the stimulus, the state of the skin, etc., can be varied at will. 5. The stimulus can be used for large and small areas of skin even though the surface be irregular. 6. The stimulus can be repeated in rapid succession without injury to the skin surface tested."

It will be seen that points 2 and 6 are open to considerable question.

There are, however, many difficulties: Heat which actually constitutes the stimulus is difficult to measure in exact terms. The temperature of the receptive

field is determined not only by the heat delivered to it but by the circulation of the area. An assumption of direct proportionality between the heat stimulus and the opposing homeostatic mechanisms of the receptor area is not justified (242). From this it follows that (a) the real stimulus cannot readily be varied by small but measurable differences and (b) the pain producing temperature cannot be varied at once. Heat cannot be applied to isolated pain receptors and the stimulating amount of heat cannot be reproduced with exactitude. Finally, the duration of the painful heat stimulus is neither measurable nor constant (242).

Ideal quantification of the thermal stimulus should, of course, depend upon measurement of the rise in temperature of the pain receptors; but, it is believed, a useful approximation of this can be made by measuring the rise in skin temperature. The energy supply to the skin has been determined by means of a radiometer (284). This is at best an indirect measure of the rate of skin temperature change. The use of a thermocouple in air as employed by some (549) has little to recommend it. It has been assumed that there is linearity between the wattmeter readings (the energy dissipated in the lamp) and the radiometer readings (23). Likewise, one may assume a linear relationship in the transfer of heat from the skin to the pain receptors in the skin, and that rise in skin temperature is a linear function of the radiant energy absorbed, providing the circulation remains unchanged—a fairly great assumption. Thus the rise in temperature of the dermal pain receptors is fairly accurately a function of the wattage in the lamp, excepting gradual changes in the filament and optical system over a long period (651).

3. Radiant heat methods. a. Fixed duration, variable intensity (284, 289). This method has, remarkably enough, been altered hardly at all in the 12 years separating the two references just given. Current procedure is described in very great detail in the second of the two and will not be repeated here except in brief form, since everyone interested in algesimetry is familiar with the method: The light and heat from a 500 or 1000 watt projection lamp is focused for precisely 3 sec on 3.5 cm^2 of blackened skin, usually the forehead of the subject. The exposure time is so short that only local heating of the skin occurs and effects from conduction at the edge of the aperture are negligible (289). A shutter provides the exposure, electrically timed. The current delivered to the filament of the lamp is the "only" variable. Increased current permits the delivery to the skin of increased heat so that the subject finally experiences a sharp jab of pain, the "threshold pain," at exactly the end of the 3-second exposure. The period between exposures is 1 minute. When the intensity of heat required to give the threshold pain is determined, a radiometer is placed in the beam instead of the forehead and the intensity of the radiation is measured in gcal/sec/cm^2. In the beginning the intensity of the beam was determined by a rheostat; later a "Variac" was used. A voltage transformer and a vacuum thermocouple to keep track of the intensity of illumination have also been used (214).

Three times as much radiant energy are required to evoke pain from a light source as from heat rays alone (216). Flodmark and Wramner (216) have employed a color filter and have not blackened the forehead since it is difficult to

get the same degree of blackening each time and also because removal of the stain is likely to produce injury to the skin with increased irritability to interfere with later tests in the same subjects (142, 216). The greater the wave-length of the heat rays, the more they act on the pain receptors. Sonne believes this is because the long rays are better absorbed than are the short rays into the skin layers where the pain receptors are found.

Continued use of the heat lamp results (227) in a reduced output of radiant heat for any given reading of the voltmeter and careful calibration with a radiometer is mandatory if the painful stimuli are to be accurately reproduced.

The originators of the method (279) state that "for the most accurate measurement" of pain threshold by the thermal radiation method, it is necessary to correct for the skin temperature. This can be done from the curve presented. Since the forehead skin has a temperature of 34° ± 0.5°C. under ordinary laboratory conditions, it is not likely that failure to correct for this error vitiates much work. Error will be introduced when the room temperature is below 20°C. or when it is above 30°C. In the latter case sweating will occur and this will interfere with endpoint determination (214, 279, 185, 405) but not according to others (131). An elevation of 10°C. caused a lowering of the pain threshold by approximately 200 mcal/sec/cm^2 (131). (See X, 7.) Cooling would have the opposite effect.

Species variations must be taken into account. Winter and Flataker (652a) have called attention to the fact that morphine produces a lowering of body temperature in many species of birds and mammals, but an elevation in the horse and the cow, and after large doses, in rats. Since dogs and rats are widely used in thermal analgesic screening procedures, and since the reaction of the animal to the stimulus is a response to the rise in skin temperature, their findings and observations of differences are important. They report that morphine produces a rise in rectal and skin temperatures in rats and a fall in dogs. They also report that the lowering of skin temperature in the dog accounts for much of the rise in threshold produced by morphine in this species. In rats, the rise in threshold associated with morphine administration "is due entirely to an increase in the temperature of reaction; indeed, an elevation in threshold in this species occurs in spite of an elevation of skin temperature." Therefore rat data appear to be much more valuable than that from dogs when the stimulus is heat to the skin.

Usually, if not always, the originators of the method have approached the threshold from below, for the very good reason that suprathreshold stimuli are likely to damage the tissues and impair the "reading" of subsequently determined "thresholds." But it must be admitted that the approach from below involves the hazard of introducing a constant error (197). Other difficulties have been recognized (197): The usefulness of the radiometer reading as an index of the amount of heat delivered to the skin depends upon identical blackening of the skin from person to person. It has been reported (414) that radiation of the skin leads to histamine release or the release of a histamine-like substance and this in turn leads to hyperalgesia and this in turn to threshold alteration (285).

Whether the threshold values of heat alone would lead to this difficulty is not clear. Higher levels of heat which lead to persistent erythema are hazardous. They can lead to great lowering of the pain threshold (289). Presumably the early studies by Hardy, Wolff and Goodell did not take this possibility into account, for it wasn't until 1949 (281) that a caution not to use the same skin area for many repetitions was mentioned. The warning was with regard to supra-threshold stimuli (197), but earlier studies (286, 287) had employed supra-threshold stimuli without this caution. These authors have not presented mathematical validation of the supposed differences they have reported, and all too often insufficient variability data are given to permit present calculation. Notwithstanding these difficulties, it must be recorded that Edwards (197) concluded that the results reported by Hardy, Wolff and Goodell "are apparently fairly stable and reproducible." This seems an unwarranted conclusion judging by the imposing and opposing data available in 1950, when Edwards' review was written, yet not included in his fairly extensive bibliography. The reader can make up his own mind as to whether this view is tenable at present, after the presentation has been made of the material in the sections to follow on pain threshold and on the effects of analgesic agents on pain threshold (see VIII, 2 and IX). Edwards' conclusion is demonstrably open to doubt.

Whyte (633) challenges the validity of the Hardy-Wolff-Goodell method. It is based on two assumptions, he says: 1) That the initial skin temperature of the forehead is constant. 2) That the rise in skin temperature effected by radiant heat is proportional to the intensity. Effects of drugs may modify skin temperature. The range of intensities used is narrow and Hardy, Wolff and Goodell assume proportionality up to threshold of pain.

It seems remarkable that some investigators (265), using the radiant heat method, have found "no great difference in peak height" between subcutaneous and oral routes of administration of drugs, "but the time to reach the peak effect was markedly increased by oral administration." An examination of these data only adds to one's questions. Take the agent Nu 1779, 10 mg dose. The threshold elevation was greater, 20.9 % on oral, as compared with 17.8 % on subcutaneous administration. Perhaps this is not significantly greater but it certainly is not less. At the same time it took twice as long, 120 minutes as compared with 65 minutes, to reach this higher peak on oral administration than it had on subcutaneous. (These are all mean values.) It seems at least possible that enough destruction of the agent would have occurred with the passage of time to influence adversely the peak effect on oral administration. Data of these kinds do not inspire confidence in the method. It would be interesting to know what the results would have been if the investigators had employed the safeguards of the "double unknowns" technique and the use of placebos also as unknowns in these relatively untrained but enthusiastic subjects. In a very much larger group of subjects (patients) Beecher *et al.* (59), in studying pathological pain and using the double unknowns technique, could find no effect of morphine, 10 mg, or codeine, 60 mg, on oral administration in comparison with a placebo, although they did find a significant effect from 0.6 g acetylsalicylic acid when given by mouth.

A number of other factors which require control in this area will be brought out in the sections to follow. In conjunction with appraisal of the method of Hardy, Wolff and Goodell it is necessary that some reference be made to these matters at this point. They have shown (285, 665) how important attitude and suggestion are in modifying both the experimental pain threshold and the reaction to pain. They report that pain threshold rises equivalent to those often effected by analgesic agents can be produced by suggestion through placebos. Even greater rises than these, although of shorter lasting effect, are produced by distraction. Also "prejudice, anxiety and doubts altered the reports on the pain threshold-raising effect of acetylsalicylic acid so that the analgesic effect was negligible." They say further, "The success or failure as therapeutic agents of such analgesics as acetylsalicylic acid is markedly influenced by the attitude engendered in the subject." One can only wonder as to why Hardy, Wolff and Goodell have not considered it necessary to introduce control of the factors mentioned when they were dealing not only with the relatively weak analgesic agents but also with the morphine class of substances. That such controls are essential with all analgesic agents, including the powerful, has been repeatedly shown by the Beecher group and others. The evidence was summarized in 1956 (53).

It is regrettable that, although Wolff and Goodell (665) made their interesting observations in a comparatively early study and there was already available to them at that time other supporting evidence of the importance of suggestion (203), for reasons not clear they appear to have considered their findings on suggestibility as chiefly applicable to the relatively weak analgesics. Their later studies would have been greatly strengthened; and in several instances reports on them would have been made unnecessary by such controls.

Notwithstanding the extensive use of the Hardy, Wolff and Goodell method over a period of years, no very satisfactory way has been worked out for handling the data (451). For example, customarily observations are made at 15 to 30 minute intervals during study of a given analgesic agent. Thus 4 to 10 observations are accumulated for each dose of the drug, with peak values occurring in 20 to 90 minutes. The percentage rise of the threshold over the pre-treatment value is calculated for each dose, and on being graphed these rises are reported to make a sigmoid curve. But it is customary to use only a part of the data. For example, Thorp (591) in studying rats, as Miller points out, "did some violence to the data" by drawing a straight line through the central portion of the data, ignored the obvious sigmoid shape of the curve, and even calculated the equation for the part he considered to be linear. As justification for this treatment he assayed two unknown solutions of morphine. With one he equated 0.29 mg/ml to 0.30. Miller points out that this was merely good luck since the increase in threshold represented here is in the flat part of the sigmoid curve. Thorp's data were more impressive for the other solution where he equated 0.35 mg/ml with 0.36. In this region the curve was changing rapidly and the agreement is excellent. Objection has been made (649) that Thorp apparently confounded intensity with rate of onset in his graded dose experiments because he had too short a standard time after treatment for threshold determination. For this reason Winder finds Thorp's graded effects difficult to interpret.

It was asserted (289) in early work that there were 21 "just noticeable differences" in intensity from pain threshold to "ceiling pain." Two such differences were called a "dol." While it is a scale of equal intervals, it is not a ratio scale; that is, it cannot be assured that a 4 dol pain is four times as intense as a 1 dol pain (289). The dol scale has been confirmed using electrical stimulation (582).

Haugen and Livingston (300) summarize their difficulties, technical and otherwise, in determining the pain threshold and the "dol" scale. A) Technical: 1) Instrument dials may not be accurate in terms of the number of millicalories actually reaching the skin. 2) The output of the lamp is subject to variation with age and use. The instrument must be calibrated with a standardized radiometer at the beginning of every experiment. 3) The opening and closing of the shutter must be checked for accord with the time intervals specified on the instrument panel. 4) The pain threshold can vary (a) with the degree of blackening of the skin, (b) with the particular area of the skin selected (forehead, hand or forearm), (c) with the time interval between tests, and (d) with the pressure of the skin against the aperture. B) End point: Here there are difficulties of decision as to (a) pain threshold and (b) the steps above threshold leading to ceiling pain.

They (300) became convinced that there was such a thing as ceiling pain and that destruction of the superficial sensory fibers marked the "end of the zenith" in this experience.

Hardy, Wolff and Goodell had called attention to all of the sources of error just mentioned, as Haugen and Livingston (300) point out. These latter investigators report that for a time their results with the "dol" scale were so consistent as to be reassuring but then would vary suddenly in an unpredictable way, and this happened so frequently as to make their results unacceptable. They present data to show how with continued testing, even though a subject's usual pain threshold was never exceeded, "something progressively deteriorated, with the accuracy of his judgment or the condition of the testing area of skin or both." This deterioration was even more striking when test doses above threshold values were used.

They (300) concluded that a single test dose of heat above the pain threshold may alter the skin sensitivity for long intervals of time, so also may repeated subthreshold tests. This, they believe, is inevitable in trying to deal with patients in a clinic and doubt if the "dol" scale has practical value there. The use of several blackened areas of skin is not sound, for the assumption that the threshold is the same in various areas does not hold in their experience: (a) Not more than four or five exposures to determine the endpoint can be employed, lest the skin tend to become sensitized. (b) A single test dose well above threshold can completely disorient an individual as to his original threshold; curiously the feeling of intense warmth that appears before the pricking pain (threshold) then dominates the sensory experience. (Is this related to the reported observation that sometimes the first a soldier knows of his wound is feeling the *warm* blood? See IV.)

Haugen and Livingston (300) suppose the pain threshold would be relatively constant provided (a) all technical sources of error are controlled, (b) only

experienced subjects are used. (But the hazard of experience in narcotic studies is evident: It is not possible to use the unknowns technique when the subject is familiar with the "aura" of a narcotic.) This implies that the subjects know exactly what end point is sought and give their full attention to this end. (c) A minimal number of tests are employed, none of them very much above the subjects' usual threshold. Constancy can hardly be the case if the reaction component is as important in threshold determination as seems to be the case. This will be discussed later (VIII).

In studying the analgesic action of meperidine and acetylsalicylic acid in guinea pigs Winder (648) plotted the maximum threshold found against the log dose, with, as Miller (451) points out, only part of the data being used. The need remains for some method which will take into account all of the data. Miller considers it likely that "the neglected values might do more than merely bolster the peak readings. There is some indication that the discrimination of the method might be greater at other points."

On the basis of extensive methodological studies in animals Winder *et al.* (651) conclude in determining radiant heat "pain" thresholds that threshold intensities (for the skin twitch) measured at a fixed duration of stimulation (original Hardy, Wolff and Goodell method) are much more uniform than are threshold durations as determined by the use of several fixed intensities (D'Amour and Smith method), that is, variable intensity at a fixed duration is more dependable in their experience than variable duration at a fixed intensity for the determination of threshold values. One reason for this, it is believed, is that latency of response could not be controlled; but it is not clear why cross-over, correlated data, would not control this variable. Possibly more important is a greater scatter of data (if true) owing to local vascular changes caused by varying periods of stimulation. However, it would take a considerable body of nice experimentation to show that this was a factor of greater importance than the vascular changes caused by varying intensities.

b. Fixed intensity, variable duration. The D'Amour and Smith (155) modification of the Hardy, Wolff and Goodell method has been found useful. A good deal of time can be saved by letting a fixed intensity of heat act for a variable time, until the threshold response is elicited. D'Amour and Smith (155) and following them, others (157, 200, 219) applied the method to animals. The heat is focused on a rat's tail, for example, which lies in a groove. When the current is turned on a stop watch is started. At the "pain" threshold, actually reflex reaction threshold, the tail is flicked away and the watch is stopped. Burns with serious tissue damage can easily occur with impairment of the accuracy of the method. In order to lessen this hazard it is customary to arrange the apparatus so that an automatic cut-off of current occurs at about two to two and one-half times the threshold time.

c. Interpretation of data. Various procedures for locating the radiant heat "pain" threshold value in guinea pigs have been tried out (651): (a) ascending or (b) descending or (c) bracketing approaches to the threshold. Each of 33 animals was studied by each approach. Slightly higher values were obtained by the descend-

ing approach, presumably because of a negative effect on irritability produced by repeated suprathreshold stimulation or a positive effect of repeated subthreshold stimulation. Possibly both are factors, as the authors point out. The only slightly higher values obtained on the descending approach offer lack of evidence for a serious cumulative positive effect of repeated stimulation above the threshold. The threshold bracketing approach gave data not significantly different from the descending approach. The former was chosen as the procedure to be employed for routine use, since it can be systematized and since the time required to determine even large changes in threshold is not particularly affected when the bracketing approach is used.

The minimal suitable recovery period has been studied (651) and it was found in guinea pigs that a rest interval of about 70 seconds between runs was free from liability of accumulation of stimulation effects. Initially a 30-second interval had been used (284) in man, and in the dog (23), but later this was extended to 60 seconds in man (74a). The effect of natural skin color as well as blackening the skin and finally the use of dark animals without blackening were studied (651) since blackening of dark animals did not usefully decrease dispersion of data.

The skin twitch used in guinea pigs (651) as indication of threshold is like that used (23) in the application of the radiant heat method to dogs. When the duration of the threshold value was increased two or three times blistering occurred. This agrees well with the observation (284) that twice the threshold stimulus for pain perception in man blistered.

It is probable that the choice of a low intensity of stimulus (since there is an intensity level below which even prolonged duration of the given intensity will not produce a threshold effect) was responsible for the unlimited duration values found by some (155, 200) as Winder *et al.* (651) point out. Extension of radiant heat threshold intensity-duration curves for pain threshold in man (74a) indicates a greater time constant for man than for the guinea pig.

Fluctuations in room temperature had a demonstrable influence on the radiant heat threshold in guinea pigs (651). This factor requires control.

Some excellent comments have been made by Miller (451) on interpretation of data derived from the D'Amour-Smith approach:

"With respect to handling the data of the D'Amour-Smith technique, it is interesting to note that, of the four groups of investigators who have used it, no two have interpreted their data in exactly the same way. D'Amour and Smith converted their results into the all-or-none type on the basis of the proportion showing 'complete' analgesia within their cut-off time of about nine seconds. Ercoli and Lewis, in 1944, calculated what they termed the 'average analgesic dose,' which lends itself poorly to quantitative comparisons between drugs. Davies and his associates found . . . the increase in reaction time in seconds plotted linearly against log dose and used this basis of effects. Foster and Carman describe an 'analgesic index' which is the square root of the ratio of the average maximum reaction time after the drug to the average pre-injection reaction time. They found that indices so obtained plotted against dose in approximately a straight line. Of these four methods, two measure the drug effects in terms of the increase in threshold, while the other two take the final level of reaction time as the better measure of effect. This lack of unanimity indicates fundamental differences in thinking.

"All of the above authors encountered the problem peculiar to this method engendered by the frequent occurrence of such complete analgesia that the test animal fails to respond within the cut-off time. Thus, there results a set of data which is a hybrid mixture of graded and quantal responses. Thus far, this situation has been met by assuming that each animal actually reacted at the cut-off time and including these assumed values in the averages. This practice introduces a bias into the results which is less or great, depending on the actual magnitude of the arbitrary cut-off time. It is especially disturbing when the responses are figured in terms of the *increases* in reaction time above the normal. However, because of the simplicity of the D'Amour-Smith procedure as a whole, this problem is worthy of serious study."

(For further data on the unsatisfactory nature of percentage rise of threshold as the criterion for judgment see V, A, 6.)

A basic question is whether the reaction time of animals (D'Amour-Smith technique) following administration of an analgesic agent can be properly correlated with the predrug reaction time. Miller (451) quotes and discusses unpublished data by Lewis and shows that the post-drug percentage increases are greatest for the animals having the lower normal thresholds. He concludes that it is apparently erroneous to assume that the increase in threshold is a true measure of analgesia and believes that the final threshold effect may be more dependable.

Winder *et al.* (651) conclude that "The radiant heat stimulus is inherently superior, in uniformity of application and absence of contact stimulation, to the conducted heat stimulus . . ." as used by Hildebrandt (315) and Woolfe and Macdonald (675). They consider it to be "far more selective in a mixed receptor field than the otherwise ideal electrical stimulus" (Bishop (80) has pointed out that the electrical threshold for pain endings may be lower than for end-organs that are more highly specialized), and far superior to the "classical" disadvantages of mechanical and chemical stimulation in a mixed receptor field.

The fact that sound objection can be raised to some of the uses to which their method has been put by themselves as well as by others and that some of their conclusions are open to question should not be allowed to obscure the fact that the introduction of the Hardy, Wolff and Goodell method of applying radiant heat in a quantified manner to evoke pain stimulated an intense interest in the measurement of pain. Their technique applied to animals has been utilized widely and with considerable satisfaction. This in itself is no small achievement. Indeed many of their findings and as yet insufficiently questioned conclusions have been so thoroughly accepted that they are in danger of being made a part of the vast body of opinion concerning pain and its relief. The word danger is used not only because too little questioned acceptance of any scientific observation is hazardous but also because, as it will be seen, there are a number of contradictions in their work.

4. Conducted heat. After exploring various methods of applying measurable stimuli to mice to produce "pain," Woolfe and Macdonald (675) proposed and used the hot plate technique. The standard time of exposure was 30 seconds, with tests following injection of analgesic agents being carried out every 10 minutes for the first hour and every 20 minutes for the next two hours, or until

sensitivity had returned to normal. The end point is raising, kicking or dancing of the hind legs. (Mice will often sit up and lick or blow on their fore paws; movement of the forelegs is not adequate for conclusion.) A temperature of 55°C. is sufficient to evoke the end point in all normal mice. Increasing temperatures of 55° to 70°C. in steps of 5°C. have been employed. Higher temperatures have not been used because of probable damage to the feet with altered threshold from this cause. Mice are customarily used in groups of 10. Reaction time is the criterion employed for comparison of one situation with another. Eddy and his associates (192a, 194) have used the method extensively and with satisfaction.

They report that "Initial reaction times for 2000 mice averaged 10.48 ± 3.5 seconds. It differed from this average by one standard deviation or less in 74.4 per cent, by not more than twice the standard deviation in 21.9 per cent, and by more than twice the standard deviation in 3.6 per cent. The two initial reaction times on the same mouse differed by 3 seconds or less in 61.5 per cent, by 4 or 5 seconds in 20.25 per cent and by more than 5 seconds in 18.25 per cent. In the last group, in 75 per cent of the instances in which a third reaction time was determined before injection, the third differed from the first reaction time by 5 seconds or less." For their criteria of effectiveness see VI, 3 and their recent article (192a).

Data provided Miller (451) by Eddy, indicated on analysis that the mice vary greatly not only from one to another but also between control readings taken 20 minutes apart. The odds were only one in a hundred that these variations were due to normal chance. Miller concludes that the Woolfe and Macdonald method is not more than a "convenient, rough screening method," because of the variation just described and because of the "generally accepted fact that mice are about the most heterogeneous small laboratory animal known." In a later paper Eddy and Leimbach (192a) report improved uniformity and reproducibility of results with the conducted heat method and describe their current criteria of effectiveness.

The pain threshold of the forehead of man was determined by a warm wire algesimeter (405). Five spots on the forehead were in contact with a wire; 4 of these were always cool. The current was adjusted until at least 3 painful stimuli out of 5 tries were produced by the heated wire. Then the current was readjusted downward until 2 painful stimuli or less were perceived on 5 wire applications. The forehead pain threshold was taken as the amperage that produced 2½ painful stimuli out of 5 wire applications. Although it is stated that one of the purposes of this study was to evaluate the warm wire method of algesimetry, this is next to impossible with the data provided since the important material on pain threshold without medication as determined with this method is not given. Thus the reader has no good idea of the constancy of this vital datum. Differences presented between mean threshold alterations produced by the drug and the placebo are hardly adequate. The overpowering dose of morphine used (20 mg) produced nausea in 7 out of 10 subjects (information volunteered) and 5 out of 10 vomited, even though the subjects were supine and not walking around. Two out of 10 are recorded as having sweated. Amperage, although used

here, is known to be less dependable than wattage for measurements of the kind attempted (317).

5. Electrical methods. The following studies, indicated by number, refer to original methods, their development and their application in the categories specified.

Man: 13, 70, 88, 116, 170, 171, 224, 244, 246, 259, 272, 275, 292, 299, 304, 310, 316–319, 324, 348, 349, 354, 392, 394, 404, 405, 416, 425, 435, 447, 448, 452, 478, 479, 485, 507, 526, 529, 539, 558, 560, 561, 582, 602, 610, 614, 624.

Animals: 165, 212, 244, 349, 375, 381, 383, 454, 553, 555.

More than 100 years ago von Helmholtz (612) used faradic currents to produce pain. He studied the phenomena associated with make and break induction shocks, as did Fleming in 1892. The modern use of electrical methods for producing pain for experimental purposes can be said to have started nearly 50 years ago. According to Fleisch and Dolivo (212), Ruckstuhl and Gordonoff first used the method in rabbits. Man was the subject of choice and galvanic, faradic, high frequency currents or condenser discharges have been used. A liquid finger electrode was used by some (447, 448 *et ante*). Others (435) applied small platinum electrodes to 4 parts of the body and drew the unwarranted conclusion that they had thereby "thus reduced the chances of error fourfold." Koll and Reffert (382, 383) used a condenser discharge stimulator in dogs and reported consistent results. Fender (207) studied the faradic stimulator and found voltage *per se* of little value as a parameter. Current, frequency and wave force he found useful. The effect of analgesic agents on the response of the rat to induction shocks was studied (437). Others (381, 394) used similar methods involving a stimulus derived from a repetitive condenser discharge, with the stimulus strength measured in milliamperes. Calculations were made from the peak voltage across a calibrated resistance in series with the stimulating electrodes. Dogs were used (381) with widening of the palpebral fissure as the sign of "pain." Lanier used human subjects and depended on their report of threshold pain.

It was found (381) that muscle reflex or skin twitch could not be used as a threshold with Knowlton and Gross' electrical shock method, for it was not altered by analgesic drugs, although they grant it seemed to work with a modification (23) of the radiant heat method. This is a curious observation. Others (165) reported, however, that electrical stimuli could be used in rats to demonstrate significant change in the pain threshold produced by narcotics. The sign of pain employed was a jump by the animal when current passed through wires in the floor of the cage.

Goetzl *et al.* (244) used a stimulator arranged to give peaks of induced current to man's and to dog's teeth through amalgam fillings. Unfortunately, details adequate for exact repetition of their work were not provided. Others (451) made a considerable effort to repeat the work but were unsuccessful. In view of the reported success of Koll and Reffert they believe the method worthy of further trial, but consider its reproducibility and discriminatory power still unproven. Although Ivy *et al.* (348) clearly believe that their method of electrical shocks to

teeth has much to recommend it, their own data are at times not reassuring. For example, they report that, following the administration of 16 mg morphine subcutaneously in man, 7 out of 16 subjects showed a fall of pain threshold rather than a rise, in 1 there was no change, and in only 6 a rise. Two were unaccounted for.

Notwithstanding data of the kind just presented, the view has persisted that electrical stimulation can be useful in pain studies (242). Goetzl considers that the skin as a site for stimulation is not very desirable since other afferent systems are unavoidably stimulated along with the pain apparatus. The skin is also subjected to influences which are difficult to control. External factors are temperature and humidity; internal are temperature and the circulation. Drugs under test may influence the skin in such a way as to alter pain thresholds through circulatory change. (There is no proof that circulatory changes produced in this way may not also interfere with pain thresholds determined in the teeth.)

Goetzl and his associates like the tooth pulp particularly as a site for stimulation. This they believe contains only pain fibers although they and others have reported a pre-pain sensation from electrical stimulation. (See below.) The tooth pulp is subject to relatively few external or internal varying influences. Goetzl reports that the tissue will long remain unharmed if the stimuli are not of "too great intensity." Just what this is is not clear.

Evidence has been presented by Reynolds and Hutchins (506a) that painful stimulation of teeth produces a hyper-irritable central state which persists from months to years. What influence this might have on repeated determinations of pain threshold by electrical stimulation of teeth is not known.

Isbell and Frank (reported by Wikler [636]) found no consistently reproducible threshold in man with electric shocks to teeth, nor did Bishop (86a). Thorp (591) attempted to use electrical stimulation in work with experimental pain but found contact resistance (rat scrotum) and the electrodes too variable and gave it up.

Goetzl (242) assumes, in common with most workers in this field, that pain threshold elevation represents analgesic action, but concludes, on the basis of an extensive study of many investigations on the effects of antipyretic drugs (including acetylsalicylic acid) on pain thresholds, that the widespread assumption of elevation of pain threshold as a measure of intensity of analgesic action is erroneous as far as the antipyretic substances go. But, a fair question would seem to be, if erroneous for them why not erroneous also for the narcotics?

In view of the remarkable inconclusiveness of the method of electrical shocks to teeth in man (yet deemed satisfactory, 348), it is difficult to accept work that depends upon the method and technique. This same group (349) reported that epinephrine was a highly effective analgesic agent, this time in dogs as well as in man. The data in this latter paper are more convincing than those in an earlier one on the same subject, even so, it is hard to believe that 0.5 mg epinephrine had four times as much effect on the human pain threshold as 16 mg morphine, but that is what they report. If this is the case it seems evident that something very different from pathological pain is under examination. As usual, the threshold changes in dogs are more impressive than in man.

A further difficulty is the observation (349) that while the 0.5 mg dose of epinephrine has a powerful effect on tooth pain sensitivity, it has no appreciable effect on pain sensitivity of the skin. The material presented in this study can be construed as evidence of a sort that pain threshold changes are not relevant to the problem of general pain relief by drugs. These authors add a puzzling statement: "Our observations on human subjects do not indicate that the analgesic effect of epinephrine 0.5 cc given subcutaneously is of definite practical significance, in view of the variable response" although they state that epinephrine is "*definitely*, although variably analgesic when administered subcutaneously." It will be recalled that they had just "shown" it averaged four times greater effect than that of a large dose of morphine. Their thesis so far has been that these threshold changes are important; now, suddenly, they are not very important. This is confusing. One wonders whether the epinephrine may have had considerable local effect on the circulation that could have impaired the tooth sensitivity. If so, the method would seem to have little usefulness.

Notwithstanding all of the difficulties and room for doubt just mentioned, the method of producing experimental pain by electrical shocks to teeth continued to attract its old devotees as well as new ones. They all seem to have been greatly influenced by Goetzl *et al.* (244) who considered the tooth pulp method to be the most promising of all methods producing experimental pain. While many have accepted the method with interest, as pointed out (292), some have received it without conviction (197, 451), since adequate data on which to judge its reliability and validity are not available. Harris and Brandel (293) had found it not sufficiently sensitive or reliable. They were unable to demonstrate constant thresholds even at 10 minute intervals.

A systematic study of the tooth pulp method was carried out (88) and the true measure of stimulation was found to be current applied, not electromotive force. It was found that a single rectangular pulse of 10 msec was best for stimulating. A uniform threshold could be achieved only when the tooth electrode was placed at the same point on a carefully dried tooth. Thresholds increased from anterior to posterior and varied in mandible and maxilla. Stability of threshold was found when the above factors were taken into account.

To these requirements others were added (292). Many (86a, 88, 116, 405, 479, 485, 558, 560, 561, 582, 636, 684) have observed that the first sensation evoked by electrical stimulation of a tooth is not painful (surely this permits some doubt that the only sensation arising in a tooth is pain as often stated) but becomes painful as the intensity of the stimulus is increased. Both the Sonnenschein and Pfeiffer groups found that the first painful sensation offered the best threshold for the study of the effects of analgesic agents. However, Switzer (583) [quoted by Harris and Blockus (292)] on studying both thresholds found a good parallelism in time-response curves after morphine administration.

Not only are placebo controls necessary but (292, 558) placebo effects should be compared with an extended control period during which no medication is given. Harris and Blockus (292) agree with the Beecher group that the double-unknowns technique, where neither subject nor observer is aware of what was

used, is essential. They (292) have carried out an extensive study to evaluate the reliability and validity of tooth pulp algesimetry where "careful control is exercised over both the mechanical and psychological variables." An important question they seem not to have asked is whether the concept that experimental pain can be employed in man to evaluate analgesic agents is sound. This will be discussed in XII.

Some (539) have boldly entered the difficult field of electrical stimulation. In a typical case the stimuli are applied to the ear lobe as they were also by others (324). The complexities of the field had been indicated in already published studies (317, 464). The last two studies deserve more attention than they seem to have received.

Amperage, voltage, frequency and resistance in circuit have all been mentioned (666) as of im portance in the electrical stimulation method of producing pain. Disturbance in any of these could lead to error.

Hill *et al.* (317) have made a systematic study of apparatus for delivering controlled electrical stimuli, with the purpose of discovering which aspect of a 60-cycle alternating current, *i.e.*, voltage, amperage, or wattage is chiefly pertinent to discrimination of shock stimuli in psychological experiments. They point out that, while electric shock is easy to apply, accurate control of it is most difficult. It is clear that control of voltage alone is quite unsatisfactory, even when considerable physical resistance is added to the circuit in series with the biological material. While many arguments persisted, it had been fairly generally agreed that the physical aspect of the electrical shock to be controlled is amperage; yet careful studies have indicated that this is not satisfactory, but that power (wattage) provides the best index of the sensory effects. In any case, if, using electrical stimuli, dependable studies are to be made, the method, as Hill and his colleagues have pointed out, must contain the possibility for accurate prediction of the voltage necessary for obtaining the amperages and wattages desired, when the skin resistance is known. They point out further that Ohm's law cannot be depended on, since capacitance must be allowed for in studies of biological circuits. This is particularly important when the skin impedance is high. These workers have therefore devised an apparatus which can deliver shocks of known wattage or amperage, and have constructed empirical power curves for pre-setting the stimulator to deliver the shock intensities desired. These workers found in experiments on discrimination where "short term disruption of behavior" was produced by electric shock that control of power was greatly superior to control of voltage, or of amperage. There was high correlation between power delivered and estimation of pain intensities. The data of this study "prove conclusively," the authors believe, that power, wattage, is a more important physical variable than amperage or voltage in determining verbal reports of the intensities of shock stimuli. Voltage is less significant than amperage. Wattage is the variable that should be under the operator's control for experimental use. They conclude that, when this is provided for, electrical shock stimuli may prove to be not only a convenient method to use in studies of pain but an accurate one. This remains to be shown.

It has been demonstrated (284) that the *energy* delivered by radiant heat is useful in studies on pain. Hill *et al.* (317) point out that, whatever the technique for producing pain, electrical, thermal, mechanical, photic, sonic or whatever, the relationship between pain intensity and the physical aspect of the stimulus can be more accurately described when the stimulus is stated in terms of energy.

In this connection see Mueller *et al.* (464) (VII, 3, p. 117) for a discussion of difficulties with electrical stimulation brought about by skin impedance and their conclusion that, when the skin impedance is high, all of the current, instead of passing through the entire electrode area, suddenly surges through a small area of breakdown of skin impedance. When the skin impedance was low they were unable to produce the necessary "prick" pain whatever the current. Thus there is great difficulty in standardizing the area of stimulation, and they question the conclusion of others (317) that the controllable stimulus can be expressed most accurately in terms of energy. Apparently to Mueller *et al.* the problem is insoluble as far as electrical stimulation is concerned.

6. Mechanical methods. The following studies, indicated by number, refer to original methods, their development and their application.

Man: 13–16, 34, 91, 106, 110, 130, 131, 147, 240, 241, 266, 267, 268, 288, 296, 308, 313, 322, 323, 326, 353, 364, 367, 400, 461, 465, 466, 481, 505, 506, 533, 534, 535, 546, 579, 605, 606, 609, 610, 611, 626, 643, 646.

Animals: 103, 180, 184–187, 198, 212, 226, 245, 271, 309, 311, 366, 375, 453, 454, 516, 540, 552, 563, 576, 622.

a. Von Frey hairs. Von Frey (609) developed a method for producing pain by acute bending of the epithelium (81). Horse hairs of various diameters and lengths were attached to a lever and the weights required to bend the hairs were determined on a balance. When insensitive areas such as the hands are used, the maximum range (0.0125 to 10 g) is not adequate when pain has been dulled with analgesic drugs (534); however, increase above 10 g was not desirable because tissue damage and bleeding occurred. Seevers and Pfeiffer (534) in a modern application of von Frey's method used sensitive areas, the upper eyelids, the right lower eyelid near the inner canthus and both lips at the vermilion line. Five spots in these areas were chosen and subjected to multiple stimuli starting at the low range and proceeding until the pain threshold was found. The data from the five spots were averaged. Determinations were usually made at 15 to 30 minute intervals after parenteral injections of drugs, and after intravenous injections as often as every five minutes. A limiting factor was the possibility of tissue damage. They found that the pain threshold varied widely from subject to subject.

By eliminating the subjects who did not show a rise in threshold (low initial threshold) and those whose thresholds were too high to record with their apparatus, Seevers and Pfeiffer were able to show satisfactory threshold elevations following the administration of powerful analgesic agents as had Mullin and Luckhardt (465, 466) somewhat earlier. Lee (403) also reported that some subjects with low initial pain threshold failed to show opiate effects on the pain threshold.

On the other hand, Gaensler (229) observed in his patients who had low pain

thresholds in response to increased hydrostatic pressure in the biliary tree, a mean elevation in response to morphine of 340 mm water, whereas patients who presented an initial high threshold showed only 125 mm water elevation of threshold effected by morphine. This same effect was demonstrated in an individual patient and in groups of patients with morphine, meperidine and codeine. Unquestionably there was a sharp decrease in threshold-elevating power with control thresholds of increasing magnitude. Along this same line Miller (451) found, in rats subjected to radiant heat stimuli, that post-drug reaction times (thresholds) were not correlated directly with the initial reaction time (threshold). He found that the greatest percentage increase in threshold due to the analgesic occurred in general in the lower normal threshold groups and "indicate(s) the bias that results from the apparently erroneous assumption that the [percentage] *increase* in threshold is the true measure of analgesia."

The von Frey method has been discussed in detail (374). It has been used in recent times by others (367). See these papers for details of special modifications of the von Frey method. The last investigators referred to have applied the method to various purposes including comparisons in quantitative terms in man of the analgesic effects of the inhaled gases, nitrous oxide, ethylene, or cyclopropane. They have done this through establishing which concentrations of the various gases are necessary to elevate the pain threshold to a given point as determined by their modification of the von Frey technique.

Bishop (81) observed that pain develops as mentioned above from acute bending of the skin, so he chose curvature as a convenient measure of sharpness. His instrument was made by fixing small rounded droplets of solder on needle points attached to a lever which registered pressure. He determined quantitatively the excitability of pain endings in the skin in terms of the pressure required to reach the pain threshold when the contact ends differed in bluntness, and concluded that the bending or the stretch caused by acute deformation, not pressure, is the form of stress to which pain endings react. He pointed out, mechanical stimulation in distorting tissues makes exact localization of pain spots difficult. The growing ends of pain fibers in the skin are more sensitive to mechanical stimulation and less sensitive to electrical stimulation than are their final sensory endings (77). These findings were qualified by the conditions under which these stimuli are necessarily applied: conductivity to current of different tissue components, depth of endings, protection by overlying tissue and so on (77).

It has been pointed out that the difficulties of determining a threshold concentration for local anesthetics are greater than might be supposed (114). Accordingly, some progress has been made (125) by developing the technique of applying the solution to be tested to the cornea of guinea pigs and thus thoroughly testing (six times, not once) at regular intervals the corneal reflex. The proportion of stimuli which evoke responses is the item of interest. Groups of guinea pigs are used and the mean rate of disappearance of anesthesia is determined. Thus comparisons between agents can be made. One difficulty with all such pressure methods is that the stimulus cannot be limited to stimulation of pain end

organs alone but involves other afferent systems as well. This difficulty is now known to apply also to the cornea (632a).

b. Gross pressure, animals. Numerous gross pressure methods are included in the listings at the beginning of this section. Special mention should be made of Eddy's (184, 185) tail pressure method used in cats to indicate "pain" threshold by producing a cry. While Eddy used this method for some years with fair satisfaction, it was not very precise and now he prefers a modification of the conducted heat method of Woolfe and Macdonald. This tail pressure method or modifications of it have been utilized by others (271). But the tail squeezing method applied to monkeys was not satisfactory (553): the animal responded slowly and no accurate measurement of "pain" threshold could be made. It was found also (226) in studies of the use of the tail pressure method in rats that, if swelling or soreness of the tail develops as a consequence of early tests, subsequent runs will be influenced by this change in the conditions of the experiment. This defect impairs all pressure methods. Friend and Harris believe that this problem can "undoubtedly be largely overcome" by using forceps which will register pressure rather than diameter. If early use has made the tail tender it is not likely that this will solve the problem.

c. Gross pressure, man. A good many individuals (241, 326, 417, 481, 535, 643) have attempted to develop simple and practicable devices and procedures for clinical use in appraising patient sensitivity to pain. Pelner (481) used pressure on the skin over a bone (thumb) as a means of evoking pain. He studied 178 human subjects by his method and also by Libman's method of pressure on the styloid process. Pelner reports 22% as "hypersensitive" by his method, whereas he found 30% "hypersensitive" when he applied Libman's method.

Others (643) found pressure on the styloid process (417) of the mastoid bone not entirely satisfactory since the quantity of pressure exerted could not be accurately evaluated. Wilder used Hollander's (326) method (food grater inside a blood pressure cuff). Pressure is increased until the subject cries out, winces, or changes his expression. These are presumably reactions to pain. The reaction threshold is said to be lower in normal women than in normal men. The reaction level appears to be lower in patients with functional disease than it is in normals or those with organic disease.

In a pilot study rather than a well rounded investigation the pain produced mechanically by blows to the fingers, compression of the finger web and by the pulling of hairs was studied; Wells' (626) interesting approaches merit standardization. Sherman used both the Libman and Hollander tests on 450 human subjects and found good corroboration of the two tests. He found in 130 patients with functional disease five times as many patients who were to be classed as hypersensitive as in 130 patients with organic disease. He reported also that the pain threshold is lower for women than for men, and higher for coal miners or Micmac Indians than for his "normal" (total) group. In 260 routine "office practice" subjects 65% were classified as having normal sensitivity to pain, 17% were hyposensitive and 18% were hypersensitive to pain. In the hypersensitive

group 72% were women, and in the hyposensitive group 90% were men. These findings suggest cultural poses or attitudes lived up to; *i.e.*, reaction was very likely a factor here.

d. Tourniquet, muscle ischaemia. For some years the writer has speculated that possibly one difficulty with experimental pain methods is that the experimental pain produced is usually sudden and fleeting, "pricks," "jabs," "stabs" of pain and so on, whereas most clinical pain, aside from some of the colics, is much more sustained. Moreover it is difficult to impossible to control with drugs the pain aroused by sudden pressure on a wound or by sudden motion of a wound, or colicky pain by even large doses of powerful narcotics. There is more than a hint in these observations that study of slowly developing or sustained pain has considerable interest for experimental purposes. In this connection Adrian's (5) comment is pertinent, "The rule that the effectiveness of the stimulus depends on the rate of change in the environment as well as on its extent applies to mechanical stimuli as well as to electrical, for a gradually increasing pressure on a nerve is far less effective than a sudden blow." With this in mind Green and Beecher (263) studied the effects of morphine on the pain threshold elicited by tourniquet with encouraging results. This work is not yet complete.

It is interesting to find that Hewer and Keele (313) using ischaemic muscle pain found 7.5 mg methadone equivalent to 7.5 mg morphine. This 1:1 relationship is exactly that found by Denton and Beecher (160), using pathological pain.

In 1931, just 100 years after the term intermittent claudication had appeared in the medical literature, Lewis *et al.* (415) published their successful data on reproducing the pain experimentally, in normal limbs. They did this by occluding the blood flow in exercising (isometric) muscles. It was their view that the pain aroused is determined by a "stable chemical or physico-chemical stimulus developed in the muscle mass during its exercise." The pain is related to the amount of exercise. With the subject performing with a constant effort at a constant rate, the pain threshold appears at a constant time. It is important that the subjects not count the contractions of the fist, lest they be influenced in calling endpoints by past experience. The authors present evidence that the pain developed is not directly due to oxygen lack of nerve endings, for if so complete obstruction of vessels for 10 minutes, causing as it does considerable loss of oxygen should perceptibly diminish the time taken for pain to appear when exercise is undertaken. It does not do so.

Harrison and Bigelow (296) modified this muscle ischaemia method to use isotonic rather than isometric contractions. A sphygmomanometer cuff is applied to the arm and the pressure elevated to 250 mm Hg. It is important to have the arm elevated when the tourniquet is applied to avoid the accumulation of blood in the distal part of the arm which can produce discomfort and obscure the pain threshold sought. The subject flexes his fingers to form a fist and then extends his fingers at the rate of once per second, with constant force. They have reported good constancy of the end point for that method of producing "visceral" pain and have found it sensitive to the action of analgesic agents. They report that

while thresholds for a given individual are remarkably constant over a period of hours, variations among individuals are great and are found in a given individual over a period of days. Fatigue appeared to raise the pain threshold.

These data as to lack of constancy are counter to those of others (528) from the same laboratory, but Harrison and Bigelow say that their observations are not pertinent to the question of universal pain threshold, since they did not control environmental temperature, vascular state of the arm, previous exercise, drug effects, perceptibility of the subject to pain threshold as by influence of pain elsewhere, suggestibility, attention, concentration. This is regrettable. This disavowal is all the more remarkable in the light of Harrison and Bigelow's statement that they carried out this study "to acquaint ourselves with the limitations of our apparatus and the controls necessary. We then began tests . . . upon drugs . . .", apparently without the controls they agree are important for standardization.

These investigators (296) set out to determine if the effect of analgesics on "visceral" pain corresponds to their effect on cutaneous pain. See also others (667). They conclude that the effects are similar.

e. Distention of the esophagus (visceral "pain"). A balloon 1½ inches long was introduced through the nose into the esophagus to a point about 2 inches above the cardiac end of the esophagus (131). The balloon was then inflated at the rate of 2 cm water pressure per sec. The observations at one minute intervals were made on each subject to determine his "pain" threshold. While this varied widely, Chapman and Jones considered that the visceral threshold correlated fairly well with the radiant heat skin pain threshold determined in the same subjects. The authors speak of "visceral pain sensitivity" but they make it clear that the end point was a sensation of substernal fullness rather than pain. They say, "A pain end point with a definite hurting quality, however, could not be measured." Occasional individuals reported "heart burn," a "cramp ache," a "sharp stab" but no one clear endpoint was agreed upon as a beginning pain. There was a gradual transition from the sensation of substernal fullness to pain-like sensations, but no exact end point could be determined. Variation in the tone of the wall of the esophagus was probably a factor in the variations encountered. Anxiety played a part in the development of tone. The method is not suited to a study of experimental pain, at least not in its present state of development.

f. Distention of the biliary tree (visceral pain). It has generally been assumed that visceral pain is a different sensation from "superficial" pain, being evoked by its own special set of stimuli and transmitted to the central nervous system through special pathways. Gaensler's observations (229) are therefore of particular interest. For this work a quantitative method had been devised (400) for measuring visceral pain thresholds by hydrostatic distention through a T-tube in the common bile duct of man. "Diseased" bile ducts were involved. Each patient acted as his own control before and after drug administration with the pain threshold determined introspectively. This method is a combination of experimental and pathological pain, since the pain elicited experimentally is in the site of recent or present disease to which the patient has become more or less conditioned or perhaps sensitized.

It is true as Adrian (4) points out that the pains which are of most interest to medical science (as well as to the patient's welfare) are less accessible to study than are those of the skin. So special interest attaches to the demonstration that the same doses of the same narcotics that block peripheral pain will also control the pain produced by distention of the biliary tree. Such observations as well as clinical experience establish confidence that much of general value can be learned by study of pain of peripheral origin. The measurement of deep pain thresholds presents not only all of the difficult problems that hold for superficial pain studies but others as well. The viscera are not only relatively inaccessible but they do not respond to the quantifiable stimuli of heat, electric shock or pin pricks. They do respond to stretch.

Gaensler's (229) work provides an important confirmation that data obtained on superficial pain thresholds is paralleled by work on deep or visceral pain. He chose the 8 mg dose of morphine as effective based on his visceral pain data. This agrees with the Beecher group's wound pain finding and so "equates" to this extent at least the two methods. Gaensler believes that muscle pain is "integumental pain" like that of the skin.

In general (124) there is not much evidence that one analgesic agent is more satisfactory than another with the several types of pain. The source of the pain usually appears to have no relationship to the effectiveness of the analgesic agent. Pain intensity and the nature of the agent used determine the quantity of analgesic agent needed for relief; however there is a suggestion that there may be some difference in effectiveness of common analgesic agents when used for different purposes. Lasagna and Beecher (395) found 50 mg meperidine per 70 kg body weight equivalent to 10 mg morphine, whereas Gaensler (229) finds that even 100 mg meperidine are inferior to 10 mg morphine in treating biliary tree pain. Such seeming conflicts of data may well be explainable on the basis of the agents' side actions. Meperidine was well shown by Gaensler to produce spasm of the sphincter of Oddi and thus to elevate pressure within the biliary tree, probably increasing through its side action, the pain its primary effect was meant to subdue. Morphine does the same.

Gaensler (229) found in 8 observations that placebos had a negligible effect if any on visceral pain thresholds, whereas, at the same time, a powerful analgesic like meperidine had a great effect on the pain threshold. This is puzzling. It is possible, although unlikely, even in 8 subjects that there might have been no placebo reactors among them. In the absence of the "double-unknowns" technique unconscious guidance by the operator could have great effect. Placebos are effective on experimental pain, for example, a significant placebo effect with the tooth stimulation method was found (558).

g. High frequency sound waves. Aching pain is produced by high frequency sound waves emitted from a suprasonic oscillator (27, *et ante*). This form of energy has some promise as a pain stimulus for use in experimental pain work. It has not yet been systematically studied for that purpose. The pain threshold depends upon the product of the intensity of the beam and the time irradiation takes place (509). Damage to hearing has been found at intensity levels that lie well below the

threshold for auditory or aural pain. See Rosenblith and Huetter (509) for a discussion of the question of dangers in ultrasonic therapy. Dangers involved may exclude this technique from use for experimental pain purposes.

h. General comment. Mechanical stimuli whether measured in terms of force or pressure seem to be well suited to the production of pain; but tissue reacts to pressure in a variable way (289) and one infers from this that painful stimulation is variably related to pressure. It is suggested that if the rate of change of pressure on the tissue and the rate of deformation of tissue were studied and recorded, it is possible that mechanicaly elicited pain thresholds might be more precisely determined than is the case at present. Also, there are few discernible steps between threshold stimulus of mechanically produced pain and the maximum discernible (289). There is great variability in what will produce pain from one time to another as far as the external stimuli are concerned. This fact is especially evident with the hollow viscus as was made evident in the foregoing brief discussion of balloons in the esophagus.

7. Chemical methods. The following studies, indicated by number, refer to original methods, their development and their application in man: 13, 17, 24, 139, 269, 401, 508, 511, 610.

If the "adequate stimulus for pain" is a chemical substance, and there is some evidence for that view (289, 415, 511, 527), then the production of experimental pain with such a substance would have considerable appeal.

Cutaneous pain has been produced experimentally with chemicals (24). It was found that injection techniques, intradermal injection or pricking through a drop of solution, gave undependable results. So a blister was raied by cantharidin, and the separated epidermis removed. The blister base was used for testing. Small quantities of the test solutions, about 0.2 ml, were then applied at intervals of 5 to 10 minutes. Between applications the area was bathed with a special isotonic electrolyte solution. Armstrong *et al.* (24) had their subjects squeeze a pressure bulb which recorded a tracing on a moving drum to indicate intensity of pain. The subjects could not see the tracing. The pain threshold response to a given chemical was found to be quite constant for a given individual. The intensity of pain is proportional to the concentration of the noxious chemical applied. The advantages found by the workers with the method (24) can be summarized: Spontaneous pain in the lesion goes away within 10 to 15 minutes. The exposed nerve endings permit immediate contact with the test solution. The same nerve endings are exposed to the various test solutions. It is said that with suitable intervals between applications, the pain receptors are in a comparable state of sensitivity for each test. The question of fluctuation in sensitivity can be controlled with the application of standard pain-producing solutions of potassium chloride or acetylcholine. The exposed area remains sensitive up to two days during which time 50 to 60 applications can be made.

Various investigators have produced pain by the use of chemical agents in peptic ulcer (504, 659, 673) and in headache (542). Some attempt at quantification has been carried out but it seems unlikely that such techniques will have very

great usefulness in solving more than very limited experimental pain problems. Others have carried on similar studies (289).

8. Miscellaneous methods. Depression of the respiration in rabbits parallels analgesic activity of narcotics in rats (592) so that, in general, a given degree of analgesia carries with it a given degree of respiratory depression. The data hold well for morphine, meperidine and methadone. This is presumably a non-reflex effect and the only such method for animal use known to the reviewer for the appraisal of analgesic agents. It would fail in man for dihydrocodeine (262); but then, N-allylnormorphine failed to be picked up as an analgesic in animals. No methods are universally effective. The Hardy, Wolff and Goodell method often fails in man but not so often in animals.

The reviewer, without knowledge of this work, proposed a similar study to the National Research Council in 1952 (45) in connection with a discussion of screening of analgesics in animals:

> "All methods now employed depend upon a reflex. It is difficult to understand why they work as well as they apparently do. We should like to investigate another approach to animal screening. From the work described (on man in the report presented at that time), there seems to be a close association between analgesic power and depression of the respiration by drugs equivalent to morphine in pain relieving strength. We should like to check, using unknowns, whether it might not be possible to identify valuable analgesics in animals more satisfactorily by depression of the respiration than by the reflex methods now in use."

The idea seems to have been sound as had already been shown (592). It deserves further exploration.

Foster and Carman (219) have attempted to use side action liability in screening new analgesics in animals. Changes in the respiration in response to electric shock have been used in monkeys to indicate the "pain"-reaction threshold (553). It has been reported that narcotics eliminate vasoconstriction in a finger following a painful stimulus (529).

Others (222, *et ante*) have employed the miotic effect in evaluating analgesic drugs in man. These investigators consider their objective method of appraisal to be an adjunct to other methods. It is especially useful for demonstrating persistence of side action. Their findings with this method made possible the prediction that the action of acetylmethadol would persist for a long time (40 to 60 hours) and that repeated doses must be given only guardedly lest cumulative poisoning develop. This method gives supplementary information concerning the appearance, intensity and duration of side effects when administered by different routes. Unfortunately, measurements of miotic effect, as the authors point out, do not correlate very well with the degree and duration of pain relief in man.

A vascular reaction (vasoconstriction) has been used in man as evidence of pain. It is reported (529) that the threshold for this is consistently elevated by narcotics.

Not only pain but also non-painful cold and touch produced a noticeable al-

teration in the encephalogram. The change was so lacking in specificity as not to be useful, however, as an indicator of pain threshold (65).

B. Pain arising in pathology

The foregoing sections have provided many indications that experimental pain has certain sharp limitations of usefulness as it has been generally employed to the present. In a later section on "Reaction" evidence will be presented which indicates what the nature of the differences is between the two types of pain, experimental and pathological. But first, methods of measurement will be discussed.

1. Lee's method. Lee (403) planned and carried out a well conceived and careful study of opiates (a) in cancer patients with chronic pain and (b) in surgical patients with acute pain. His purposes were to determine the minimal effective clinical analgesic dose and duration of effect of morphine and new morphine derivatives, to find the incidence and duration of sleep accompanying analgesic action, to determine the occurrence of side effects from single or repeated doses, and finally to discover evidence for the development of tolerance to and dependence upon a drug, "administered in its minimal effective dose at intervals consistent with its duration of action over a prolonged period of time."

In his system, Lee gave smaller doses than he judged would be necessary, to patients free of narcotic and in need of pain relief. The dose was gradually stepped up until "complete relief of pain occurred in most cases," or until it was evident none would occur at reasonable dosage levels. Placebos were "occasionally" used. Four kinds of data were collected: Observations were made by nurses as to analgesia, sleep, toxic or other side effects. The double unknowns technique was used. How often the nurses' inspections were carried out is not clear. A physician examined and questioned the patients (at intervals not stated) as to the patient's impression of his pain and the immediate and "chronic" effect of the drug used, that is, both pre-injection sensations and inter-injection comfort. At about two-week intervals opiates were withheld for 6 to 22 hours and abstinence signs looked for. Following the periods of withdrawal a smaller dose than formerly was given, and this was adjusted upward as needed. At least once weekly at 15-minute intervals for an hour or more after a usual dose of drug, information as to the following, blood pressure, temperature, heart rate, respiratory rate, comfort or discomfort and "psychic condition" were charted. There were also notes by the patient, based upon a questionnaire, utilized twice daily. This part of the study did not last long, for "the patients were apathetic toward following the schedule as long as they were comfortable and otherwise entirely and emphatically unreasonable in their exaggeration of their discomfort." This is very like the experience of Houde and Wallenstein (332) and not in line with Keele's (365) reports. (See V, B, 4.) Keele, it must be remembered, dealt with very few patients. If they were highly selected for cooperativeness, the incidence of placebo reactors was probably high (398). Finally, an attempt was made to get at the patients' pain threshold using a modification (534) of von Frey's method. Lee confirmed Seevers and Pfeiffer's objections to the method. He found, as Seevers and

Pfeiffer had, that some individuals with a low threshold showed no elevation with opiates.

It is interesting to observe that Lee (403) found with his method, in 776 patients who got morphine for acute pain in the Massachusetts General Hospital, the average individual dose of morphine was 9.6 mg, in excellent agreement with Lasagna and Beecher's later observations (397). For 20 patients in the State Cancer Hospital with chronic pain, he found the average dose of morphine to be 13.1 mg. Undoubtedly some tolerance had developed in the chronically ill patients.

It is quite clear from Lee's 9.6 mg average dose of morphine for patients with acute pain that he has obtained as correct a figure as others. Lee has, in effect, done in a polished way what able practitioners do in evaluating drugs. More recently Troxil (601) has carried out much the same kind of study. With Lee's hundreds of patients and thousands of doses he has arrived at the same value as others. But the method is ponderous and not flexible; it is expensive, especially in terms of time and effort. The Beecher group and the Houde group have shown that more precise data can be obtained with a relatively few patients in a much shorter time and with greater flexibility and adaptability to the problems of the evaluation of new agents.

2. The Beecher group's method. Although pathological pain had from times of antiquity provided the occasion for the trial of medicinal agents intended to relieve suffering, and although Lee (403) and others as just described, had refined the ancient trial-and-error methods, the Beecher group, beginning in 1946, were the first to systematize the use of pathological pain for the study of analgesic agents and for study of mechanisms of action of these agents. Houde and Wallenstein at the Sloan-Kettering Laboratory in New York have, beginning in 1950, employed similar techniques and have developed their own very successful and useful approaches to the use of patholgical material, shortly to be described in some detail. Former members of the Beecher group have continued to use these techniques or modifications of them: Keats at Baylor University and Lasagna at the Johns Hopkins. Likewise, laboratories, at Randolph Air Force Base, at the National Institutes of Health, laboratories in Pennsylvania, Cincinnati and in London have all used and reported confirmation of the usefulness of these techniques. Evidently they have filled a need. Beecher has emphasized the differences between experimental and pathological pain (see XII). He has called attention to the limitations of usefulness of experimental pain (44, 50, 54, 55, 56, 67, 159).

In work extending over a period of years, more than a score of subjective responses have been studied. This work has been summarized in three papers (44, 51, 54). Pain has served usefully as a prototype for guidance of study of other subjective responses, and the principles of control worked out with pain apply as well to work on other subjective responses. The basic method remains that evolved from 1946 to 1949 (159, 160, 161) and improved in 1950 (361). Special methods have been developed for hypnotics (394), for euphoria (399, 608) and for antitussives (261).

In essence, this method requires the use of a group of cooperative individuals who report on the sensation under study. Arbitrary criteria of change in, or relief of, a disturbing symptom are set up: The usual requirement for "relief" is pain 50% gone at 45 and at 90 minutes following drug injection. This is a judgment patients have found easy to make.[4] Apparently it means great pain relief at the two stated times. The judgment is reproducible in the Harvard laboratory and also in others. See the confirmation of this in Houde's laboratory, below. Duration of pain relief has also been determined (262, 397). Essential considerations are not only pain relief, but also its duration and the concomitant side effects. The necessary controls are the use of the "double unknowns" technique, that is, neither subject nor observer must know what or when test agents are employed. Placebos are inserted, also as unknowns. A standard of reference is employed (such as morphine in studies of analgesic agents). The order of administration of the test drugs, standard of reference, and placebo is randomized. Correlated data are used; that is, all agents are employed in all subjects, and mathematical validation is used to establish supposed differences of effect between agents. In all new problems and in many other cases this is best done by a professional statistician who has first-hand familiarity with the work in progress. The importance of these controls has now been confirmed by many investigators. The contrary view of Keutman and Foldes (372), that to follow these properly "would practically exclude clinicians from the study of this primarily clinical problem," seems rather wide of the mark.

Man is, of course, essential for study of subjective responses. As a working hypothesis it seems necessary at present to carry the requirements farther than this and to say that appraisal of therapeutic agents designed to modify subjective responses arising in disease or trauma must usually be studied where they arise spontaneously. The supporting evidence for this hypothesis is presented and discussed elsewhere (44, 50, 54) and in other sections of this review. However, some convincing evidence has now been presented that subjective responses arising in disease or trauma can be successfully mimicked (316, 318, 319, 384, 438, 439, 440, 443). It must be emphasized that the above is merely a useful working hypothesis, not yet disproved; however, in view of the data presented it seems unwise to ignore the possibility that this may turn out to be more than a hypothesis when further tests have been made. If it turns out that the use of patholog-

[4] The "quantitative assessment of subjective magnitude" is the problem here. The Beecher group's data on severe postoperative pain have been confirmed with remarkable agreement by the Houde group where severe pain produced by malignant disease was utilized, when drugs were given to produce "50% or more pain relief." (See V, B, 2, a and Table I.) Stevens (568, 569) has worked with a similar problem as applied to loudness of sound. In studying the relationship between subjective loudness and the physical intensity of the stimulating tone he employed 65 unpracticed observers. In their *first* judgments they were able to produce consistent determinations of loudness ratios (569). In another study (568) the observers merely assigned whatever numbers that seemed appropriate to describe the loudness of a series of intensities which were presented in an irregular order. On other occasions a standard loudness was assigned as 1, 10 or 100 and the subject thus assigned appropriate numbers to the variables. Sometimes the ranges as determined subjectively covered a spread as wide as 1 to 1000. Remarkable consistency in these value judgments was found.

ical material is as essential for most work as now seems may be the case, it is probable that the explanation will lie in the 60-year-old concept of the importance of the reaction component of suffering (54, 446, 578), to be discussed later (XII).

a. Dependability of method—Reasons for confidence. The Beecher group has, as indicated, utilized postoperative wound pain. It is necessary to show that the patients studied are capable of making the necessary discriminations. The following evidence establishes this.

1) A disinterested individual not a member of the research team prepared two series of flasks, six in each. These contained "unknown" solutions. The task was to find which flask of one series was comparable in analgesic power to which flask of the other. At the end it was found (361) all of one series contained 10 mg morphine per ml, and in the other series the concentration of morphine had varied. On graphing the paired doses against differential percentage of pain relief it was found that 10 mg morphine of one series was equivalent to 10.8 mg in the other, an 8% error. When the regression lines are calculated out this adds 2% more for a total error of 10%, for patients in severe postoperative pain. (This degree of error in measuring the subjective effect, pain, is not different from the degree of error encountered in making objective medical measurements in man.)

2) An unexpected confirmation of different type came in studies of a new analgesic (358), designated as WIN 1161-2. Assurance had been given that the compound was chemically stable; however, the dose required for a given percentage of pain relief increased steadily with the passage of time, indicating that the new compound was not stable. Following repeated assurances of stability, the experiments were repeated with the same result. A completely independent chemical study showed that this compound was not as stable as first thought. The biological assay had detected the instability before the chemists were aware of it.

3) The power of the postoperative patients to discriminate consistently and significantly between morphine and a placebo (160, 361, 397) and even between a placebo and acetylsalicylic acid (59) is strong evidence, even proof, of the discriminatory ability of the postoperative subjects involved.

4) The data presented below in discussion of Houde's methods showed effectiveness identical with Beecher's data concerning (a) a placebo and (b) the 10 mg dose of morphine. (See Table 1.) The latter data were obtained from patients

TABLE 1

Pain relief effected by 10 mg morphine and by a placebo

Investigators	Studies	No. of Patients	Per Cent Relieved	
			Morphine, 10 mg s.c.	Placebo
Lasagna and Beecher (397), postoperative wound pain	1952	66	65.8	39.0*
	1953	56	69.3	
Houde and Wallenstein (333), chronic pain in cancer patients	1952–1953	67	65.0	42.0

* Averaged data from Lasagna *et al.* (398).

who had been subjected to anesthesia and the data of the former had not. The power of discrimination of the two groups was the same. Clearly discrimination had not been impaired by the preceding anesthesia in the Beecher group's data; this is the point at issue.

5) Reproducibility of data in the Beecher laboratory, when relatively small numbers of subjects are used, adds support but not proof. There is, for example, the satisfactory constancy of the effect of the 10 mg dose of morphine per 70 kg body weight over a period of some years in treating pain under accurately defined conditions. There is good reproducibility, working of course always with double unknowns. Examples are as follows: 1952: 70% relieved (359); 1953: 66% (395); 1954: 69% (397); 1956: 71% (262).

A severer test of the method was made when two groups of investigators from the last study appraised the power of dihydroisocodeine with reference to morphine. The second group worked after a three-year interval without knowledge of the findings of the first group. The excellent checks are shown in Table 2.

6) Finally, six other laboratories in other parts of the United States are using these techniques and report excellent confirmation.

Items 1, 2, 3 and 4, above, establish that the preceding anesthesia had not impaired the ability of the postoperative subjects to discriminate and to make valid judgments.

b. Most advantageous area for study. The ideal situation for study is the area where the dose-effect curve is changing rapidly; in this region differences between small doses can be brought out most sharply. This is, in a sense, a mathematical certainty, as far as differences in effect of given doses go. The advantages have often been considered, of working at an AD50 level (satisfactory pain relief in 50% of the patients). Practically, however, there is considerable limitation of this possibility, for if, over a rather long period, the medications are often ineffective in controlling the severe postoperative wound pain that serves as the material, the investigator begins to lose the cooperation of the patients and the ward personnel. The best pain for study is incompletely relieved pain, whether one deals with moderately severe pain only partially (about half) relieved by small doses of morphine or very severe pain nearly maximally relieved by large doses of morphine. The first situation is best, for it is then that the dose-effectiveness curve is changing rapidly.

TABLE 2

Relief of Pain from dihydroisocodeine compared with standard dose of morphine

	No. of Patients	Dose of Dihydroisocodeine, mg/70 kg	Per Cent Relief	Dose of Morphine, mg/70 kg	Per Cent Relief
First group	12	15	61	10	72
	30	30	74	10	70
[3-year interval] Second group	27	15	63	10	72
	35	30	68	10	68

c. Maximum power. Even with powerful narcotics like morphine the "average pain" of a group of individuals in severe, steady pain cannot be completely relieved with reasonable (safe) doses. (See XI, H.) The effectiveness of narcotics is shown by the inverse relationship between severity of pain and percentage of individuals relieved. It must be appreciated that the maximum safe pain-relieving power, when steady, really severe pain is under consideration, is represented roughly by an AD75 (75% of the group satisfactorily relieved) by 15 mg morphine per 70 kg body weight (397). This limitation appears to exist with the drugs used to alter other subjective responses. However, this view needs to be established.

d. Use of correlated data, paired doses of drugs. When subjective responses are under study, the experiment should be arranged so that as many variables as possible cancel out by the use of correlated data, that is, the placebo pitted against the active agent in the same individual, or two doses of the same drug compared in the same individual, under comparable circumstances. Specifically, persistent individual peculiarities or characteristics can be made to cancel out in many cases when such paired doses are used. The quite unsatisfactory alternative to this technique is to use a tremendous mass of data. It is always advisable to have more than two agents in any study to minimize chance detection of the placebo.

e. "Double-blind" technique and drug-wise subjects. The elimination of bias on the part of the subject or the observer emerges clearly as a basic and essential requirement, yet some investigators still insist that only highly trained subjects with long experience are useful. (See X, 14.) The contradiction in these two views seems evident (50) when any drugs are under study that reveal their use to the individual by side effect, nearly always true of agents designed to produce subjective therapeutic effect. The widely experienced subject quickly learns to identify the "aura" of a narcotic, for example, or the barbiturate effect with its "hang-over." Thus, with experienced subjects, it becomes impossible to preserve the essential unknowns technique in such areas. This is quite obvious in the use of analgesics to control pain; it is also true with the smaller doses of narcotic used to control cough. Highly trained subjects come to have a vested interest in the outcome, whether scientific or pecuniary (continuance as paid subjects) or egoistic (personal attention); the failure to eliminate their bias can have devastating results. To be sure, learning on the part of the subject is always a hazard to be watched for and minimized with proper controls, but the hazard is far greater with the experienced group. It is best to use as subjects, when experimental pain is under study, individuals who have no knowledge of the work in progress and no interest in its outcome, who are not familiar with the drugs studied and who after a brief period will be followed by other subjects.

f. Subjective effect revealed by objective change. A cooperative statement by the subject must take first rank as an indication of the existence of a subjective response or of change in it. Supporting evidence or, in areas of sensation very difficult or impossible for the subject to estimate or communicate, useful presumptive evidence of a concomitant subjective effect can sometimes be revealed in objective change as, for example, when the face of the patient in pain assumes

a relaxed, cheerful appearance denoting comfort. In other studies it has been possible to demonstrate the mental effect of a drug by alteration in psychomotor tests (254, 607) and to record objectively alteration in sleep pattern by changes in ratios of alpha and delta wave frequency in electroencephalogram (101). Cough is objective evidence of a subjective desire to cough and vomiting is evidence of nausea (in normal individuals). The use of a tachistoscope to study the effects of drugs on the time to recognize "charged" words has proved useful in studying subjective change through objective manifestation. But the cooperative statement of the subject remains by far the most useful criterion of change in subjective response.

g. Appraisal of side effects. There is a vague but commonly held view that analgesic action depends in large part on side effects of the agents involved. It has been said (289) ". . . only those agents which have conspicuous and perhaps from a social point of view, dangerous 'side effects' best relieve suffering." The report of Gravenstein *et al.* (262) on dihydrocodeine indicates that this common point of view does not necessarily hold, for dihydrocodeine, although a strong analgesic agent, has hardly any acute side effects at the 30 mg dose. Seevers and Pfeiffer (534) have made a rather clear differentiation between analgesia and what they call "narcosis" or "subjective depression." They believe that analgesia can and does occur independently of the "subjective depression." Dihydrocodeine is, as mentioned, a case in point (262).

Comparison of the side effects of any two therapeutic agents can be made soundly only when therapeutically equally effective doses are considered. It is surprising how often this obvious requirement is ignored. The statement sometimes made that meperidine, for example, is ⅕ as strong as morphine is misleading: in optimum dose, considering analgesic power and side effects, they are equianalgesic (395). Another problem in this area arises with the assumption that the side effects of narcotic agents for example, can be appraised easily in postoperative, sick individuals. Some toxic effects of narcotics (notably nausea and vomiting) are much like the common afflictions of the sick. Thus it becomes difficult, unless special teams of observers are employed and many, preferably hundreds to thousands of cases are evaluated, to get valid information (in postoperative subjects).

In a small series (136) no respiratory depression in 69 postoperative patients receiving meperidine was reported after the use of methadone, yet Denton and Beecher (161) found evidence to indicate that the methadones are as depressing as morphine. Batterman and Mulholland (32) reported only one case of respiratory depression in 1119 postoperative and medical patients but others (215) show that in equianalgesic dose 50 mg meperidine is nearly as depressing to the respiration as 10 mg morphine. This finding of powerful depression of the respiration by meperidine is in accord with the observations of still others (424a, 494). The failure to get adequate information in postoperative patients, as indicated by the work just described, is perhaps a sufficient commentary on the hazards involved in the use of patients to get at side effect information.

Even with the most careful, full-time observation the Beecher group could

devise, it was impossible for them to evaluate the side effects of these agents in sick, postoperative patients. The casual observations of busy doctors or ward nurses is without value, a point not adequately appreciated. The use of normal subjects for the study of toxic effects has been the custom. This is not very satisfactory either since it is possible that pain, for example, may be associated with a lower incidence of nausea produced by morphine in the sick than in the well. Here, just as with appraisal of the primary therapeutic effect, the "double unknowns" technique, insertion of placebos as unknowns, randomization, use of correlated data, and the mathematical validation of differences must be used if the incidence of toxic effects is to be established.

The appraisal of analgesic agents thus involves three stages: 1) Screening in animals, for analgesic power and toxic effects, and this is fraught with the uncertainties of possible species differences and the use of doses usually not comparable to those used in man. 2) Evaluation in man as to pain relieving power, duration of action, and toxic effects, with all of the problems and hazards of human experimentation. 3) Judgment, evoked by wide experience under many conditions, as to comparative advantages and disadvantages with respect to other agents.

3. Houde group's method. Interest in the fundamental problems associated with analgesic agents and analgesic action has been the motivating force underlying the Houde and the Beecher groups of investigators. A rather tedious but first concern has had to be given to tools of measurement and methods of attack, to possibilities of quantification and dependability of method. It is fair to say that at present considerable success has been achieved along these lines. (See V, B, 2, a.)

Houde and Wallenstein (332) point out reasonably enough that results on analgesics obtained "in patients *recovering* from operative trauma may not necessarily apply to patients *dying* from inoperable cancer." They have directed their attention to the use of patients with chronic pain for the screening and appraisal of analgesic agents, and, since the individuals with chronic pain have in most cases had an extensive history of opiate administration, these investigators do not make any claims that their conclusions necessarily apply to other populations of patients (333).

They epitomize their viewpoint and procedures as follows: "An essential feature of our studies is the adherence to principles of blind and controlled research such as has been advocated by Dr. Beecher and his associates for the measurement of subjective responses. This includes the use of full time observers, the coding, disguising and randomization of drugs in accordance with the 'unknown' technique, the use of placebos and reference standards, and the reliance on the patients' own subjective responses to objective questioning.

"Moreover, we have designed our experiment so that each subject serves as his own control thereby matching the sample-population as to age, sex, disease, type of pain, and other physical and personality factors. In the selection of subjects, only well-oriented patients capable of communicating their subjective experiences, and to whom the drugs may be given safely, were chosen. However, when the test drugs were to be administered orally the subjects were chosen, for the most part, from among patients who were already receiving their analgetic medications by mouth, and thus they represent somewhat dif-

ferent populations from those of the parenteral studies where most subjects were usually previously receiving parenteral analgetics. Undoubtedly many in the latter groups were tolerant to some extent to narcotics and although we did avoid including patients who were receiving more than ordinary doses of narcotics, we recognize the limitations that this imposes on the interpretation of our results."

They employ a full-time nurse who works 8 hours a day 5 days a week and in this way they differ from the Beecher group where trained technicians are utilized as observers throughout the 24 hours of the day. Each system has its advantages and its disadvantages: The single individual working for a limited time undoubtedly obtains more consistent results and has a more constant relationship with her patients than several individuals could; on the other hand 24-hour observation probably includes cyclic changes in the patients' analgesic needs not obtained with the limited observation period.

In common with the Beecher group they do not accept sleep as proof of the absence of pain. The Beecher group have on occasion presented both kinds of data; *i.e.*, considering sleep as an indication of pain relief and not so considering it (262).

The latter view seems to the Beecher group as well as to Houde and Wallenstein as the preferable approach. But problems arise in the 24-hour observation system when one proposes to awaken patients and question them as to the presence of pain. These matters have been discussed by Gravenstein and Beecher (260).

Taking into account that the relief of pain is not an all-or-none affair, but rather a continuum from none to most severe, Houde and Wallenstein's goal has been to develop a categorization of pain which would be sensitive to rather small analgesic effects. First they attempted to separate the patients' pain into two kinds: bearable or unbearable. This was not successful probably because "the ability to bear pain is dependent on other factors—physiological, psychological and temporal—(rather) than the mere severity of pain itself, and even slight pains will become unbearable in some patients if endured over long periods of time."

The categories of pain finally employed are similar to those described by Keele (365) (see V, B, 4): none, slight, moderate, severe, agony. This last category is rare and has contributed little, so they are considering abandoning it (333). They also have divided the responses according to whether the medication produced 50% relief or comfort or both (398). An attempt was made to have all patients keep their own pain charts as Keele had done. This did not work out well, as Lee also had found (V, B, 1), for data were lost owing to failure of patients to fill out their charts regularly, inaccuracies in doing so occurred, and introspection concerning their pain which led to the influence of emotional factors greatly lessened the value of the system.

Houde and Wallenstein (333) have used three fundamental study plans: Their usual initial screening procedure was to administer an arbitrary dose of the drug to be tested, a reference standard and a placebo, in a randomized order. Later, a factorial design was employed in which the drug under test, the standard and a placebo were administered singly and in combination. Finally, when precision

was sought, the test drug, the standard of reference, and graded doses of test and standard were administered.

The categories of pain from none to agony were labeled 1 to 5, for statistical purposes. The pain relief score was compared by difference each hour after drug administration with the score just before the drug was given. Such data permit plotting of time-effect relationship, peak effects and total effects. Data of this type permit careful statistical examination of the effects found.

This approach permits great flexibility of use and Houde and Wallenstein (332) were able to compare "weak" (acetylsalicylic acid) and "strong" (morphine) analgesics, one given by mouth and the other parenterally. The differentiations between drugs and placebos were sufficiently sharp so that they considered themselves justified in undertaking evaluations of new drugs.

When agents are compared one of which is to be administered orally, as acetylsalicylic acid, and others parenterally, as morphine, patients are given both an oral medication and a hypodermic injection at the same time. Thus they were able to test the effects of a placebo, acetylsalicylic acid, morphine and a combination of morphine and acetylsalicylic acid by this ingenious arrangement.

Houde and Wallenstein (332) point out that questions can be raised as to the "linearity" of their pain groups. Even if the pain categories do not bear a linear relationship to one another, they do represent gross differences in sensation and, since they have no evidence that any scale is better than the arithmetic, they have accepted it (333). They have provided data to show that the category-score data can be used to establish significant difference with the Chi^2 test without assuming linearity. They were able to show the same effects with beautifully similar curves whether their pain categories or 50% relief criteria were used. The same attributes seem to have been measured by the two systems.

They recognize that different patients may have differing criteria of need for analgesics. The patient who receives maximal relief of a slight pain would have that relief represented by a smaller number than would be the case with a patient with more severe pain. They have overcome this problem at least in part by dealing with "moderate" or "severe" pain rather than slight. The fact that each patient served as his own control may account for the fairly uniform distribution of the categories for each drug. "Total effects" have been stressed in their evaluation, since this is the most important factor. As they point out, peak effects can also be determined, but unless differences are great, larger numbers of observations will be required than was the case for total effect estimations.

The composition of the patient-pain groups is manifestly important: a weak analgesic may be differentiable from a placebo when good discriminators are involved, and yet failure to show a significant difference with even a powerful analgesic as compared with a placebo may occur when a relatively high proportion of non-discriminators is present (332). They do not consider it advisable to try to screen out poor discriminators. By the use of "correlated data" or "cross-over" studies, where each patient acts as his own control, they have consistently been able to show significant differences between acetylsalicylic acid or morphine and their placebos with 10 to 25 patients. When 2 drugs of similar analgesic

power are compared, more patients will obviously be needed than when the difference in drugs is greater. Houde and Wallenstein (332) have concluded that when the drug tested gives a significantly different score from the placebo but not from the standard that it will probably be more profitable to compare the regression slopes of graded doses of test and standard drugs than to persist with the preliminary screening method. Tests are usually extended until the trial drug shows a significant difference from the standard or the placebo or both (333).

One must agree with these investigators that no clinical method can be more sensitive than the population in which the tests are made. Sensitivity of such methods is limited by the discriminatory ability of the patients involved. But to return to the question raised at the outset of this section as to whether pain data obtained "in patients *recovering* from operative trauma" may apply "to patients *dying* from inoperable cancer," it can be said that a remarkable confirmation has been established that the two approaches give the same information, as shown in Table 1 where recent observations obtained in relatively large numbers by the two groups are recorded.

The excellent agreement of the data obtained by the two techniques adds strong support to the reasons to believe that patients utilized in the postoperative period by the Beecher group are fully as able to discriminate as patients suffering from chronic pain, whose situation has not been complicated by recent anesthesia. Evidence establishing this has been presented above.

As pointed out by Houde and Wallenstein (333, 335), the methods just discussed could be applied to other problems, such as the rate of development of tolerance, the study of maximal drug effects, the problem of selective activity.

4. Keele's method. Keele (313, 314, 365) recognized, as all have done who have worked with pain problems, the difficulty of verbalizing descriptions of pain. He recognized too the patient's confusion as to what features of his pain experience should be reported to the observer and, finally, the difficulties of remembering that experience. With these things in mind Keele planned what amounts to a time-intensity curve, a pain chart, to be kept at regular intervals by the patient. This provides a quantitative record of severity; qualitative features of pain are ignored.

Following a study of words used by patients in pain, Keele constructed his chart with five grades along the ordinate: none, slight, moderate, severe, and agonizing pain, and with the abscissa expressing time in hours. Observations by the patient were to be charted at hourly intervals before and after the administration of analgesics. The method appeared to be especially suitable for patients with chronic pain.

It was found (314) that morphine (15 mg) on being given on 33 occasions to 12 patients, abolished severe (grade 3) or very severe (grade 4) pain one hour after injection on 20 out of 33 occasions (61%). When a placebo was used on 33 occasions in 15 patients, pain of severe degree (grade 3) was abolished 1 hour after injection on 14 out of 33 occasions (43%). While these data are not strictly comparable (here the dose is 15 not 10 mg and complete pain relief occurred) to those of Lasagna and Beecher (397) or of Houde and Wallenstein (333), the result stresses the unsatisfactoriness of the patient's own pain chart.

Keele reported that the task of charting their pain was welcomed by the patient; however, others (332, 403) who had tried a similar method did not agree; they found the patients' records so inaccurate and misleading as to require that it be given up. One judges that this group also found the records kept by the patients unsatisfactory in postoperative patients, for Flintan and Keele (215) substituted for their early method, when dealing with "acute pain," group questioning by an observer who then kept a pain chart.

This modification, as they said, "came near(er) to the procedure described by Keats, Beecher and Mosteller (361)" than to the original Keele method. They mention that their method differs however from Keats *et al.* in the following ways. 1) They did not use the "unknowns" techniques as far as the observer was concerned, for they were obliged to be on the lookout for toxic effects of the untried agent, and did not consider the use of unknowns safe. 2) They did not consider it justifiable to use saline controls. 3) They regarded sleep as indicating complete relief of pain.

Flintan and Keele (215) agree with Denton and Beecher's (159, 160, 161) reasons for the use of pathological pain to assay analgesic drugs and with their reasons for studying side effects in normal subjects, unsatisfactory as this is. They also agree with Beecher (42) "that a clinical trial is the only satisfactory way of estimating the analgesic potency of a drug."

VI. STATISTICAL PROBLEMS AND THEIR SOLUTION[5]

Prepared by Professor Frederick Mosteller

1. Experimental design. For drug assessment, working with postoperative patients, Keats and Beecher (358) tried to find a dose level of the "new" drug comparable to a standard dose of 10 mg of morphine per 70 kg of body weight. By alternating doses within single patients, it was possible to compare per cent relief from the standard morphine dose within groups of patients with per cent relief from the test drug. Differences in per cent relief for each dose level of the unknown were plotted against dose level of the unknown drug. A regression line is fitted to the points, and the position where the regression line crosses zero per cent difference in relief is taken as the dose level of the unknown equivalent to the standard dose. The device is quite simple to carry out and flexible in its sequential approach to the level. The Beecher group have used postoperative

[5] Familiarity with the original articles discussed in this review makes it quite clear in most cases that when a "significant" effect is claimed, this can be demonstrated mathematically. The trouble is, in a good many cases, better experimentation has shown the "significant" effect to be in error. Plainly the solution to the conflict must be sought elsewhere. The solution seems to lie in many places: experimental design, choice of material, or in incorrect application of statistical procedures, to name a few sources of error. While a statistical analysis of even the best of the studies covered here would be unutterably tedious and without reasonable profit in a review, there is a need for comment on statistical matters by a professional mathematician who has a first-hand familiarity with pain problems.

For a decade Dr. Frederick Mosteller, Professor of Mathematical Statistics at Harvard University, has saved the reviewer from many an error; this is acknowledged with appreciation. During this decade it has become increasingly clear that statistical guidance in this complex field is for the expert.

wound pain and have clearly established the ability of their subjects to discriminate among drugs and placebos and among given doses of given drugs. (See V, B, 2, a.)

The technique has been validated by assessing an unknown amount of morphine against variable known morphine (361). In this assessment, the unknown happened to be 10 mg/70 kg and was estimated at 10.8 mg.

A useful design has been suggested by Houde and Wallenstein (335) (in association with Dr. Irwin Bross). The approach has two important features: (a) it allows the assessment of the dose-effect curve of an unknown in comparison with that of a standard; (b) the approach can be used sequentially.

The steps in the procedure are as follows: First, the dose scale is laid off in equal logarithmic units, the unit being determined by two dose levels assigned to the standard. For example, in a study of "Numorphan" as compared with morphine, the morphine was used at 2 standard doses—8 and 16 mg. The remainder of the scale (because "Numorphan" seemed more potent than morphine) would be 4, 2, 1, 0.5, . . . mg. In addition to the 2 standard doses of morphine, x_1, x_2, 2 doses of the unknown (doses adjacent on the grid) are chosen, say y_1, y_2—one of the pairs (8,16), (4,8), (2,4), (1,2), . . . in the example given. Now that the 2 standard doses and the 2 unknown doses are chosen, the 4 doses x_1, x_2, y_1, y_2 form the primary experimental unit, called a quartet. A group of patients starts out on a single quartet, each patient receives the quartet in some order—the possibility of balancing exists—for example, a set of 4 patients might be assigned the dose order in a Latin square design:

	Order of administration			
Patient 1:	x_1	x_2	y_1	y_2
2:	x_2	y_2	x_1	y_1
3:	y_1	x_1	y_2	x_2
4:	y_2	y_1	x_2	x_1

Also a patient may be given more than one administration of a quartet—possibly in a new order. (It seems to be an assumption of the method that the drugs do not interact.)

If, on the basis of results for a given quartet, it appears that the response is not comparable in magnitude between the unknown and the standard, a new y_1, y_2 pair is chosen to be combined with the 2 standard doses to form a new quartet (several randomly selected groups of patients can start out on different quartets if this is desirable). As the data accumulate, more emphasis is put upon quartets where the y_1, y_2 pair appears to yield responses comparable to the x_1, x_2 pair.

The analysis goes as follows. For a given patient and quartet, let the measured responses to the doses x_1, x_2, y_1, y_2 be X_1, X_2, Y_1, Y_2 respectively. Then 3 quantities are computed. First,

$$Z_1 = (X_2 - X_1) + (Y_2 - Y_1).$$

This is essentially the sum of the regressions for the given patient-quartet. If one regards the difference $\log x_2 - \log x_1$ as one dose unit, then $X_2 - X_1$ is the observed slope for the standard and $Y_2 - Y_1$ is the observed slope for the unknown, because in any quartet $\log y_2 - \log y_1$ is also one dose unit. The two slopes have been summed to form Z_1. To measure whether the drugs are being evaluated in the same general range of potency, a second score Z_2 is computed:

$$Z_2 = (X_2 + X_1) - (Y_2 + Y_1).$$

Insofar as Z_2 is nearly zero, the observation suggests that the dose pairs x_1, x_2 and y_1, y_2 are equipotent. Estimates of relative potency usually assume that the slopes for both drugs with dose plotted on a logarithmic scale are equal. To assess this equality of slopes, a third quantity

$$Z_3 = (X_2 - X_1) - (Y_2 - Y_1)$$

is computed. This is essentially the difference of the observed slopes in the quartet. Insofar as it tends to vanish, the slopes tend to be equal.

To get the relative potency (assuming the average value of Z_3 is small), one first estimates the common slope from the average of the Z_1 values (averaged over patient-quartets). This estimate is

$$B = \frac{\bar{Z}_1}{2(\log x_2 - \log x_1)}.$$

In the denominator, the 2 comes from the fact that Z_1 summed the slopes, the logarithm of the interval length returns the scale to the original dosage units. For any quartet, let

$$W = \log \frac{x_1 x_2}{y_1 y_2}$$

be the assessment of the ratios of the 2 drugs. (Of course, $\frac{x_1}{y_1} = \frac{x_2}{y_2}$ if the adjacent-pair routine has been followed, so that $W = 2 \log \frac{x_1}{y_1}$. However, if one wishes to follow the derivation of the potency formula, it is convenient to write W in the more symmetrical form.) Finally, the logarithm of the potency ϕ can be estimated using

$$\log \phi = \frac{B\bar{W} - \bar{Z}_2}{2B}.$$

Here $\bar{W}$ is the average of the W's for the different quartets used, weighted according to their frequency of use, and $\bar{Z}_2$ is similarly the average of the observed Z_2 values.

It is suggested that approximate confidence limits for relative potency may

be derived by substituting upper and lower confidence limits for Z_2 in the expression for log ϕ.[6]

As an illustration, the quartet analysis on the "Numorphan" example, as described by Houde and Wallenstein (335), is given below.

"Thirty-eight patients were started on one or more of the quartets and cross-over data was obtained on 26 of them. Eight and 16 mgm. of morphine sulfate were used as standard medication, and the four quartets included, respectively, doses of 1 and 2, 0.5 and 1, 1 and 2 and 2 and 4 mgm. of 'Numorphan'. A total of 158 I.M. doses of each drug were administered. All drugs in the quartets were superior to the saline controls. . . . The regression estimate for the combined slope was significant beyond the 1% level and there were no significant deviations from the regression (Table 3). The overall range of analgesic effectiveness of the combined 'Numorphan' doses did not differ significantly from that of the two morphine doses used. Table 4 summarizes the estimates of relative potency derived from these data. The ratio of potency of 'Numorphan' to morphine is 8.95 to 1. It would appear from this study that 'Numorphan' is a potent analgesic, 1.12 mgm. of the drug being equivalent in effectivensss to 10 mgm. of morphine sulfate with the estimate ranging from 0.90 to 1.65 mgm. with confidence limits at the 5% level."

The sequential aspect of the approach has been tested by 3 groups working independently on the evaluation of piperidyl methadone at 3 different institutions. The results for 2 of the institutions have been reported with potency assays of 2.04 and 2.12, respectively, a most encouraging comparison.

The general approach seems to have many ramifications and offers possibilities for the study of other questions such as tolerance and cross-tolerance. The limitation seems to be the requirement of getting responses to the 4 doses of a quartet from the same patient. Whether the technique, or some modification of it, could be used with postoperative patients, as in the investigations of Beecher's group, would require both mathematical and empirical investigation. Those interested in a discussion of sequential experimentation more closely allied to Wald's work may find Bross (105) useful.

2. On the scoring of categorical subjective responses. Houde and Wallenstein (332, 333, 335) have developed a method for evaluating analgesics in patients with chronic pain. A feature of the method is that a graded response is obtained from the patient concerning the severity of the pain. These responses are "none," "slight," "moderate," "severe," and "agony." "Agony" is assigned only on the combined judgment of patient and observer. (It is reported that this category is rarely used and that the investigators are considering eliminating it from the scale.) These reports are arbitrarily assigned the scores 1, 2, 3, 4, 5. By assessing a patient's pain before medication and again each hour for a six-hour period thereafter, an hourly relief score is obtained. Thus, a reduction of pain from "severe" to "slight" gives a relief score of 2. However, increases in pain over the premedication reading are recorded as zero relief; similarly, if the patient requires

[6] Dr. Irwin Bross, in a personal communication, points out that this approximation neglects the fact that B is a random variable. After preliminary investigation he reports that taking account of this variability leaves the length of the confidence interval essentially unchanged, but shifts its position somewhat. Dr. Bross was kind enough to go over a number of points in the design that were not originally clear.

TABLE 3

Quartet analysis—Morphine vs. "Numorphan"

	Z_1 Regression estimate	Z_2 Equivalent Drug-Effects	Z_3 Deviation from Regression
N	79	79	79
SZ	254	30	62
$\bar{Z}$	3.215	0.380	0.785
$S(Z - \bar{Z})^2$	3495.342	3228.608	2431.342
$se\ Z$	0.753	0.724	0.632
t	4.270*	0.525	1.242

$p(0.05) = 1.991$.
$p(0.01) = 2.640$.
* Significant at 1% level.

TABLE 4

Quartet analysis—Morphine (MS) vs. "Numorphan" (NM)
Relative potency assay

Dose ratio	$\bar{W} = 1.913$
Slope	$B = 5.185$
Relative potency (NM:MS)	$\phi = 8.95$ (+1.821, −1.061)*
Best estimate	10 mg MS = 1.12 mg "Numorphan"
	= 0.90 to 1.65 mg "Numorphan"*

* 5% confidence limits.

additional medication within the six-hour period, he is scored as having zero relief for the remainder of the period. The relief scores for a six-hour period are totaled and then manipulated to assess drug effects. The use of such arbitrary scoring from 1 to 5 sometimes is criticized not only for its arbitrariness, but also because the numbers (or categories) may mean different things to different patients. Investigators using such devices hope that, by using the patient as his own control, directionality and magnitude of change are consistent within the patient. Insofar as a category changes meaning for the same patient from time to time, there should be more variability in the over-all assessment of a drug. Insofar as some other set of numbers, say 0.8, 1.2, 2.1, 3.5, 6.0, might better have been assigned to the categories than the ones used, the problem has to do with weighting. A good deal of mathematical investigation of the use of weights when scores are to be summated has been carried out in the field of educational testing, and the general conclusion has been that modest changes in weights in situations where many scores are added change the conclusions very little (644). The parallel here is that drug assessment is carried out essentially by summing over the patients' summary scores. Differences in the use of the scale by different patients, such as tending to use only a pair of adjacent categories (say "none" and "moderate") as opposed to use of the full range of the scale, seems also to be a mere weighting issue—that is, some patients tend to contribute more to the over-all evaluation of the analgesics than others. At any rate, the method of

assessment seems to give satisfactory results. The argument for scoring increases in pain as simply zero relief can also be put on the basis that negative relief scores are to be weighted zero. However, it is not entirely clear why this action is taken. Houde and Wallenstein state "As our primary concern is with analgesia rather than with random fluctuations in pain, any increase in pain over the premedication reading is recorded as zero relief" (333). Since random fluctuations in degree of pain presumably go down as well as up, the reasoning does not seem to be adequate. One adequate reason would be that drug assessment is more stable or accurate with this weighting than with the obvious one.

3. Use of areas in measuring analgesic effect. Miller (451) states "Since analgesia has two qualities, that of intensity as well as duration, it is conceivable that potency estimates might be based on either or both. Thus far, however, no one has worked out a means of combining measurements of both of these into a single parameter so that, if considered at all, they are taken separately." If intensity and duration are not related in some very systematic way, the fact is that the two qualities are separate and that an adequate appraisal of both requires separate analyses. It is a commonplace that multivariate questions often have multivariate answers. As Winter (652) puts it "No method of expressing results then, no matter what mathematical labors may be put into it, can give the total picture of the effect of increased dosage, if only one dimension is taken into consideration." (See also 474a.)

Nevertheless, the desire to get a single figure in answer to a multivariate question is strong. In animal experimentation Eddy *et al.* (194), employing the hot-plate method with mice, used areas as a device to decide whether or not an animal had been affected by the dose. Essentially a curve of response time in seconds is plotted against time in minutes after injection. The calculated 60-minute post-injection reaction-time area for any drugged mouse had to differ from its own normal reaction-time area (average initial reaction-time $\times$ 60) by at least twice the standard deviation of the plotted areas of the undrugged group in order that a mouse be considered to have shown a significant variation in its reaction-time area due to drugging. The percentage of mice showing such a significant effect was computed for each dose level for purposes of assessing the drug. The per cent affected plots up approximately linearly on log-probit paper. (Eddy and associates report time to onset, peak effect, and duration.) They recommend 10 animals per dose for screening and 30 to 40 per dose for establishing dose-effect relations. In a further modification Eddy and Leimbach (192a) attempt to arrive at total area variation and give specifications for termination of observation. They also modified procedure to balance out other variables from one group of animals to another.

In a panel discussion, Mosteller,[7] following Eddy and associates and in response to correspondence with E. Brown Robbins, used the excess area over initial reaction time of rats subjected to the tail-flick method as a direct measure of response to dose. These areas were then expressed as a percentage of the maxi-

[7] Joint meeting of the Biometric Society and American Society for Pharmacology and Experimental Therapeutics, Atlantic City, 1950.

mum possible excess. If the initial reaction time varies little from animal to animal, there seems little advantage in turning to the percentages. Mosteller used the area for a fixed period (90 minutes). These areas plotted approximately linearly against dosage, see Table 5. From the original data it was clear that for higher dose levels some rats far from returning to their initial reaction times of about six seconds at the end of 90 minutes were still near their maximum response times of 20 seconds. Stopping, therefore, at a fixed time does not use the area idea to the hilt.

Winter (652) using the tail-flick method for rats measures the reaction time until the rat has more or less returned to normal. More specifically, in Winter's technique 3 preinjection trials are made and reaction time in seconds measured (average 4.35 sec) and a degree of heat is used that makes these times quite stable (a standard deviation of 0.36 sec or about 8% of the mean has been observed). In the examples given by Winter, the reaction times are measured at 15-minute intervals through the first hour after injection and at 30-minute intervals thereafter. Heat is cut off after 10 seconds if the rat has not responded. The excess in area over the original reaction-time level is measured until the responses have practically reached a baseline again. The exact rule for ending the measurement process is not given in the reference cited. Winter finds the excess in area over the initial reaction time for each animal. He finds that these areas when plotted against the logarithm of the dose are approximately linear.

The cut-off time for the tail-flick data in Table 5 was 20 sec; Winter uses 10 sec. Naturally, this time is to be determined so as to leave the tissue undamaged. It seems reasonable that if the cut-off time is short enough, the area depends largely on the duration of effect at larger dose levels. However, duration itself is a rather ill-defined concept that may vary a great deal with the rule for stopping the measurements. The area should not be quite so sensitive to such an arbitrary rule because the main contribution to the area ordinarily comes from that part of the response curve where the drug is having its most powerful effect on response time and not from the less definite tail part of the curve. The areas have the advantage that they yield a numerical value for each individual separately and therefore produce a direct measure of animal-to-animal variability. Winter suggests that the potency of an unknown can be assessed a standard error of 25% on the basis of 6 animals for the standard and 6 for the unknown. He suggests that the standard error can be cut to 15% with 17 animals. The method appears to be promising.

It is worth noting that Houde and Wallenstein's method is also an area method based on the relief scores. They use a fixed total time period of 6 hours. Pre-

TABLE 5

Response to morphine sulfate in rats

Dosage, mg/kg	Saline (0)	0.8	1.2	1.8	2.5
Average % maximum possible gain	12	35	58	74	90

sumably for the drugs and dose levels employed, the response curve has been completed at the end of this period.

4. Testing for change with correlated proportions. The problem of testing for change in a 2 × 2 table has sometimes been mishandled in the past and is only beginning to be routinely recognized by workers in the assessment of drugs. The problem is easily illustrated by a study of incidence of side effects in the comparative testing of 2 analgesics. A number of experimental patients has been treated on 2 different occasions with Drug A and Drug B.

Noting which patients had nausea following each dose leads to a record of one of the following 4 types for each patient:

Patient	Drug A	Drug B
Jones, A. B.	Nausea	Nausea
Smith, C. D.	Nausea	—
Johnson, E. F.	—	Nausea
Williams, G. H.	—	—

With this information in hand, 2 questions are commonly asked. The first concerns the frequency of occurrence of nausea with either or both drugs. This is a usual question that classical binomial methods are suitable for solving and does not need to be pursued further here. The second common question is whether Drug A is more likely to produce nausea than Drug B, and this is the question that is often mishandled.

The first way of mishandling the data is to set up a table like Table 6 (labeled "Mishandling No. 1"). The same 100 patients have received both Drug A and Drug B. With Drug A 18 show nausea, and with Drug B 10 show nausea. The standard chi-square method (or t-test) might then be applied incorrectly to the difference between proportions in the lines for Drugs A and B, even though there is matching. The principal mistake here is that the basic unit is a patient, not a dose. It is a common finding that patients experiencing nausea after Drug A may be more likely than others to experience nausea after Drug B and *vice versa*. This expected correlation of outcome is one reason for using the matched doses on the same patients. What is needed is a reclassification of the data using patients as the unit. This reclassification leads to the appropriate table—Table 7.

In Table 7 the joint outcome for the two drugs is shown. Nine cases had nausea with both drugs; 81 cases never had nausea. Drug A produced nausea in 9 cases when Drug B did not, and there is one case with nausea from Drug B but no nausea from Drug A.

TABLE 6

Example of mishandling (No. 1)

	Nausea	Not-Nausea	Total
Drug A	18	82	100
Drug B	10	90	100
Total	28	172	200

TABLE 7

Example of appropriate table

	Drug A		
	Nausea	Not-Nausea	Total
Drug B			
Nausea	9 (C)	1 (D)	10
Not-Nausea	9 (E)	81 (F)	90
Total	18	82	100

$$z = \frac{|E - D| - 1}{\sqrt{E + D}} = \frac{|9 - 1| - 1}{\sqrt{10}} = \frac{7}{3.16} = 2.22 \text{ st. dev.}$$

$P(z \geq 2.22) = 0.013$ (one-sided test).

A second mishandling of these data would apply the ordinary chi-square analysis to Table 7. Such a test for association would test whether patients tend to respond similarly, or possibly oppositely, to the 2 drugs, rather than on differential incidence.

The primary interest is whether Drug A produces nausea more often on the average than Drug B. For this purpose, one is not interested in the whole table but only in the two terms of the diagonal labeled E and D. The question asked is whether C + D is significantly different from C + E, or equivalently whether D and E can be regarded as equal. Here there are only 10 cases that give information about the differential incidence of nausea for the 2 drugs. The facts that some patients had nausea both times and that others had no nausea on both occasions is good information for other purposes, but not for testing whether Drug A differs from Drug B with respect to nausea incidence. This is determined from the frequencies in cells E and D of Table 7 by the standard test, shown immediately below Table 7. The difference between D and E, neglecting the sign, is diminished by one and divided by the square root of the sum of D and E to obtain 2.22 standard deviations. The significance of the result is obtained from a table of the normal distribution. The subtraction of unity is a correction for continuity equivalent to Yates' correction of one-half in the usual chi-square test. In the example, there is good reason to think that Drug A is really worse than Drug B with respect to producing nausea.

The quick test just described is an approximation to the exact test whether the 2 cells have the same probability on the basis of the outcome of E + D binomial trials. It is possible therefore to use exact rather than approximate methods. The probability of getting 9 or more heads in a sample of 10 coin flips is $(1 + 10)/2^{10} = 11/1024 = 0.011$, which agrees closely, of course, with the probability associated with a z-value equal to or greater than +2.22, which was 0.013.

McNemar (431) is believed to have originated the test. It is discussed also in (143, 197, 432, 459) and used extensively, for example, by Denton and Beecher

(159, 160, 161) (with a slightly different formula) in comparing the side effects of several paired drugs. Cochran's paper extends the method to the study of situations where more than 2 observations are taken for an individual, to illustrate—if each experimental patient receives 3 drugs, the question may be asked whether the 3 drugs differ in their production of nausea.

5. Random numbers. In setting up experimental groups of animals or patients, or in arranging orders of administration, some investigators still randomize by writing numbers on slips of paper, mixing them, and then drawing them blindfold from a hat. It is rather difficult to mix or shuffle physical objects like slips of paper, so most people now use random numbers. Some sources are the RAND random numbers (The RAND Corporation [496]) which gives both random uniform digits (numbers 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 drawn with equal probability), and random normal deviates. The latter numbers are especially useful in trying a theoretical run of a new statistical technique. The Fisher-Yates (211) tables provide random uniform digits, as well as Latin Squares and instructions for randomizing these. Arranging sets of objects in a random order is an irksome and time-consuming task, but Cochran and Cox (144) at the suggestion of Professor George W. Snedecor have constructed a set of tables of random permutations of 9 and of 16 objects. From these one can obtain random permutations of smaller numbers of objects. In using random numbers it is well to record not only the source book but the actual location in the table from which the numbers were drawn. It is astonishing how frequently occasions arise when it is desirable to re-examine the original numbers.

6. Comparison of means in the analysis of variance. In the study of responses to drugs the analysis of variance is widely used in the assessment of effects and in the allocation of variability to its sources. No purpose would be served by a long list of references to document this point, but Miller's (451) critique of analgesic testing methods and Winder's (650) statistical examples in pharmacology might be mentioned to illustrate respectively a rather straightforward and a quite complex design and analysis.

For those who are unacquainted with this methodology but who wish to extend their information in this field, a wide variety of books is available: Fisher (210), some parts of Finney (209), Snedecor (554), Cochran and Cox (144), Federer (205), Kempthorne (368)—the list is ordered roughly from easy to very hard reading (though ease in reading Fisher is quite deceptive).

The Winder (650) reference is particularly instructive for its careful study of possible transformations of the data that may lead to more appropriate analysis. An elementary discussion of the use of transformations in analysis of variance is given by Quenouille (495). Generally speaking, transformations in the analysis of variance are used 1) to improve normality of distribution, 2) to stabilize variances—that is, to equalize the variability of several sets of data (especially when variability depends on the magnitude of the mean), 3) to achieve additivity or linearity and thus simplify interpretation or analysis, or finally 4) because they lead to a clearer physical interpretation. In bioassay, two transformations quite commonly used in tandem are the logarithm of the dosage and a probit rather than the per cent responding.

There have been some important developments in the field of analysis of variance that may be useful in the study of pain. In the simplest analysis of variance situation there are several drugs, treatments, or conditions being tested. The classical analysis of variance is designed to test whether there are differences in the results achieved by the several treatments (as well as other questions such as those concerned with interaction). For many years it has been an irksome question just how one should proceed after deciding that the several treatments do give different results. Usually it is desired to state that the apparently best treatment is really the best one with some approximate degree of confidence attached, or to set confidence limits on the difference between a pair of means.

It would be fair to say that before 1950 no technique of reaching such a decision together with a satisfactory probability statement was available. Usually workers merely made all possible pairs of comparisons. Then probability statements were attached appropriate for the comparison of a pair of treatments in the absence of others. Since 1950, numerous publications have appeared suggesting various methods for handling this problem. A key reference is Duncan (174) because of the background it gives for this general problem including a discussion of many special considerations, because of its comparative study of the various methods proposed, and because of its references.

In Duncan's technique it is possible to present the treatments ordered in accordance with their effects in such a way as to show which treatment is significantly distinguishable from each of the other treatments and which treatments must be regarded as grouped. All possible pairs of comparisons are made. To illustrate, an experiment on yields of barley gave for 7 varieties A, B, ..., G means arranged as shown below in order of magnitude and underscored in accordance with Duncan's analysis:

Varieties	A	F	G	D	C	B	E
Mean yields	49.6	58.1	61.0	61.5	67.6	71.2	71.3

Duncan's analysis leads to the interpretation:

(a) Any two means *not underscored* by the same line are *significantly different* (5% level).

(b) Any two means *underscored* by the same line are *not significantly different.*

Thus for this example, while A is not distinguishable from F, and F is not distinguishable from G, a difference is recognized between A and G.

A complete description of the technique requires more space than is available here, but in outline, the following steps are required. First, an initial analysis of variance is made to obtain the standard error for a treatment mean, then Duncan's table (pp. 3, 4) is consulted to discover for the given significance level the required multipliers of the standard error to be used in comparing the difference between a pair of treatment means. The multiplier depends on the particular pair of means to be compared. When the means are ordered, a comparison between A and F in the example corresponds to a multiplier using the fact that only 2 adjacent means are involved, whereas a comparison of A and G includes the knowledge that there is an additional mean, F, between A and G. Once the

initial analysis of variance is made, it is very easy to carry out an analysis based on Duncan's technique.

Scheffé's (517) technique involves a more general idea than merely the comparison of every pair of means. He suggests the possibility of studying all possible contrasts in an analysis of variance. A contrast is a weighted sum of means that has the property that the sum of the weights is zero. Let C, A, and F be the true mean yields in the example above. Then using Scheffé's method, one could ask whether C + A − 2F was significantly different from zero, or set confidence limits on such an expression, and, indeed, all other such expressions simultaneously. It is not obvious that such general contrasts will be widely used in the field of analgesics or biometry, but interactions take this form. For example, suppose that, as in the experiment of Houde and Wallenstein (332), several patients each received doses of lactose, "aspirin," codeine, and a combination of "aspirin" and codeine. It might be supposed that a dose of medication was composed of an effect owing to administration (L) plus additive effects owing to the particular medication used—"aspirin" (A) or codeine (C). Then for the factorial design the 4 effects would be

administration of lactose	= L
administration of "aspirin"	= A
administration of codeine	= L + C
administration of "aspirin" + codeine	= L + A + C

One test of this model is to evaluate the interaction or contrast (L + A + C) + (L) − (L + A) − (L + C). If the model is true, the observed contrast should be nearly zero. Houde and Wallenstein's corresponding mean relief scores were 7.2 + 2.2 − 4.8 − 4.1 = 0.5. Scheffé's technique would set confidence limits on the true mean of such a combination. The purpose in describing the interaction at such length here is to indicate that some questions about contrasts do occur rather naturally, and thus to prevent a too immediate dismissal of Scheffé's approach. Most situations require only the comparisons of pairs of means and in these situations the extra size of the confidence region required to be able to make confidence statements for the more complicated kinds of contrasts are not justified.

For the simplest kinds of analysis of variance tables, either one-way classification with the same number of observations in each column or a two-way classification with one observation per cell, a method developed by Link and Wallace for comparing all possible pairs of treatments is described in Mosteller and Bush (460). These methods are particularly easy to carry out because they depend only upon computing sums and ranges and consulting tables.

A related problem that may be of particular interest in bioassay occurs when several different treatments are to be compared with a single control or with a single standard. The same general difficulties have been encountered in attempting to make suitable confidence statements about such comparisons, and one technique for handling this problem is given in Dunnett (177).

VII. THE PAIN THRESHOLD

1. Definition. The pain threshold can be defined as the first barely perceptible pain to appear in an instructed (665) subject under given conditions of noxious stimulation. Its presence is revealed by a verbal statement. It is measured in terms of the lowest intensity of stimulus which will evoke it. The pain threshold can be determined and studied only in conscious and cooperative man; however, reflex signs of reaction to presumed pain in animals permit useful studies to be carried out in various species.

2. Man's report vs. animal's reflex: A semantical problem. Evidence that a painful stimulus has been operating requires as delicate yet precise an indicator as can be devised. By common agreement the "pain threshold" concept has been used. A source of misunderstanding has been the curious failure of many to appreciate that while the term used, "pain threshold" is the same for man and for animals, in actuality very different things are referred to by the same term: In man the threshold is determined by a conscious judgment in the cortex; but in animals it is determined by a reflex, which may be a spinal reflex only.

In animals since the type of objective response utilized as an indication of pain is actually a reaction to pain, it may be beyond the pain threshold (80, 244). In man "pain" threshold refers to a perception; in animals to a *reaction* to supposed pain. These differences have been brought out by Beecher (56). Many experimentalists have made a great deal of prick as a threshold in man; but Bishop (86a) points out that the threshold for prick is not in any way equivalent to what an animal will react to. He states further that some of the things interpreted as painful reaction can be obtained from touch in a lightly anesthetized animal.

The flexor reflex to radiant heat in a paraplegic man compared well with his pain threshold (289). So there is evidence in man for parallelism here.

The problem of how to determine whether an animal experiences pain in response to a presumably noxious stimulus is a difficult one. The response has to be objective. It is hazardous, to say the least, to conclude that an observed motor response in an animal reflects what is going on in the realm of sensation. Unfortunately there is no bodily reaction in man which occurs only in response to pain. The evidence available (666) appears to indicate that little or no correlation exists between the perception of pain and reactions to painful stimuli such as changes in skin resistance. These matters have been discussed by Irwin *et al.* (344). Pain perception and the obvious reactions to pain are very different phenomena. These investigators indicate that the phenomena frequently associated with pain in animals are mediated within the spinal cord or brain stem below the levels of perception. These reflexes may share the neural pathways for pain, if at all, for only short distances.

It has been reported (157) that, using a thermal stimulus, "the anesthetic effect" of morphine in a rat fully anesthetized with a barbiturate could be demonstrated.

On the other hand it is remarkable that animal testing methods are as useful as they are in predicting analgesic power of new drugs. These methods all depend upon reflexes. For example there is the tail flick of the rat (155), the back skin twitch of the rat (200), guinea pig (651), dog (23), the lifting of the hind leg from the hot plate in mice (194, 675). The heat stimulus seems to have been most useful.

As Irwin and his associates point out, it had been suspected that the back skin twitch of Ercoli and Lewis is a spinal reflex. It has been shown (92, 634) that morphine and similar agents affect spinal reflexes. Accordingly, Irwin and his colleagues set out to define in physiological terms what is measured by these screening methods in animals. They showed that the tail flick elicited by radiant heat as in the D'Amour-Smith method persisted after spinal cord section. It was like that observed in normal rats. It is unquestionably a spinal reflex which persists even when the pathways to the integrative levels for pain perception are interrupted. By a similar approach the back skin twitch was also shown to depend on a spinal reflex.

With the single exception of N-allylnormorphine all of the known potent analgesics have been shown to produce significant elevations of the thresholds of response in animals when radiant heat was used to produce a tail flick or a back skin twitch. The next problem was then to determine whether the changes observed were effects of the drugs on these reflexes. The effects of morphine, methadone and meperidine were tested on the thresholds of rats (D'Amour-Smith method) or dogs (23) were studied. Significant rises in thresholds were obtained after each of these analgesic agents, but the rises were less in spinal animals than those found in intact animals.

Wikler (634, 635) showed that both morphine and methadone when tested in spinal cats and dogs consistently depressed only those hindlimb reflexes which are characterized by considerable after-discharge and did not depress but actually increased in some cases those hindlimb reflexes that had little or no after-discharge. Wikler therefore concluded that the site of action of these drugs was on the internuncial neurone system of the spinal cord.

Irwin and his associates speculate that the internuncial neurone chains may play a part in the pain experience, since it is now fairly certain that complex cortical and subcortical association pathways are involved in the appreciation of unpleasant sensations.

The back skin twitch and tail flick reflexes have similarity to other multineurone reflexes. Study of such reflexes in spinal cats (635) showed that morphine depressed these action potentials.

Evidence is presented (344) that morphine and methadone augment supraspinal inhibitory mechanisms involved in the tail reflex besides directly affecting the reflex arc. The same workers have observed in response to radiant heat stimuli small, localized tail movements in rats that were deeply etherized, pithed or dead. Such responses cannot be distinguished from reflexes greatly depressed by analgesic agents; so they have suggested and defined the use of a maximal measurable effect ceiling for any given intensity of stimulus used.

In animals, "painful" stimuli evoke reflex responses; these increase as the intensity of stimulation increases. And as the intensity of stimulation increases higher and higher centers respond. In man, domination of the cortex makes it difficult or impossible to separate out and use such reflexes, but in animals such separation is possible, and so is it in man with spinal cord injury. It has been reported (69) from a study of men with spinal cord injury where one leg is anesthetic and the other is not, that reflex muscular activity in the anesthetic leg occurs in response to radiant heat stimulation at an "almost always identical" level of stimulation as was necessary for the pain threshold to be perceived in the unanesthetized leg. This supports the view that the skin twitch, for example, in normal animals in response to stimulation corresponds reasonably well to the pain threshold. Denny-Brown in discussion of this paper said that sensation occurring at the same level as the associated reflex response perhaps could be explained by the pain afferents going to the higher levels being branches of the internuncial of the reflex afferents. Goetzl (242) points out that practical separation between the reflex levels appears to be greater the lower the species. He assumes that a specific threshold exists for each level of reflex activity. In analgesimetric studies of antipyretic agents in animals, squeaking, crying, defensive movements, lid reflex, leg withdrawal, pupillary and psychogalvanic reflexes have all been used by various investigators.

A few investigators have attempted to sensitize the test area in man to the radiant heat stimulus by the prior use of ultraviolet radiation. In animals subcutaneous injection of croton oil has been used for the same purpose (242).

Small doses of barbiturates have been administered to animals (454) to increase their visible reactions to painful stimuli. This is in line with the evidence (357) that barbiturates block internuncial neurones and in effect produce a "pharmacological lobotomy." Evidence of greater motor reactivity than before to painful stimuli in man following lobotomy has been found (132, 133). The use of a barbiturate makes it easier to get more accurate data on analgesic action of drugs under study by this method (454). Barbiturates in rats produce their depressant effects (hypnosis) without altering pain threshold at least as often as they produce a significant rise in pain threshold (298). Hart and Weaver conclude that barbiturates cannot be relied upon to reduce sensitivity to pain in animals, but Keats and Beecher (357) found true analgesic effects of barbiturates in man.

3. Stimuli and tissues involved. The great varieties of these have been indicated in the section on Methods.

In a study of the nature of the reception of cutaneous stimuli, the hypothesis was set up (624) that when a stimulus impinges upon a cutaneous receptor it produces a chemical reaction which gives rise to a neural impulse. It was supposed further that raising the skin temperature would increase sensitivity, that is, lower thresholds. This was found to be true for vibratory sensations and for pressure. In this study Weitz was concerned with the effects of skin temperature on pain sensitivity. The pain stimulus was produced by shocks from a Harvard inductorium. He found a sharp fall of pain threshold with rising skin temperature and concluded that elevations of 2.5° to 9°C. above the normal skin tem-

perature produce an optimal increase in skin sensitivity. Increase above this produced decreased sensitivity, elevated pain threshold. The point relevant to the review is this: Sensitivity to cutaneous pain stimuli is a function of skin temperature as has been shown with electric shock pain (624) and for compression and percussion pain (626) and for radiant heat (see V, A, 3). There is an optimum temperature for maximum sensitivity. Here is one more item which requires control for precise pain threshold measurements. The pallor, that is, circulatory change in the skin, produced by narcotics with or without nausea would certainly lower the skin temperature. A further item to be controlled is the effect of pain on skin circulation (467).

Considerable discussion has been given to the question of the physiological mechanism (305a) involved in the pain sensation. Heat pain has variously been attributed (64): 1) to the absolute temperature applied, 2) to the rise of temperature above a physiological zero level, 3) to the rate of temperature change, 4) to the temperature gradient across the skin (626) and 5) to the temperature difference between adjoining cutaneous regions. These views have been neither proved nor disproved. Buettner (112) holds that heat pain is a function of an absolute temperature below the skin surface and places this receptor point at 0.1 mm down. Benjamin's data (64) indicate that this is 1.0 mm down. Buettner concludes that the actual threshold temperature is 44.8°C., whereas Benjamin found it to be about 40°C. Presumably the effects of circulatory changes on skin temperature and pain response were controlled by the design of Benjamin's experiments, but this is not entirely clear.

Benjamin (64) working with human subjects has shown that the surface temperature when the pain threshold is reached is directly related to the heat energy input and also that the temperature gradient across the skin when the pain threshold is reached is directly related to the heat energy input. The rate of warming is a factor of importance. Benjamin repeated the simple experiment originally performed by Lewis of placing the hand in water which was gradually heated. In this case the pain threshold was found at 43°C. When the hand was placed in a series of basins at different temperatures, the pain threshold was at 47°C.

The temperature for the heat pricking sensation has been variously recorded, 43.9°C. (19), 43°C. (Rein, see 414), 41°C. (594). The steepness of the gradient determines primarily the induction of a sensation of warmth, but is secondary in the production of pain by thermal stimulation, according to von Frey and Rein.

It has been shown with the radiant heat method (485) that a fall of 3–5°C. in the skin site tested caused an approximate rise of 30% in the pain threshold. It seems evident that the threshold intensity of skin pain due to heat is closely related to the initial skin temperature. The possibilities for error if this is not recognized are very great. A drug that reduces the circulation in the skin (pallor, reduced circulation produced by nausea or by pain or circulation reduced by direct drug action or by pressure) could produce a rise in threshold quite unrelated to real analgesic effect but of the same order as the changes often relied upon as

indicative of analgesic effect. The effects of drowsiness, of emotional states, and so on, could easily mislead the unwary and probably account for some of the contradictory reports. It is evident from the work of Pfeiffer and his colleagues that no study involving heat to the skin and which fails to control skin temperature can be considered as really dependable.

Lloyd-Smith and Mendelssohn (424) report 44.6 ± 0.7°C. standard deviation as the tolerance limit for skin temperature. They found a small, yet statistically significant difference in tolerance limits between the epigastric and interscapular skin areas. Various other data are given as to the response of patients to different radiation intensities.

This problem has been further examined (279, 527, 626) with the radiant heat method. Skin temperatures were measured with a radiometer. Two room temperatures were used, 8°C. and 26°C. In cold pain, vasospasm may be a contributing factor (657). A nice relationship was demonstrated between skin temperature and pain threshold. Heating of the skin of the forehead 10°C. caused a lowering of the pain threshold of about 200 mcal/sec/cm^2. The relationship holds as a straight line which runs through zero stimulus at 44.9°C. This suggests that skin must be raised to this temperature, regardless of the initial skin temperature, to be painfully stimulated. From this, these writers conclude that it is the actual skin temperature rather than the rate of skin temperature rise or the amount of skin temperature elevation that makes for painful stimulation of the skin. It is plain that skin temperature must be controlled whatever the method of stimulation as long as the skin is involved.

It has been shown (111, 305) that tissue damage to the skin is produced by temperatures of 44–45°C. Others have found a temperature of 44.9°C. to be necessary to evoke a painful stimulus (279). Wertheimer and Ward (629) confirm with an extrapolated temperature of 44.1°C., Hardy, Goodell and Wolff's (279) 44.9°C., and Buettner's (111) and Henriques and Moritz' (305) 44° to 45°C. as the critical temperature where skin damage is produced and skin pain elicited. Hardy, Goodell and Wolff infer from this a close relationship between tissue damage and threshold pain. They believe that "the adequate stimulus for pain is tissue injury." But even great tissue injury is often not an adequate stimulus, for Beecher (57) showed that significance of the wound often is the determinant of whether pain will or will not appear.

To this reviewer the work on heat also implies that repeated testing in the same skin area is clouded with uncertainty of meaning of the results found, for even a prompt second test in the same area, if the above be true is made on abnormal tissue.

It is clear that one of the leading problems in pain threshold determination is the choice of a valid, repeatable end point. Mueller *et al.* (464) have discussed in detail some of the conditions necessary to standardize an electrical pain stimulus. They agree with Bishop (80) that the threshold pain from electrical stimulation is a prick. They found however when skin impedance was lowered that they were unable to reproduce the prick sensation whatever the current. They explained this on the basis that, when the skin impedance was high, a breakdown of

impedance "occurred in only one small area and all of the current, instead of passing through the entire electrode area, suddenly surged through the small area of breakdown. Thus, for the same total electrode current the current density would be much greater than when skin impedance was initially low." They studied the manner in which breakdown occurs and the conditions which are required to evoke a prick sensation. They concluded that an electrical stimulus is not easily controlled and summarized the disadvantages of an electrical stimulus for pain threshold testing. Although the pricking sensation represents a clear-cut end point, the prick depends on the dielectric strength of the skin; it is not a measure of threshold stimulation. Mueller *et al.* were unable to find any other reproducible end point.

While they were unable to explain the mechanism of electrical prick production, they suggest that histamine may play a part. Evidence has been found that electrical stimuli liberate histamine at pain threshold levels (512). Experimental evidence that histamine is the chemical mediator for cutaneous pain has been presented (510).

4. Galvanic skin response as an indicator of the pain threshold. The galvanic skin response has been used to indicate the threshold for reaction to pain (669) and this threshold has been found lower than the pain threshold on occasion. A relationship between galvanic skin response and intensity of pain has been reported (227) but it was also found on repetition of the pains that they had lost their effectiveness to produce the galvanic skin response. It is believed (227) that the galvanic skin response is an indicator of the threat contained in the procedure and is thus only indirectly related to pain intensity. Others (141) concur. Still others have found the galvanic skin responses to vary independently of pain perception thresholds. For several references see Edwards (197).

Appreciation and description of the heat pain end point must involve a complex series of neural pathways including the cerebral cortex (22). Andrews pointed out further that skin resistance, being under the control of the autonomic nervous system is only secondarily affected by the cortex. He hoped that through simultaneous determination of pain threshold and skin resistance he could have a means for differentiating between autonomic effects and those involving higher centers, with thus "an objective check on the accuracy of the subjective reports" of threshold. This hope seems to have been too optimistic in view of the undoubted fact, well stated by Andrews himself (22) that ". . . when the stimulus exceeds the pain threshold, there is a sharp increase in the emotional content of the stimulation and a sudden increase in the magnitude of the skin resistance change would be anticipated." Possibly skin resistance is "only secondarily affected by the cerebrum," but it seems doubtful if this can be dismissed. On the basis of his data he concluded, "It appears that the skin resistance response cannot be used as an objective measure of the endpoint in the determination of pain thresholds, for the response following a "P" [pain] report is not invariably greater than with weaker stimuli."

The use of the galvanic skin response as an objective indicator of pain threshold has been proposed and compared with the pain threshold as determined by

the radiant heat technique (141). This pain threshold method presents the necessity of discriminating between two sensations: warmth and pain. It also is unpleasant. These factors make for difficulty in pain threshold determination, especially since unpleasantness while not necessarily the same thing as pain, may be equated with it. It is not clear why in the light of the prior unsatisfactory experience of others just described, Clausen and his associates chose to study the galvanic skin response as an indicator of pain threshold.

VIII. "CONSTANCY" OF THE PAIN THRESHOLD

Sherrington held that the pain ending is one in which the surface may be disturbed by various agents, and that a discharge of impulses can start from wherever surface breakdown occurs. There is evidence that this can occur over a considerable length of a given fiber (4). The pain fiber gives off terminal branches at many levels, all accessible to stimulation. The view is appealing that a given stimulus to a given portion of this pain apparatus should be detected by all normal men at the same level of stimulation. Admittedly such a simple concept ignores the complexities of the "reaction component," (see XII) and the probable contamination of "threshold" values with "reaction" (see below). One might suppose, however, that if he could in fact devise an experimental situation divorced from reaction that he could demonstrate constancy of the pain threshold. Such constancy would, then, support the view that the variable reaction had been either eliminated or rigidly controlled. Failure to demonstrate constancy of the pain threshold is, conversely, support for the view, if the above hypothesis is correct, that the reaction component has not been sufficiently controlled or eliminated. Thus considerable interest can be attached to the much debated question of whether there is constancy of the pain threshold as Hardy and Wolff and their associates aver. Speculation is fruitless; the available data must be examined.

1. Reports of constancy of the pain threshold in man. Notwithstanding earlier work to the contrary (435, 447) it was reported (284) that there was great uniformity of the pain threshold (radiant heat) from person to person as well as constancy in a given individual from time to time. The subjects were the three investigators and studies were carried out almost daily for nearly a year. All observations were within $\pm 12\%$ of the mean. Unquestionably the radiant heat method of stimulation developed by this group offered a great increase in precision of stimulation. Their work was extended (528) to cover 150 subjects under ordinary living conditions. In the light of their disavowal from time to time of untrained subjects it is interesting to find here that they say "the threshold was easily recognized even by untrained subjects." A single value was obtained for each subject; this consisted of an average of all observations made on the subject.

Schumacher *et al.* (528) state for the 150 persons involved in their study that the pain threshold is 0.206 ± 0.03 gcal/sec/cm^2. The range of threshold readings was from 0.173 to 0.232 gcal/sec/cm^2. These data are a little (10%) lower than the earlier average obtained by Hardy, Wolff and Goodell on the three subjects.

Schumacher and his associates report that 91% of all determinations fell within ±8%, with a standard deviation for the group of ±1%. They report that the pain threshold could not be correlated with the subject's estimates of pain sensitivity and that the threshold is uniform throughout the 24-hour day. (See X, 24 for a contrary finding.) They state in conclusion, "Individual reactions to pain are not the result of individual variations in pain threshold." Evidence in conflict with the findings reported in this study give some reason to state the sentence just quoted in a reverse way: Variations in pain threshold are the result of individual reactions to pain; but see below.

Javert and Hardy (352) report "remarkably uniform" pain thresholds (radiant heat) in women in labor. Some 300 determinations were made before, during and after labor. They say further, "All of the obstetrical patients had a constant skin pain threshold." This, too, is surprising in view of the patients' lack of training (see X, 14), and the distraction and emotion (see X, 18, 20), inevitably attendant on childbirth, especially in the absence of analgesic medication.

Potelunas *et al.* (493) in studying the pain thresholds on the *normal* skin of 65 patients with diseases of the skin, report a considerably wider spread of pain threshold (radiant heat method) than the same group had found with normal subjects. Potelunas *et al.* report that 61% of the patients fall within the normal range, 210–250 mcal/sec/cm^2 reported (284) for trained subjects, 8% had lower and 31% had higher pain thresholds. The average was 235 mcal/sec/cm^2, with a range from 170 to 330 mcal/sec/cm^2. It has been reported (129) that the pain threshold to radiant heat is "similar" for psychoneurotic and normal subjects.

If the reviewer's belief is correct that the explanation for variation in pain threshold, when all technical problems are controlled, is interjection of the reaction component, then these data showing wider than usual spread of the threshold data support his view in that it would be supposed that subjects with skin disease (focus of attention) would be likely to have more than a normal response to pain in the skin, even though the skin tested be normal. The matter will be discussed in the section on reaction (XII).

Hardy *et al.* (289) report that the pain threshold is approximately uniform over the body surface, as measured by the thermal radiation method. This is not in agreement with earlier work of others using electric shock stimuli (435) where great spread of pain threshold was found over several parts of the body. Nor is it supported by a report (424) of significant differences in tolerance limits to radiant heat between the epigastric and interscapular skin areas. Much greater spontaneous variation in radiant heat pain threshold on the hand than on the forehead has been found (558).

Miller (451), on re-examining old data provided by Goodell and Wolff where they studied pre-drug threshold effects, found good consistency of data among the three subjects on a given day, but enormous variations between days, "far greater than would be expected once in a thousand times through chance." It is evident that there is day to day variation.

Miller (451) has also examined Gross' findings and reports remarkable consistency using the Hardy, Wolff and Goodell method in 4 subjects on 3 separate

days. The normal pain thresholds were determined twice for each subject for each day. The 24 readings thus obtained *all* lay between 228 and 235 mcal/sec/cm². Such extraordinary constancy is not the usual experience in biological investigation. Since the details of these experiments were not given, further comment is not in order, but it may be fair to comment that such precision is not the rule where the design of the experiment is such as to eliminate unconscious guidance. It would be interesting to see this experiment repeated so that the operator did not know whether a narcotic had been administered or not. Denton and Beecher (159) found that a widely experienced operator who was called in to correct their failure to use the radiant heat method successfully got consistent data as long as he knew what had been administered; he failed to do so when he did not. This is by no means to impute dishonesty; it merely indicates how devastating are the results of unconscious guidance when subjective responses are involved.

2. Failures to confirm constancy of pain threshold in man. a. Radiant heat method. Some partial failures to confirm constancy are mentioned in the preceding section. Using the radiant heat method of Hardy, Wolff and Goodell, Chapman and Jones (131) found in studying the pain threshold of 200 normal subjects that the threshold varied much more widely (−40% to +50%) than Hardy, Wolff and Goodell had reported (±12%). Chapman *et al.* (128) showed in 44 healthy control subjects a spread of pain threshold to radiant heat stimuli as follows: a range of 0.241 to 0.356, with a mean of 0.287 ± 0.024 (S.D.) gcal/sec/cm². Pain thresholds are the same for patients with neurocirculatory asthenia as for normals, but the reaction level (wince) is lower for the latter group.

Several others using the radiant heat technique have failed to find the pain threshold constant (142, 402, 515, 549).

b. Electric shock method. Lanier (394) put to test the generality of the conclusion that pain thresholds are uniform. To do this he used electric shocks to measure the pain threshold in a series of 15 college women on 2 days. With his technique, modified from Fender (207), condenser discharges are amplified and delivered through such high resistance that variations in the subject's skin resistance have little effect on the current flowing in the stimulus circuit. On converting his variability indices into relative units he found a range which represented a variation around the mean of −80 to +300%. The standard deviation was ±55% of the mean. The variability of these pain threshold measurements is thus much greater than that reported by Hardy's group for the radiant heat stimuli. Their standard deviation represented, it will be recalled, a variation of ±1%, whereas Lanier's corresponding coefficients of variation in 2 series of experiments were above 50%.

Granting that frequency distribution, as calculated by the Hardy group based upon averages of all threshold determinations for each subject, would normally show less variation than a distribution of single threshold measurements, Lanier recalculated his data in this manner and found, nevertheless, that his pain threshold data still showed almost fifty times greater variability than that of the Hardy group.

The conclusion is inescapable that as carried out here, pain thresholds for this type of electrical stimulation are neither uniform nor constant in different individuals.

To test the question of whether individuals with, say, a low threshold for one series of measurements continue to exhibit the same level of sensitivity in subsequent tests on different days, rank-difference correlation coefficients were computed between several series of measurements (394). To do this the averages of all thresholds for one day were correlated with those of the second day. The coefficient was 0.55, a moderately high degree of correlation, but far too low for any accuracy in predicting an individual's standing from one day to the next. Lanier called attention to his finding that half the subjects had almost identical ranks, on the 2 days of the study (the hazard in using 3 subjects is evident, very often the case in the Hardy work), while the other half showed the variability which lowered the correlation.

Lanier next examined the consistency of the 2 sets of threshold measurements made upon the same skin spot. Four spots had been examined, arm, head, head, arm. He found high correlations between the averages of each of the two series, for all four of the spots tested on the first day. The coefficients for arm, head, head, arm were, respectively, 0.86, 0.91, 0.89, 0.94. However, the correlations among average thresholds for different spots in the same body area were much lower, from 0.32 to 0.44. Finally, averages of all threshold determinations made for the arm for a given day were correlated with corresponding averages for the forehead. Correlations for 2 sets of values obtained on different days showed the same coefficient, 0.60.

It can be concluded from this careful study that the electrical pain threshold of an individual may vary widely from day to day and from one skin area to another. Certain subjects are comparatively stable, while others vary over a wide threshold range. The factors which cause such variability are not clear. The reviewer supposes that the reaction component, impossible to separate here from "perception" is largely responsible for the variation. This will be discussed below.

Early work with electrical stimulation of the skin showed considerable threshold variation (447). Also with electrical stimulation of the skin others (485) found that the threshold varies widely from animal to animal and from man to man. Electrical stimulation of the scrotum of rats showed (437) the standard deviation was 58% of the mean reactive threshold. This spread in animals agrees exceptionally well with that of Lanier (349) who in studying electrical pain threshold in man found a corresponding figure of 56%. These are far greater variations than were reported (528) for radiant heat threshold variation. On this basis Pfeiffer discarded electrical stimulation of skin as a feasible method. Others (292) using the electrical stimulation of tooth pulp method, found significant variation of threshold among human subjects. With the same method still others (478) found a remarkably wide spread of threshold values, 0.2 to 1.8 volts.

c. Mechanical methods. Seevers and Pfeiffer (534) using a modification of the von Frey hair technique, found that the pain threshold varied widely from subject to subject; 14 individuals ranged from 0.4 to 6.0 g and the given indi-

vidual's pain threshold varied widely from week to week. Mechanical distortion of the skin indicated that the spread of pain thresholds in man is much greater than that of sensation thresholds (506).

d. Visceral stimulation. Using ischaemic muscle pain produced by isotonic contractions it was shown (296) that thresholds for a given individual were satisfactorily constant over a period of hours, but not over a period of days. Great variations occurred among individuals.

Great variation in the biliary tree pain threshold from one patient to another (229), but less variation in a given patient from one time to another was found. The saving factor which makes this method useful is the finding that the variations in threshold in the same patient during the course of a single study were very small. In 10 patients repeated threshold determination on the same day varied less than 5 mm of water. In 15 patients out of 36 the threshold was practically constant for many weeks. All pain threshold measurements in the same patients on the same day were found to be at least within $\pm 10\%$ of their respective average values. Such patients were well suited for the comparative study of a number of analgesic drugs. "Uniformity of pain threshold from individual to individual obtained [by others] by thermal radiation of the skin could not be duplicated with visceral pain threshold determination" (229). This despite a very careful examination of the most favorable patients in Gaensler's series.

A wide spread in visceral "pain" threshold (balloon in esophagus), from -60% to $+58\%$ of the mean average value of 37 cm water has been reported (130, 131).

3. Failures and partial failures to confirm constancy of "pain" threshold in animals. Various methods. Andrews and Workman (23) report that the constancy of the radiant heat "pain" threshold for dogs is at about the same level as for man. The same threshold value is obtained even when the area of stimulation is changed. The threshold is independent of the area stimulated. With constancy of area stimulated the intensity-time relationship is quite similar to that obtained in man. They report that the threshold changes with the administration of drugs are also similar to those found in man. With conducted heat considerable variation among animals has been reported (675).

Miller (451) reports with rats that D'Amour and Smith found the standard deviation to be about 12% of the normal threshold, whereas he, Miller, found in his work the figure to be about 8% with the radiant heat technique.

It has been pointed out (80, 294) that just as man senses a painful stimulus before an avoidance reaction is initiated it is reasonable to assume that this may also be the case in animals; so their reflex responses may give an inaccurate indication of the true pain threshold. It was found (246), using electric shocks to teeth in dogs, that the "pain threshold" varied greatly among animals, as much as 100%, based upon averages obtained over a 16-week period. The variations within a given animal seemed large. Wide variations in animals' thresholds to electric shock stimuli have been reported by others (485).

In studies of 2 dogs subjected to electrical shocks it was found (381) that the threshold of "pain" was not constant from day to day but varied widely. It was satisfactorily constant, however, for a period of several hours.

In a rather small number of guinea pigs it was found (651) that coefficients

of interanimal variability of threshold among various experimental conditions ranged between 9 and 23% of the respective mean value in watts. This is in sharp contrast to the 1 to 2% reported by others (528) for man. The Winder group's experience is more nearly that of Chapman and Jones (131) in man. It is to be observed that this latter group found a similar variability when they dealt with the wince response, presumably more nearly comparable to the guinea pig's skin twitch than man's pain threshold data.

The pain threshold of rats was determined by the tail pressure method (226). If the first day's data are discarded and days 2 to 5 used, there is no constancy of threshold from rat to rat. This finding is at the 1% level of significance. Differences among test days are also significant, in this case at the 5% level. These findings in animals do not support observations of the Hardy group as to the constancy of the pain threshold in man.

4. General comment. When radiant heat is used, the first "sharp prick" or "stab" of pain is usually taken to indicate the "pain threshold." The assumption is that this can be duplicated on subsequent trials and after drugs have been administered. While this is accepted as fact by those who depend on this method, it must remain an assumption for man at least until it is considerably better established than is the case at present. The considerable number of investigators who have failed to confirm Hardy, Wolff and Goodell's observations is a case in point. However, even if the constancy of the pain threshold were a fact, and if there were constant responses to drugs, it still remains to be shown that the observations have any important relevance to the pain relief problem. Many reasons for doubt are presented in the sections to follow (see especially XI).

Time and again the reviewer has come up against conflicting data as to the constancy of the pain threshold, for example. From the data submitted on opposite sides of this question a certain explanation for the contradictory conclusions is often not evident. In such a situation it seems reasonable to take the stand that if a factor is in truth a constant, this will be generally confirmed. Voices to the contrary, if more than one or two, must be accepted as evidence that either the factor is not constant or that proper experiments to demonstrate its constancy have not yet been devised, and final judgment is then to be reserved.

Suppose one eliminated all subjects with a variable pain threshold (Lanier said half his subjects were quite stable), one would surely be on more definite and perhaps sounder ground. Surely it is of interest, even though of limited value to take the stable ones when attempts are made to get at the perception-reaction dichotomy, if it is true that variations in threshold are the result of the reaction component entering into the threshold (perception) determination. Then a further control in threshold studies is essential, one not yet observed by any group: Elimination of those subjects with variable pain threshold, inclusion only of those with stable threshold. Perhaps constant and reproducible data *can* be obtained by elimination of a considerable percentage of subjects; but it is hard to say what the meaning of this would be. As Colin White has said, some samples are representative of nothing but themselves.

IX. "PURITY" OF THE PAIN THRESHOLD

The terms sensation, perception and reaction to pain all need special definition. The first two will be dealt with here. The involved problem of reaction will be considered below (XII).

In the eighteenth and especially the nineteenth centuries British philosophers liked "to distinguish perception from sensation—sensation as the bare content given to mind, perception as the apprehension of an object. An object, they contended, is . . . actually a meaning" (98). There are both anatomical and physiological reasons, to be referred to below, for doubting that pain at least is ever a "pure" sensation by the time it emerges in consciousness: The impulses set up by noxious stimuli have evidently been subjected to "processing" at the spinal cord level and upward. This processing is, in a word, part of the reaction to be considered in detail later on. For the purposes here present the philosophical contentions can be avoided by accepting Watson's view [1913] that dependable knowledge about sensation can be obtained only when the subject experiencing it makes discriminations. Watson's behaviorism was succeeded by the logical positivists [1931] and from them flows the current operationism which equates sensation with discrimination (see 98). Whatever the philosophical shortcomings of this may be, acceptance of this view, if followed to its reasonable conclusion, might have avoided the tremendous efforts recounted in a preceding section to prove and then to disprove that the pain threshold is a universal constant, for if the reduction of sensation to discrimination had been accepted it must have been evident that the pain threshold was most unlikely to be a constant but rather a mixture of original sensation and reaction and to vary as the reaction component varied from one situation to another. The great variation in the pain threshold reported by many investigators fits this view.

A basic tenet of most investigators who employ experimental pain in their work has been that the pain threshold represents a pure "perception" of pain. In this they have for the most part followed Hardy, Wolff and Goodell who also believe (*vide supra*) ". . . that the threshold for the *perception* of pain under normal circumstances is approximately the same in all subjects and in the same subject at varying times of day" (673).

Chapman and Jones (131) express the view long held by Hardy, Wolff and Goodell that ". . . pain perception probably represents a purely sensory phenomenon." A failure to make sharp distinctions and to stick to them is indicated in the following confusing passage from Hardy, Wolff and Goodell's most recent (289) long discussion of the matter.

> "The perceptual characteristic of pain lies in the fundamental nature of the sensation . . . one of the difficulties in considerations of the introspectional aspects of pain has been the confusion of the perceptual features of the pain sensation as such with the feeling states that often accompany it. It is the point of view of the present authors that an adequate analysis of the pain experience requires a separation of the two aspects. If this be accepted, pain stands clearly as a sensation from the perceptual point of view."

It seems clear that Hardy, Wolff and Goodell have rejected the classic distinctions between sensation and perception; but it is not at all clear what their "perceptual features of the pain sensation" may be. From the classical viewpoint "feeling states" would have been included in perception. But now they say one of the difficulties is that these features are confused. Finally, they have decided that adequate analysis of the pain experience requires a separation of the "perceptual features of the pain sensation" from the "feeling states that often accompany it." In the light of the available data this would appear to be an impossible task.

Extensive data were provided in VIII, to indicate the notable lack of confirmation of the often stated view, that the pain threshold is a constant, not only with the radiant heat stimulus but with the electrical and mechanical as well. Hardy, Wolff and Goodell appear to use pain sensation as synonymous with pain perception, but as observed above, perception by definition includes the meaning or significance of the sensation, which in this review is spoken of as processing or reaction. The real difficulty arises when they seek to define the "perception" as something sharply different from reaction. It will be seen that there is good reason to believe that the two components cannot be separated out in their pure forms. A survey of the abundant literature on the subject presented above forces one to conclude that the pain threshold is not constant from one individual to another nor even in a given individual from one time to another.

The lack of constancy is much less surprising in fact than the much advocated view of constancy would be, for constancy would indicate that the pain impulse was not influenced by individual differences or by a time factor or by past or present experience, or by training, from its origination until its eruption into consciousness has occurred. There is good reason to believe this is not so. The inconstancy of the pain threshold is probably to be explained by contamination of it with reaction component of what doubtless started out as a pure perception. There is a good anatomical basis for this in the nerve nets in the spinal cord. Individual nerve fibers have wide ramifications with the extensive conducting apparatus. Several fibers innervate each "pain" spot in the skin for example and these supply other spots as well. Pain reactions are based upon at least a three neurone arc with one or more neurones in the gray matter (4, 426). Many more references along this line could be given. This hardly seems necessary for the purposes of this review, since these anatomical facts are everywhere accepted.

Ray and Wolff (498) have shown that when they produce a high cordotomy giving unilateral analgesia, that noxious stimulation in the analgesic area may be followed by burning pain at a corresponding point on the opposite side of the body. There are wide interconnections within the spinal cord.

Wikler (634, 635) showed that both morphine and methadone when tested in spinal cats and dogs consistently depressed only those hindlimb reflexes which are characterized by considerable after-discharge and did not depress but actually increased in some cases those hindlimb reflexes that had little or no after-discharge. He concluded that a site of action of these drugs was on the internuncial

neurone system of the spinal cord. This is further evidence for ramification of pathways with possibilities for spread of impulses within the spinal cord.

Pain does not occur in the periphery; it is a phenomenon of the central nervous system. Evidence has been accumulating that consciousness of pain has more to do with the cortex than was once believed. Gerard (238) has summarized several findings to support this view: The pain which appeared with focal epilepsy has been relieved by excising a little of the cortex (450). Phantom limb pain has been cured by surgery of the cortex (158). Stimulation of the post-central gyrus has evoked pain (Bumke and Foerster, quoted in 238), even though handling of the cortex is not usually painful; indeed bilateral pain is possible even when an entire hemisphere is missing with corresponding thalamic degeneration (615), and pain may be absent with what appears to be a normal cortex (391). Even unilateral leukotomy can relieve the unpleasant affect of pain. The leukotomy appears not so much to relieve the sensation as to relieve attention to the sensation (514). Possibly leukotomy and morphine, as dissimilar as two pain relieving agents can be, have in common the power to distract.

In considering factors involved in alterations of the pain threshold Bishop (80) said, "It is not clear in view of the obvious central effect of drugs whether they have any effect on the periphery in ordinary analgesic dosage, nor is it always clear whether the increased perceptual threshold under drugs, *etc.*, is in effect a result of changed mental attitude, lack of attention, interest or less careful discrimination, for instance, which to be sure are themselves factors in the complex act of perception itself." Along the same line Cattell (124) said, "It may well be that the threshold raising effect [of analgesics] is secondary to influences on the mental state of the subject, who otherwise is likely to be preoccupied with the painful experience. Just as environmental distractions cause a rise in pain threshold, so do mood changes or the interference with mental processes through drug action. The rise in threshold which may accompany analgesia must then be looked upon as incidental to the changes in mental function, with awareness of pain not necessarily altered.

Both of the above statements cast serious doubt on the purity of the pain threshold as a measure of perception alone. They strongly suggest the possibility of a reaction component in the threshold response, Wolff, Hardy and Goodell notwithstanding.

When one couples the anatomical possibilities for communication and spread of impulses with the undoubted fact that determination of a pain threshold requires judgment, *i.e.*, comparison of the non-painful sensation with the barely painful, and this involves memory, it is not difficult to understand how the reaction component could be involved in perception. Pain perception is greatly influenced by placebos, by emotion, by anxiety, to mention three powerful factors at random. Their effectiveness is easily demonstrated. These are all parts of the reaction component (see XII). How, then, is one to suppose that pain thresholds can ever be pure perception. It is doubtful if there is any such thing as a pure perception. Probably all perceptions are contaminated with

reaction component. This can be stated as an assumption. The fact is, the pain threshold has not been shown to be constant, and the probable explanation is contamination with reaction component. The latter will shortly be discussed.

X. FACTORS WHICH ARE SAID TO PRODUCE VARIATION IN THE PAIN THRESHOLD OTHER THAN ANALGESICS

It is an arresting fact that while the concept of a constant pain threshold has been vigorously advocated in the last decade and a half, in about this same time nearly four score articles have presented more than a score of factors, other than analgesics, which are said to cause the pain threshold to vary. One observation does not necessarily cancel the other, but the disturbing fact is, no studies on pain threshold have controlled even the majority of the possibly significant sources of variation. Most conclusions in this entire area must, therefore, be tentative. There is, however, the plain indication in these data that if dependable work is to be done on the effect of analgesic agents on pain threshold these 27 types of factors must be studied and if relevant or possibly relevant must be controlled in such work.

1. Race. Negroes and Southern Europeans perceive pain at a lower level than do those of North European stock (131). The Negro reacts to pain at or near his pain "perception" level, whereas the North European's spread between perception and reaction is distinguishable. However, Meehan *et al.* (449a) report no significant difference between Indian, Eskimo and white subjects.

2. Sex. Women are said to have a greater pain sensitiveness than men (150, 535, 643). This has been denied (289). Others have reported that the difference is not significant (131, 582) although woman's daily variability is slightly greater than man's (582).

3. Ageing. Both pain perception (131, 142, 150) and pain reaction (131) are reported to decrease with age. This stated effect on perception has also been denied (286, 289).

4. Autonomic nervous system. Observations reported in X, 5, 6, 7, 13, 20 and 24 are wholly or in part also under the influence of the autonomic nervous system.

It is possible that agents which stimulate the autonomic nervous system elevate the pain threshold; but it will be seen there are difficulties in the way of accepting this elevation as representing general analgesia. Gross *et al.* (264) agree apparently with the general assumption that narcotic agents "exert their pain-relieving action through a depression of the thalamic region of the central nervous system." The evidence for this is slender. They also point out and summarize evidence that the autonomic nervous system may be involved in the production of analgesia. Unfortunately, the evidence for this is also tenuous: the experimental design of most of the bolstering work is not adequate for reassurance on this score.

It can be said, however, that the work to be mentioned provides interesting hints which deserve better examination than they yet have had. For example, there is the "potentiation" (sic) of opiate analgesia by prostigmine (548). This has been "confirmed" (548a). It is claimed that 8 mg morphine plus 0.5 mg

prostigmine produces as good an anesthesia as 15 mg morphine. Andrew (20) was unable to confirm the observations of Slaughter's group. It was only when very severe pain (397) but not when moderate pain (160, 361) was used that the Beecher group could demonstrate any difference in analgesic power between the two doses of morphine. The dose effectiveness curve of morphine breaks sharply at about 8 mg morphine. Then there is the "production of analgesia" by epinephrine (349), and other vasopressor amines (348), the "production of analgesia" by prostigmine and physostigmine (216). There is evidence that the cholinergic depressants, scopolamine and atropine, "tend to decrease both the intensity and duration of analgesia" (136). Adrenalectomized rats showed less analgesia from morphine than normal rats did (295). Morphine is known to stimulate the adrenal glands (339, 340, 341). Pain itself has been "shown" to produce analgesia which persists after the original pain has ceased (478). The assumption in the present connection is that analgesia results from adrenal stimulation. (It can be observed in passing that here is still another factor to throw off experimental pain threshold determinations.) Gross *et al.* (264) support in dogs the observations (226, 295) that adrenalectomy reduces the effectiveness of narcotics. Specifically, the pain threshold response to morphine, meperidine and methadone is lowered by adrenalectomy, according to Gross and his associates. (The size of the threshold changes is not very impressive.) While considerable discussion is given (264) to the question of a relationship between possible vasomotor changes and analgesia, the most likely possibility is not mentioned, namely, that epinephrine does indeed elevate the pain threshold, especially when radiant heat to the skin is used to produce pain, through its constricting effect on the skin blood vessels. Ischaemia of the skin is known (284, 571, 633) to elevate pain thresholds. If this likely explanation is correct, there is no longer much mystery left in the "analgesic" effects of epinephrine. If experimental pain thresholds are to be relied on, it is evident that this possibility requires control, however difficult it may be.

As in most matters in this field, a contrary voice has been raised. It has been reported (284) that epinephrine preceding the administration of morphine "completely obliterated" the threshold-raising effect of 15 mg morphine in 2 out of 3 subjects and greatly reduced the rise in the third. Others (131) have reported that about 0.5 mg epinephrine subcutaneously had no effect on either pain threshold or reaction.

5. Circulatory change. Pain itself can cause peripheral vasoconstriction (467). With the radiant heat technique, pressure on the skin by the apparatus near the area tested produced an elevation of pain threshold (571, 633). Factors which influence the rate of heat loss from the skin also elevated it (285). Constriction of the head by a tight bandage, with impairment of circulation produced a rise in threshold of only 4 to 6% according to some (284). Whether the reduced circulation in the skin (shown by pallor) associated with the use of morphine in large dose (with nausea, see below) (405) accounted for the "significant" elevation of pain threshold produced by morphine is not clear. Possibly the reported effect of epinephrine in elevating the pain threshold is on a circula-

tory basis. There is no constancy of threshold effect of cold or pain on blood pressure in normal subjects in the same age group (9). The foot and leg can withstand water at a temperature of 44.5°C. but if the circulation in the leg is arrested this temperature becomes intolerable (571).

6. Skin temperature. (See also VII, 3.) The well known triad of narcotic effects involves pinpoint pupils, depressed respiration *and a fall of rectal temperature* (221). This fall of internal temperature is probably associated with reduced skin temperature. This can alter pain thresholds determined by the radiant heat method (19, 285). The pain threshold elicited by percussion and by compression bears a direct relationship to skin temperature (626).

The relationsbip of skin temperature and pain threshold has been studied (628, 629) with the threshold measured in terms of *duration* of a constant stimulus. This system has the advantage of a single trial quickly run giving quantitative information, whereas the original (284) technique required several runs and a much longer time to bracket the threshold. This technique avoids, theoretically at least, the danger of hyperalgesia produced by repeated trials. Also with the new technique calibration is less time-consuming than with the old.

There is some evidence (424) that radiant heat of "comfortable" degree exerts an analgesic effect. With pin pricks to an area exposed to radiant heat in 39 subjects, 29 reported dulling over the exposure area, one increased sensitivity, and 9 no difference. Since there was no spread to areas with similar nerve supply, the authors conclude that the findings represent an effect on peripheral nerve endings. The possibility that such effects could account for pain threshold elevations must be kept in mind.

Acetanilid produced a slight but definite lowering of body temperature and so did morphine, as the "pain" threshold in monkeys was elevated (553). The "pain" threshold was determined according to the voltage required to produce the change in respiration considered to be the end point.

In paraplegic men the reflex movement threshold of a dermatome can be raised or lowered by thermal stimulation (69). This is believed to indicate that there is production in the spinal cord of a central inhibitory state or a central excitatory state as a consequence of the various levels of stimulation. Possibly an analogous effect occurs in the brain in normal subjects during experimental pain studies and accounts in part for the observed variations in the "pain threshold."

7. Sweating. When a thermal stimulus is used, even invisible perspiration on the skin can alter the threshold determination (214, 405). "Sweating caused a great decrease in this type of stimulus" (279, 285). On the other hand, it has been stated that even profuse sweating does not influence the threshold for thermal pain (131).

8. Elevation of carbon dioxide tension. The fact is well established that the narcotics commonly tested in experimental pain studies and widely used clinically usually depress the respiration severely (358, 395, 396, 397) with sharp elevation of the carbon dioxide tension in the subject and failure of the subject's respiration to respond normally to stimulation by carbon dioxide (*loc. cit* and

182, 183). The important observations of Stokes *et al.* (571) on the effect on pain threshold of a rise of carbon dioxide in the body has been entirely neglected, even by the discoverers in subsequent work. They found that breathing 10% oxygen did not affect the radiant heat pain threshold as elicited by the Hardy, Wolff and Goodell technique. Thus hypoxia appears to affect skin pain less than it affects vision. Breathing 5 or 7.5% carbon dioxide for only a few minutes elevated the pain threshold by 13 to 28%, respectively. Certainly the study merits repetition. Since the latter value is sometimes the change accepted as evidence of the primary action of an analgesic, it becomes evident that a highly important factor, respiratory depression (minute volume depression and carbon dioxide tension elevation) must be controlled, that is, observed and corrected for in pain threshold studies. This, unfortunately, has not been done. It is not possible to say just how destructive to dozens of studies this neglect may have been; it needs to be determined.

These investigators have shown that the analgesic action of carbon dioxide is central, not peripheral, for it recurred when the pain threshold was tested on an extremity where blood flow had been stopped by a tourniquet. They also showed by the same technique that the analgesic effects of nitrous oxide are central. This supports the view that analgesic agents in general act centrally and not on the peripheral pain apparatus.

9. Hyperalgesia. Sunburn can lower the radiant heat pain threshold by as much as 50% (285). The thermal pain threshold is greatly lowered in areas of primary hyperalgesia, that is in the area of tissue damage, but not in areas of secondary hyperalgesia, as in an area of referred pain (288). In this same study it was found that whereas spatial summation of pain does not occur in normal tissues it does occur in hyperalgesic areas.

In various referred hyperalgesic states measurement of pain threshold revealed (285) notwithstanding the hyperalgesia a normal pain threshold which "differed in no way from that of a corresponding and normal area similarly tested. It is inferred that such changes in sensation as occur in the 'hyperalgesia' associated with referred pain are not the result of lowered threshold. They represent instead a change in the evaluation of the intensity of the stimulus," a change in processing or reaction (see XII).

10. Other forms of trauma. Skin lesions, traumatic deformation of tissues, calluses, denudement, or tissue injury near the nerve endings can all alter the pain threshold. Local anesthetization can obliterate it (285), so also can transection of afferent nerve fibers. Nerve injury can alter (raise) the pain threshold. In the central nervous system syringomyelia can raise the pain threshold so also can lesions in the region of the internal capsule and lesions near the thalamus. Structural defects of the neural apparatus always raise the pain threshold if they alter it at all, according to some (285). Others (620) have found that morphologically abnormal nerve endings in the skin are associated with a lowered pain threshold. Lowering of the pain threshold is often the result of tissue damage in the vicinity of the peripheral end organs of the area stimulated (285). The question can be raised as to whether this lowering could be explained

by a conditioned sensitive attitude on the part of the subject toward the damaged areas being stimulated, in other words, evidence for a reaction component in their pain threshold determination.

There is always the possibility that suprathreshold stimuli from any experimental pain method will so modify subsequent determinations as to make them unreliable. Several observers have found this hazard to be great with the radiant heat technique; however, Hardy *et al.* (284) carried out daily measurements on themselves for about a year with reproducible results. Presumably a good many determinations were made on the same skin areas; therefore it seems unlikely that any persisting tissue damage is associated with proper use of the stimuli *at pain levels they were working with.*

11. Nausea. "Extensive nausea seemed definitely to lower the pain threshold (von Frey technique) and prevent the analgesic action of all the drugs" (534). One might have supposed, as suggested under circulatory changes, that the reduced circulation in the skin (pallor) might have led to an *elevated* pain threshold, and in fact in another report one of the above authors has found this (warm wire algesimeter) (405). The distraction and emotion also associated with nausea presumably would lead to an elevated pain threshold (see below).

12. Fatigue. This can alter, usually elevate, the pain threshold according to a number of observers using a thermal stimulus (19, 214, 285), with ischaemic muscle pain (296), and with an electric shock method (448). But according to others (131) using the radiant heat stimulus, acute physical fatigue did not alter the pain threshold, but "mental fatigue" after an 8-hour study period caused a fall of 8 to 10% in pain threshold below the limits of normal variation in 3 subjects. In 3 others the pain threshold fell to the lower limits of their established normal variation. Pain reaction values also fell in a parallel way. Four subjects showed no change after mental fatigue became a possible factor. In their 1947 review, Wolff and Hardy say that the pain threshold is independent of fatigue.

13. Anxiety and fear. A determining influence of anxiety on the appearance of pain and its relief by morphine has been studied extensively by Malmo and Shagass (439, 440). Hill *et al.* (318, 319), using electric shocks, have studied the extent to which anxiety and morphine alter pain intensity estimation in post drug addicts. From their studies they conclude that pain threshold measurements to be useful must include control of the important variable of anticipatory fear of pain. Failure to do so probably accounts in part for the great variations found in reports of measurement of pain threshold.

These investigators also conclude that under conditions which promote anxiety or fear of pain, the subjects tend to overestimate the intensities of painful stimuli. It was found that morphine reduces such anxiety; when the conditions of anxiety are eliminated for the most part, little overestimation occurs, and morphine does not affect the ability of the subjects to estimate accurately the intensities of painful stimuli.

Kornetsky (384), extending the work just mentioned, emphasizes that a possible source of variation in threshold studies, certainly one to be controlled,

is the anxiety-producing qualities of the experimental circumstances. His work with the radiant heat method of stimulation indicates that very different responses are obtained when anxiety is present and when active steps are taken to dispel it. This agrees with the earlier parallel work of Hill *et al.* (318, 319) using an electric shock stimulus. It would hardly seem likely that the anxiety factor alone would explain the great pain threshold changes found by Hardy, Wolff and Goodell in themselves, for early in their long experience anxiety must have become slight or non-existent. Nervous tension before an examination for internship produced a fall in pain threshold in a third of a group of twelve (131).

Beecher (57) has shown with pain of pathological origin how anxiety appears to determine the development of pain. Since anxiety, tension, fear are demonstrably of such great importance it is urgent that they be controlled in threshold studies. However, others (285) have reported that variations of mood did not alter the pain threshold.

14. Training (man). The radiant heat method of producing pain for experimental purposes has been used far more often than all other methods combined. Perhaps this accounts at least in part for the many statements made about the training of subjects used with this technique. It can hardly account for the conflict in the statements made when this technique was employed. It may be well to take a look at the record, first to see what the current view as to the need for training of the subjects used really is. For sample data see Table 8. Wikler (641), noting the divergent results obtained by Hardy *et al.* and by Denton *et al.*, says "... thresholds of perception of painful radiant heat stimuli are elevated by opiates in trained subjects, but not in untrained individuals." In the studies of Hill *et al.* (318) morphine reduced the overestimation of intensities of painful electric shock stimuli which was associated with fear and apprehension but had no effect on pain intensity estimation when these factors were absent. This seems to be evidence for the psychic reaction component influencing the pain threshold, and, incidentally, evidence that the so-called pain threshold is not a pure perception (see IX). Miller (451) in commenting on the work of Denton *et al.* (162), who had concluded that the Hardy, Wolff and Goodell method was not satisfactory in untrained subjects, said, "Thus, it is possible

TABLE 8

The average pain threshold and index of variability reported by various investigators upon untrained subjects*

Investigator	N	M	SD	Variation Coefficient	Range
Schumacher *et al.* (7)	150	206	21	1	173–232
Chapman and Jones (4)	200	305	45	14.7	175–462
Chapman *et al.* (3)	56	283			229–376
Chapman *et al.* (2)	44	287	24	8.4	241–356
Schilling and Musser (6)	138	348			

* In mcal/sec/cm^2.

that lack of training may have been responsible for the failures on human subjects reported recently from two British laboratories (165, 591)." Others believe that training is important.

What is meant by "training" is, of course, relative. Miller (451) presents and discusses "well-balanced" data sent to him by Gross concerning the change in the radiant heat pain threshold of 4 "green" subjects over a 4-day period; ". . . the subjects had settled down to practically the same threshold value by the second day," he says. It is interesting to recall that Denton and Beecher's (159) "untrained" subjects were "intelligent, cooperative, college men" who had been drilled in the technique before the study started (and it) was applied to each man (29 subjects) 11 times in a 5-week period. Thus Denton and Beecher's subjects were far more numerous and far more trained than Gross had found necessary. Nevertheless, they (159) reported that "Inspection of the data on pain thresholds determined by the Wolff-Hardy technique revealed such gross inconsistencies that a detailed statistical analysis was not justified. Some thresholds were higher after the injection of isotonic sodium chloride solution; some were lower after the administration of morphine, and these discrepancies were common." But here is an interesting thing: A well-known investigator with years of experience with the Hardy, Wolff and Goodell method was the one who established the unreliability of the method under the circumstances just described. This unreliability was evident as long as this operator was kept in ignorance of what the subjects had been injected with. When this operator knew that the subjects had received morphine he had no trouble in demonstrating a suitable rise in pain threshold with these same "untrained" subjects! This is not to impugn his honesty, but it is to emphasize the necessity to rule out bias insofar as this is possible. It is not possible to accept Miller's explanation of untrained subjects as at the bottom of the problem if he accepts Gross' fewer and far less (than Denton and Beecher's) trained subjects as "trained." The fact that the pain threshold rose in an expected fashion after the administration of morphine in Denton and Beecher's subjects when the operator knew what the subjects had had but failed utterly when he did not know is sufficient comment on the question of whether these particular subjects were "trained" or not.

While the experience of Hardy, Wolff and Goodell has been wide, they have not held a consistent attitude toward the problem of training. There are a series of contradictions in successive statements as to who are suitable subjects for the radiant heat technique and where dependable data can be obtained. For example, Hardy *et al.* repeatedly have stated that only experienced subjects are suitable (291). They say specifically that medical students, described as intelligent (287) are *not* satisfactory (277): "It is concluded that untrained subjects (160 medical students), even of high intelligence, cannot be used successfully to measure the threshold raising effects of aspirin, codeine, and meperidine (100 mg) . . ." So far this is consistent. It is perhaps significant that this is one of the earliest studies on their part (perhaps the first one) where they have used the double unknowns technique, and placebos as unknowns, and have finally

got away from the use of sophisticated, drug-wise subjects. These essential controls may explain their failure to show consistent pain threshold changes rather than the *untrained* characteristic of the subjects; it is, however, to this latter fact that the authors attribute their failure, possibly incorrectly.

In noteworthy distinction to the Hardy group's insistence (at times; see below) on the use of only trained subjects, Gross *et al.* (265) found that medical students were "particularly reliable in these studies (using the Hardy, Wolff, Goodell technique in man) because of their great interest in the drug effects." These students were trained only "about 10 days until they could consistently recognize the normal end point." Leaving out early inconsistencies such as the statement (668) that "this threshold pain was easily recognized even by untrained subjects," and passing on to more recent work, carried out in the same period as the studies just referred to above, 1948 to 1950, one finds that medical students are satisfactory (287): "The second group of experiments, done by medical students under supervision, indicates the scatter of reports from untrained but intelligent subjects and observers. In general, the average of the reports of the intensity of pain evoked by each unknown stimulus was within one dol of the value determined by the method of just noticeable differences and the scatter of reports was approximately the same as that obtained with experienced observers." In this same paper, they say further, "The accuracy of estimation does not depend upon the subject's experience with the method. . . ." And a little later, "Experience in reporting pain intensities did not increase the accuracy of the estimation." They have also said in another paper (286) when the three authors were the only subjects, that they, ". . . were agreed that this experiment (pain intensity judgments, dol scale work) required much more in the way of concentration and attention than did measurements of pain thresholds . . ." yet they say students gave data "approximately the same as that obtained with experienced observers." Yet again they have said (288) that students are not satisfactory even for the simpler pain threshold measurement described above.

The confusion is compounded further. While Hardy, Wolff and Goodell have often rejected the work of others when it failed to agree with theirs, on the basis that they used trained subjects and the others did not, Potelunas *et al.* (493) working in the same period, studied the pain threshold in a group of 65 patients with dermatological lesions. They say, "In these experiments the patients received no prior instruction regarding the test (Hardy, Wolff and Goodell radiant heat method) . . ." A series of heat stimuli were administered and they state, "In most cases there was no difficulty in recognizing this change in the sensation (*i.e.*, the end point)." How can one accept work in the clinic with these untrained, certainly often unintelligent patients, when they have sometimes denied, as shown above, that much more promising untrained subjects can be used? Again and again they have used untrained subjects in the clinic and then subsequently referred to these data as dependable. They have even used women in labor (352), at the same time maintaining that untrained subjects were not dependable.

Furer and Hardy (227) [Furer in the discussion] say: ". . . patients, after very few contacts with the procedure have little difficulty identifying the dol stimuli." This does not agree with the comments of Haugen and Livingston (300) who say that even after many months of trying they ran into difficulties when they tried to formulate an accurate concept of the 'dol' scale. Their judgment was still so seriously at fault they did not consider that the method has value in the clinic. There are plainly many problems in the field under discussion.

15. Training (animals). Some have insisted (96,591) that it is necessary to train rats before they are used for pain threshold determinations. However, in very careful studies on animals, Winder (647, 648, 649, 651) successfully used untrained guinea pigs in such a way that each animal served as its own control. Miller (451), in line with the general experience of many investigators, also found he could get satisfactory information from untrained rats and suggested that more intelligence on the part of the operators required less of the animals.

To sum up the matter of training: It is evident that training in man has certain advantages which are quickly achieved (by the second or third day) and that drug experience introduces the very great hazard of loss of the "unknowns" requirement. This coupled with an interest in the outcome can be ruinous. The extensive experience of many investigators demonstrates that training of animals to discriminate the threshold value is not necessary.

16. Bias. It is generally agreed by investigators in this field that the double unknowns technique must be employed. But what has not yet been sufficiently recognized is the fact, pointed out by Beecher (50), that drug-wise, sophisticated subjects cannot be kept in ignorance of whether a powerful narcotic has been used in distinction to a placebo. Such knowledge coupled with a vested interest in the result can be devastating, as already mentioned in conjunction with training. Bias almost certainly plays a large part in the great elevation of pain threshold at one time so easily "demonstrated" by the use of powerful analgesic agents (see XI). The double unknowns technique includes the operator as well as the subject. When Denton and Beecher (159) first began their work with the radiant heat method they had no doubt of its usefulness in man to appraise the effects through pain threshold elevation by powerful analgesic agents. They were quite unable to reproduce the then generally obtained threshold rise with morphine. The double unknowns technique was used. The different result obtained by an "informed" investigator was described in X, 14.

Bias is always a problem to rule out. The best solution appears to be to use, for a short time, subjects who have no knowledge of drugs and who have no interest in, or knowledge of, the outcome of the experiments, and to turn to fresh subjects before the old ones become drug-wise. The investigator is obliged to pick his way, if he can, between an experimental procedure which may give rise to anxiety in the new subject and thus modify the results obtained, and the hazards referred to which are associated with breadth of experience. It is also possible that breadth of experience may add new and subtly conditioned reaction components.

17. Adaptation. Adaptation to pain has been studied experimentally for half a century. It seems clear that under certain well defined circumstances adaptation to pain does occur and it can occur quickly, that is, soon enough to raise a question as to whether it may not influence pain threshold determinations. No systematic studies with the purpose of settling this question have been carried out; they should be. On the other hand there is some indication (141, 142) that when repeated threshold determinations are made in the same body area at one sitting, the second threshold is somewhat lower than the first. Possibly this is to be accounted for by primary hyperesthesia (see I).

The cutaneous pain aroused by a needle leads to adaptation (115) provided the stimulus is of unvarying intensity. Adaptation progresses from maximal pain to pressure to indifference. The authors point out that reports of adaptation to pain had been previously presented by several others (577). (See especially the references given (115) to the work of von Frey, Murray, Goldscheider.) In the present work (115) it is interesting to observe that adaptation occurred in the usual period of time required for pain threshold studies, although there was great spread in this, for one set of observations from 6 to 780 sec, for another from 4 to 160 sec, for a third from 5 to 110 sec. The average adaptation times for three subjects were 34.7 sec for 2.5 g stimulus weight, 56.1 sec for 5.0 g and 86.6 sec for 7.5 g.

Straus and Uhlman (577) quote Murray as saying that superficial pain adapts out almost as readily as does superficial contact. They have attacked the question of conditions necessary for pain adaptation and time necessary for adaptation to various intensities of pain. Pain spots were localized on the volar surface of the shaven forearm and needle pricks were used to produce pain. They were regularly able to demonstrate adaptation to pain. For a 3 g-stimulus adaptation occurred in one subject in 5 sec; for another subject in 11.9 sec, for a 5.5 g-stimulus adaptation occurred in 14 sec for one subject and in 26.3 sec for another; for an 8 g-stimulus adaptation occurred in 19 sec for one subject and for another in 44.1 sec. These times are such, especially for the weaker stimuli, as to suggest possible interference with pain threshold determination under conditions at all comparable to those of this experiment.

The data are too few and too varied to permit any conclusion that intensity of the stimulus conditions adaptation; but this is a possibility worthy of study. Adaptation to radiant heat pain was demonstrated (572) in about 2 minutes, sometimes less.

Pain mechanically produced gives way to a feeling of pressure (195), pain produced by radiant heat gives way to a feeling of warmth and pain produced by cold usually gives way to a feeling of cold. One wonders if the last case may not simply be an example of cold anesthesia. It is concluded that pain is adaptable. Adaptation after arousal of pain occurred in 3 to 5 minutes (195).

Adaptation in general and to pain is discussed by others (98, 321, 574). Using needle pricks several investigators (115, 573, 625) found "complete pain adaptation" in 80 to 100 % of the trials. All agree that there is a "tremendously variable" adaptation time both in data from a single individual and in group data. Others

(195, 572) found adaptation to thermal pain appearing in almost all cases. "Within the range of stimulus intensities used adaptation of the pain threshold is a function of both the size of the original threshold and of the intensity of stimulation to which the subject has been exposed" (582). Probably this holds for various kinds of stimulation and all experimental pain methods. Others (673) claim that no true adaptation to pain occurs as it does to touch.

When the necessary systematic study is made of this matter it will be important to study the question of whether disappearance of anxiety (see the above section concerning this subject) on repetition of the painful stimuli, may not account for the disappearance of pain, or, to state it in another way, the appearance of adaptation.

18. Distraction, inattention, lethargy. Gripping a bar as tightly as possible raised the radiant heat pain threshold in one subject 7% and in another 15%. An extremely loud noise behind them produced a rise of 14 and 32%, respectively, in 2 subjects (284, 285). Distraction, inattention, lack of concentration are referred to by others as factors which may cause variation in the radiant heat pain threshold (19, 142, 200, 373) and in the ischaemic muscle pain threshold (296).

Lethargy increases the suggestibility of subjects (665). Thus drugs which produce lethargy may result in elevation of the pain threshold in two ways: increased suggestibility and lack of attention. Here are other factors to control in threshold determination as altered by drugs, for most analgesics, at least of the narcotic type, increase lethargy. Perhaps it is this which is being measured, rather than pain relieving power.

19. Judgment impaired by drugs. Not only analgesics, but other agents as well, have effects on the mind which lead to difficult decision (19, 257, 258, 320). Drug effects make recognition of the pain threshold difficult (591). It has been observed that the degree of psychic effect produced by morphine coincides with the elevation of threshold (289), with the psychic effects persisting longer than the analgesic effects. Thus the drugs studied may make it difficult to determine end points.

It was reported (560), following a study of nitrous oxide analgesia (electric shocks to tooth pulp method), that this form of analgesia is associated with impairment of psychomotor performance; and it was concluded that analgesia is probably a manifestation of general depression of the central nervous system. The generality of this conclusion may be questioned in the light of findings concerning dihydrocodeine, which can be used at a dosage with considerable analgesic power yet with few side effects (262).

20. Suggestion and emotion. The opiates, alcohol and ether are said to increase suggestibility (257, 258, 320). With subjects under such drug effects, it is possible that suggestion carried by the knowing operator's voice, tone and inflection, may have produced threshold elevation especially in the highly drug-experienced group. Suggestibility apparently is a learning process. At any rate, this possibility is a strong argument for the double unknowns technique. The effects of hypnotism (for detailed discussion see XII) have been studied (630)

on pain perception and galvanic skin response. Past studies have dealt with physiologic studies of galvanic skin response (see VII, 4), heart rate, facial flinch, respiration and vasomotor reactions. Using the radiant heat technique, it was found (665) that light hypnosis and suggestion of anesthesia raised the pain threshold 40%. Wishing to separate pain perception and pain reaction, these investigators used the galvanic skin response as an objective indicator of pain reaction. West *et al.* (630) follow Landis in believing that the galvanic skin response consists of 1) decreased apparent resistance of the skin under the control of the autonomic nervous system, following sensory or mental stimulation, and 2) increased afferent electromotive force of the skin. Fusion of these effects into a single response can be photographically recorded. Evidence has been found that the galvanic skin response is an indicator of the "threat content" of a painful stimulus (227). This led to a study of the same technique with hypnotic anesthesia. The galvanic skin response was decreased by 20% by hypnotic suggestion in the "anesthetized" limb as compared with the normal (532). It was found too that hypnotic anesthesia reduced greatly pulse rate variation and nearly eliminated the facial flinch and response of the respiration to pain (532). This was confirmed; little effect on the galvanic skin response was found (179). Brown and Vogel (106) raised an opposing voice. They did not find that the hypnotic state eliminated physiological responses to sensory stimuli, but did report that suggestions of hypersensitivity greatly increased these reactions. Others (169) found, however, that suggestions of anesthesia led through hypnotism to a decrease in vasomotor responses to pain. Following a consideration of this background, West *et al.* (630) added the considerable advantages of using several stages of hypnotism plus quantified stimuli (radiant heat) rather than pin prick, with measurement of changes in the radiant heat pain thresholds and finally they obtained quantitative records of the galvanic skin responses in both control and hypnotized states.

In the majority of cases definite elevation of pain threshold was found as a consequence of hypnotic suggestion of anesthesia (630). The effect of hypnotic suggestion was much greater in deep than in light trance. Their results show unquestionably that hypnotic suggestion reduces the galvanic skin response to painful stimuli. "Attitude and suggestion may modify both the pain threshold and the manner of reaction to pain" (665). It may be asked, believing this, how can the Hardy, Wolff and Goodell group insist on the wide constancy of the pain threshold? It seems probable that, when pain threshold is altered in these ways, an element of the reaction component is present; that is, it is not possible to obtain pure thresholds. It is difficult to see how they can cling to their concept of the pain threshold as pure perception. Clearly the threshold is modified and modifiable by many things.

It has been shown that the attitudes of the subject and of the operator are very important: "doubts, lack of confidence, relative alertness or carelessness, and increased suggestibility with lethargy were seen to be relevant" (665). Wikler (641) has discussed the importance of the operator's attitude. See X, 16 for a relevant experience of Denton and Beecher (159).

Wolff and Goodell (665) have recognized the effectiveness of suggestion in altering pain thresholds but did not, in their original report, adequately take this into account where they reported that acetylsalicylic acid raised the pain threshold. Others (558) have restudied the problem using both radiant heat stimuli and electric shocks to teeth in man. This work was carried out at 9:00 a.m. or 3:30 p.m. and ignored the possible effects of a diurnal change in pain threshold which has been reported (see X, 24). When body temperature changes, it seems likely that changes in circulation in the skin would occur diurnally and possibly affect pain threshold. (See X, 6 for evidence that skin temperature affects pain threshold.) In the study just mentioned, the investigators (558) used the inaccurate *voltage* as their parameter of stimulation. They ignored an essential control in that the observer knew the nature of the agent used.

The Hardy, Wolff, Goodell method is most vulnerable (451) because of the great effects emotional and psychological influences can have on the pain threshold. Wolff and others (142) have emphasized this. The importance of emotion and suggestibility has been recognized by still others (296). When the experimental pain intensity (radiant heat) exceeds the pain threshold there is a swift increase in the emotional content of the situation (22). One might suppose this would influence pain threshold determination to a widely variable degree.

Isbell and Frank (see 636) observed that, when a crucial emotional state was produced by a search of postnarcotic addicts for concealed narcotics, morphine failed during this emotional state to elevate the pain threshold; elevation was usually found when the subjects were not emotionally disturbed.

Sensitiveness to pain is diminished during crying (417). This agrees with the observations of many, including the reviewer, that emotion can block pain. Libman speaks of sensitizing or desensitizing factors. Some emotional factors which alter pain sensitivity are: Worry, fear, anger, sorrow, fatigue, diversion of attention and joy.

Lanier (394) found that about half of his subjects were stable and gave reasonably constant thresholds. Possibly threshold studies had better be limited to such subjects. However, it would then be difficult to assess the meaning of the data.

21. Warmth and cold. (See also X, 6). Cold rooms and strong drafts will affect radiant heat pain thresholds (214, 285, 651). With warmth sensation there is summation (284, 285), that is, the bigger the area stimulated the lower is the threshold, but with pain, increase of the area stimulated does not lower the pain threshold. It has been concluded that spatial summation operates in the case of warmth but not pain. This has two important meanings: 1) it indicates that pain and temperature senses are different and 2) intensity of pain is dependent on intensity of stimulus and not on area stimulated. This does not, so it is thought (284, 285), contradict the common observation that the greater the area traumatized, the greater the suffering.

22. Multiple stimuli and extinction phenomena. Hardy *et al.* (284) reported that intense pain in any part of the body (tourniquet pain) raised the pain threshold of the skin as much as 35%. This has been confirmed: Brief ischaemic

muscle pain was found "invariably" to produce a long lasting elevation of tooth pain thresholds, whereas acetylsalicylic acid had no such effect (479). In other experiments, acetylsalicylic acid, when its administration preceded the induction of ischaemic muscle pain, prevented the elevation of tooth pain thresholds otherwise produced by the ischaemic muscle pain. It is not stated whether the acetylsalicylic acid might have interfered with the development of the induced (ischaemic muscle) pain. If the above findings are valid, they help to explain how counterirritation relieves pain. Others (142, 176, 296) also report that pain elsewhere will influence pain threshold determination.

It has been reported (289) that pain produced in various ways (ischaemic muscle, or immersion of hands or feet in ice water, distention of a duodenal balloon, compression of the trapezius muscles by clamps) altered the degree and duration of the action of morphine: the longer the interval between the administration of the morphine and the induced pain, the less effect the induced pain had on the threshold-raising effect of the morphine; but, if pain was induced near the time of morphine injection, the threshold-raising effect of the morphine was greatly reduced. This observation has been confirmed (348).

Gammon and Starr (233) produced pain in themselves by the subcutaneous injection of 10% sodium chloride and by the application of irritant ointments. Various forms of counterirritation (heat, cold, electric current, vibration, tactile stimulation) produced relief. They then isolated sensory nerves of cats and found nerve impulse phenomena (in response to the kinds of stimulation they had used in themselves) which were analogous to the changes in sensation experienced by themselves in some cases. Radiant heat greatly increased the pain produced in themselves by capsicum ointment; nerve impulse frequency in a similar experiment was greatly increased in the cats nerves by heat. Cold decreased this pain in the man and in the cats reduced the nerve activity. Counterirritation appears to produce pain relief in some cases, but not in all, by peripheral effects. The authors summarize the evidence for a central nervous system component and explain why they believe *cessation* of counterirritation is under some circumstances effective in relieving pain.

Parsons and Goetzl (478) produced pain in 11 subjects by spraying ethyl chloride over the tibiae for 20 seconds. This pain lasted for 2 to 3 minutes at most, yet they report "analgesic effects," *i.e.*, elevation of pain threshold (electric shocks to teeth), lasted for 90 to 120 minutes! They claim that the induced pain elevated the pain threshold, *i.e.*, produced analgesic effects in all instances, yet in another study (348) by the same group 16 mg morphine raised the pain threshold in only about half the instances. One could "reasonably" draw the erroneous conclusion from this technique that counterirritation was far more effective in relieving pain than a large dose of morphine. That this is demonstrably not so, does not deter the authors in the least. It seems not to occur to them that such observations cast real doubt on the validity of their method.

Hazouri and Mueller (301), in a study of 3 paraplegic patients with intractable pain, found that their pain threshold was elevated over that of 100 paraplegic patients who did not have a pain problem (for the 100 patients, this was

230 ± 10 mcal/sec/cm²). When the intractable pain was relieved by surgical procedure the thresholds for pain perception returned to normal. This agrees with Hardy, Wolff and Goodell's observations (284) that pain in one part of the body elevates the pain threshold in another part. Hazouri and Mueller used increase of 10 per minute in pulse rate in response to radiant heat as the "reaction" threshold.

Bender *et al.* (63, *et ante*) have presented work on perception of touch and pin prick on simultaneous stimulation of face and hand. The failure of the subject to report one of two simultaneous stimuli is called the "phenomenon of sensory extinction" or "extinction." The part of the body where the phenomenon was perceived is said to be "dominant." The pattern of face dominance and hand extinction was typical. No explanation for the phenomenon was offered. One can speculate that it may be related to other types of extinction phenomena: the injured man whose attention was first directed to his painless wound by the warmth of the blood on his skin; the absence of pain in a wound received in the presence of strong emotion; the elimination of pain by the elimination of anxiety (57, 316, 318, 319, 439, 440). Or, to turn to another situation, the extinction of hearing when the attention is otherwise engaged as in reading something of great interest. Or the relief of pain by counterirritation.

The extinction phenomena may be relevant to the studies where experimental pain is produced in 2 areas, radiant heat to forehead or arm and perineal pain of childbirth (see 281), or tourniquet and graters to arm and heat to forehead.

The evidence that pain in one part of the body will raise the pain threshold in another area is additional evidence for the importance of the central processing of pain phenomena and evidence for the subservient position of pain perception to the central processing phenomenon (reaction). The same holds for the inhibition of pain by sexual stimulation and for the inhibition of pain by other skin senses as well as for inhibition of pain by the cortex (emotion).

The effect on a given pain threshold of multiple sites of simultaneous stimulation has as indicated received some attention but as yet not as much as might well be rewarding. A second stimulus, whether pain, sound or kinesthetic stimulation produced a decrease in the intensity of the original pain (176). On the other hand it was reported that a subthreshold stimulation became pain when the stimulus was increased by electrical stimulation applied to 2 fingers (299) instead of one.

23. Placebos. ". . . a subject who knows he has been given an analgesic will demonstrate more pain threshold-elevating effects of the agent than does the subject who, receiving the same agent, is convinced that he has not received an analgesic" (289). The fair question can be raised as to how the Hardy group can, believing this, continue to use 3 drug-wise subjects from whom the use of a narcotic cannot be hidden. They have agreed that placebos are important. As a matter of fact they learned early, 1943, in their studies of pain (665) that placebos could on occasion produce as much elevation of pain threshold as the analgesic agents they were studying. This of itself would appear to be strong evidence that they were not dealing with a pure perception but rather one

contaminated with reaction component (see XII). The puzzling thing is why they did not ever after employ this essential placebo control. Others have questioned the use of the radiant heat method in man for threshold variations which lie within the range of effects produced by placebos or suggestion (200). There is no reason why this observation should be limited to the radiant heat method. It applies to all methods. Beecher has shown how effective the placebo can be in relieving many kinds of symptoms (53), with 35.2 ± 2.2% of patients relieved.

It is of interest and it should be sobering to observe (292) that, when given orally, placebos, acetylsalicylic acid and a mixture of the latter with phenacetin and codeine all significantly elevate the threshold, but *there are no significant differences among their effects.*

Sonnenschein and Ivy (558), while not finding any significant change in pain threshold after administration of acetylsalicylic acid, did find a significant change in threshold (elevation) produced by a placebo. (The acetylsalicylic acid threshold change was corrected for the placebo effect.) They believe that the positive findings of others (284) are, possibly, to be explained by their lack of placebo controls.

Flodmark and Wramner (216) employed a placebo in 4 subjects but, since this produced a maximal deviation of only ±0.1%, it was considered within the normal variation of the method. This is hardly an acceptable control, for it is quite possible that the 4 were placebo "resistors", whereas in the 19 subjects on which the work depends a considerable number would certainly have been placebo reactors (398). If the placebo effect is as small as Flodmark and Wramner believe, this is evidence (a) that the experimental pain situation is unlike the pathological one or (b) that the subjects were guided, notwithstanding the use of the "unknowns to subject technique," by the lack of the narcotic aura, or through unconscious guidance by the operators who were aware that a placebo had been used. In any case, compare their results with the opposite obtained by Hardy and Wolff. Hewer and Keele (313) got "consistently negative" results with placebos (ischaemic muscle pain) as unknowns to the subject but apparently not to the observer.

In their work on experimentally produced anxiety and pain Hill *et al.* (318, 319) found that placebos had no such effects as morphine in these studies, but it must be remembered that their subjects were post-drug addicts and it may not have been possible to use placebos in them as successfully as in non-addicts, *i.e.*, as in unsophisticated subjects, since, presumably the post-addicts could detect the morphine "aura" as opposed to the placebo. Work in rats (66) showed that a placebo increased the reaction time to radiant heat "pain" 36%.

24. Diurnal variation. While Martin and Grabfield and Martin (259) using a faradic current as stimulus report a diurnal variation in pain threshold, Macht and associates (435) using a similar method could not confirm this, nor could Hardy *et al.* (284) using radiant heat.

Grabfield and Martin (259) restudied the sensory threshold to faradic stimulation with a view to determining what factors cause it to vary. They confirmed

a diurnal variation. Peak of irritability occurred at 10 to 11 o'clock in the morning, with another rise beginning in the late afternoon. They point out that their findings agree closely with the observations on "ergographic" output and in general with reaction time observations of others. The authors conclude from these parallel findings that diurnal variation is central rather than peripheral and that the sensory threshold is "a reliable index to the general nervous condition of the subject." These findings suggest another possible source of error in experimental pain studies.

Some evidence for a diurnal variation of pain threshold was found (131) in a group of subjects tested at 9:00 a.m. or at 5:00 p.m. In most cases the morning values were near the subjects' upper limit and in the afternoon near the lower limit.

A consistent curve of diurnal variation in pain sensitivity with electric shocks to teeth has been reported (354).

25. The passage of time. The pain threshold on electrical stimulation of a tooth tends to rise over a period of months (116). But as time passed during a given session of experimentation, the pain threshold fell slightly.

With the radiant heat stimulus in guinea pigs utilized over a 4-hour experimental period, it was found (651) that a significant downward drift in threshold occurred. This amounted to about a 10% change. Eddy and associates (194) have found a similar effect in mice exposed to conducted heat. The investigators point out the importance of using each animal as his own control rather than the more variable "absolute" levels. Such use of correlated data in man has been found by the Beecher group and the Houde group to be indispensable if modest numbers are to be worked with satisfactorily.

A slow rise of the radiant heat pain threshold was found (571) over a period of weeks. It amounted to about 15% rise in 5 weeks. The rise was slow enough not to interfere with acute studies, but indicated the importance of subjecting all individuals studied to the same experience. This is a further necessary control. It is also important to control the time interval between exposures to the radiant heat stimulus, if variation in the pain threshold is to be kept at a minimal level (142).

With the passage of time and continued testing, it was found (300) that "something progressively deteriorated, with the accuracy of (the subjects') judgment or the condition of the testing area of skin or both," and obvious error appeared in the data.

A curious periodicity in tolerance to morphine (analgesic effect) over a 50-day period of morphine administration has been reported (246). The investigators believe that their data "unequivocally demonstrate" the development of chronic tolerance to morphine in the dog as judged by tooth pain. They have confirmed observations (588) that complete tolerance to depression and drowsiness does not occur on the administration of 3 mg morphine sulfate per kg body weight in dogs over a long period.

26. Miscellaneous factors. Severe acidosis, severe alkalosis, or 24-hour fasting had no effect on pain threshold or reaction (131). A head cold or constipation

can disturb pain threshold determinations (214), so also can the wetness or the blackening of the skin exposed to radiant heat stimuli (142, 216, 289). The phenomenon of double pain responses (fast and slow, see 236) to stimulation perhaps complicates the end point determinations in all experimental pain studies. It might be supposed that this would be particularly great with the radiant heat techniques, especially for untrained or partially trained observers. Variations in conducted heat, area of body stimulated, reporting method, educational level may all produce differences (142, 216) in pain threshold determinations.

27. Lowered pain threshold. No chemical agent introduced into the circulation has been reported to lower the pain threshold, except as indicated below; however, in unpublished work, Eddy (189a) has observed repeatedly, with conducted heat in mice, "a greater than anticipated downward trend of reaction time after drugging especially when the agent appears to produce general hyperirritability." With the exception of injured or inflamed skin (289, 527) the only instances of lowered pain threshold to radiant heat were in hysterical or anxious patients (surely the reaction component had intruded into these threshold measurements) and in malingerers (285).

An increased sensitivity, that is, a lowered threshold to painful stimuli has been reported (465, 466, 534) after the primary action of opiates has worn off. Lowering of the pain threshold has been reported to follow noxious stimulation of a tooth (507).

Various reports of relief of somatic pain of organic origin after bilateral and unilateral frontal lobotomy have been referred to (376). Six patients had unilateral frontal lobotomy performed for the relief of pain, all but one were successful. Of the 5 improved patients the thermal pain thresholds were lowered bilaterally in 4, and in the fifth, lowering occurred on the same side as the lobotomy and elevation on the other side. The patient not relieved by the lobotomy was the only one showing bilateral elevation of the cutaneous pain thresholds after operation. The point of interest is the tendency of the peripheral pain threshold to be slightly lowered, not elevated, in patients undergoing frontal lobotomy for pain. If this difference can be shown to be significant, the point is important. The effect of lobotomy on pain is perhaps due to its effect in relieving anxiety.

It has been reported (620) that morphologically abnormal nerve endings in the skin are associated with a decrease in pain threshold. Trotter (599) and Trotter and Davies (600) believe that changes in the physicochemical state of the endings might produce a similar result. Using a radiant heat stimulus it has not been possible (666) to show any significant lowering of the pain threshold in hyperalgesic areas of skin associated with deep pain.

XI. PAIN THRESHOLD AND ANALGESIC AGENTS

A. General

An adequate working definition of an analgesic agent is the following: an agent which brings about relief of pain without significantly dulling conscious-

ness. It is customary to exclude agents which act by removing the cause of the pain and agents which block pain impulses peripherally. This definition, unlike the definition of pain itself, is fairly satisfactory.

The question of whether or not the pain threshold is elevated *in man* by narcotics is of importance. If it is, then narcotics may indeed influence peripheral pain mechanisms to a great extent, and C-fiber studies, with and without morphine are indicated. However, there is no direct evidence that morphine affects conduction in peripheral nerves. If the pain threshold is not dependably elevated by analgesics, then this can be construed as very strong evidence that analgesic drugs do not act to an important degree on the peripheral pain apparatus, but act centrally, presumably on the reaction component. In other words, a pain threshold unchanged by narcotic agents means that pain is getting through to the central nervous system. That is to say, there is no particular need to study the effect of a painful stimulus on C-fiber activity with and without morphine.

Evidence has been obtained by Wikler (634, 635) that analgesics acted on spinal reflexes associated with after-discharge, that is, presumably, on multineurone reflex arcs. Such action appears to be a minor part, if any, of the essential pain-relieving consequences of the use of such agents. He also showed (640) that the lip-twitch response of the dog to electrical stimulation of a tooth-pulp nerve is depressed by subcortical action of analgesic agents. Along this same line it has been shown (331) that the tail flick of rats and the back skin-twitch of dogs can be depressed by analgesic agents in spinal animals. Irwin *et al.* (344) and Houde and Wikler (336) obtained evidence that morphine augments supra-spinal inhibition of these reflexes, also an action that must be central. If such effects were of much importance with the doses of analgesic agents known to be clinically effective in relieving pain in man, it might be supposed that this could be made evident in the effects of analgesics on the pain threshold. While the evidence on this score is conflicting, no such clear-cut and dependable demonstration has been made in man.

What might be called the opposite side of this problem is also interesting (for details see XII). In conjunction with the question of whether the peripheral pain apparatus can still function yet pain be not perceived, several observations can be made. Emotion or distraction can block the perception of pain; this is common knowledge. Both in hypnotic suggestion and in hysterical anesthesia, pain is not felt in response to noxious stimulation, yet the pain apparatus is anatomically unimpaired. It has been shown in four patients with hysterical anesthesia (580) that although these individuals presented a hysterically anesthetized limb they none-the-less showed a cold pressor response like that of the normal limb, yet denied subjective sensations of cold. Hysterical anesthesia thus does not block sensory stimuli at low segmental levels.

The assumption of most investigators in this area has been that the pain threshold is dependably elevated by analgesic agents. The majority seem never to have had any doubts as to the validity of this view, notwithstanding the

formidable array of inconclusive and contrary data. In this field a number of investigators who may have had some doubts appear to have had an irresistilbe temptation to reassure themselves by analogy and then to proceed incautiously from that shaky base. Parallels are drawn (451) among analgesics on one hand and antispasmodics or antihistaminics on the other hand, for example. It is hazardous to make comparisons between agents designed to alter subjective response and those planned to produce objective change. The danger lies in the unproved assumption that the "pain threshold" change produced in man by analgesics has much if anything to do with pain relief, whereas the antispasmodics in relieving smooth muscle spasm have accomplished their mission and are beyond dispute effective in so doing. It will be seen that the strongest evidence *in man* is against any important relationship between "pain threshold" change and pain relief. Most of the evidence also indicates that pain relief has a close connection with the effect of analgesic agents on the reaction component. (See XII.)

It has been stated (284, 364) that morphine relieves pain in 3 ways: (a) by elevating the pain threshold, (b) by influence on the reaction to the original sensation (apprehension allayed), producing a sort of "reversible pharmacological leukotomy," similar in consequence to a surgical leukotomy (357), (c) by inducing lethargy and sleep.

Dependable work in animals has led to the uncritical assumption that this establishes a general clinical relationship between the action of analgesic agents and pain threshold elevation, notwithstanding the fact, already pointed out, that "pain threshold" in the different species, man and animals, are very different things based on unlike criteria.

There seems to be no easy and well marked path here. The fact that one can on occasion, despite the many factors which can cause the pain threshold to vary (see X), find some human subjects who do appear to show a dependable relationship of analgesic action to pain threshold elevation then poses the question as to what such a painfully arrived at small sample really represents.

B. The production of analgesia

A characteristic of a sense organ with such endings as are found in pain spots is that even a single brief stimulus has a persistent "after-effect"; *i.e.*, a single shock to the nerve ending sets up in the fiber a repetitive series of nerve impulses. This is unlike the situation with a nerve fiber where a single shock sets up a single impulse (5, 76, 77, 80).

It may be supposed that the perception of "original sensation" requires the function of several structures: (a) the specific pain receptors, (b) the conducting pathways, the nerve fibers, (c) intervening synapses, all the way up the central nervous system until awareness of sensation is achieved. No systematically administered analgesic agent is known which will abolish function in the pain receptors or the conducting nerve fibers; therefore, if "original sensation" is to be depressed by analgesic agents, presumably it must be done by action on

synapses. These are known to be vulnerable to a number of agents, but there is no evidence that customary doses of analgesics used in man systematically administered can influence them (86, 218).

Wikler's (634, 635) observations on the effects of morphine on the reflexes of spinal animals where reflexes associated with after-discharge were depressed by morphine but reflexes not associated with after-discharge or with little after-discharge were either not depressed or were actually heightened—all of this indicates that morphine can work at a cord level and on multineurone reflexes, presumably on synapses.

Batterman and Himmelsbach (31) believe that clinical analgesia is probably the result of one or more of the following effects: 1) interruption or reduction of afferent pain sensations in the midbrain or the thalamic area, 2) altered reaction component (reduction of the "fear reaction"), 3) increased threshold to pain at the periphery. This last one appears to be of "minor importance" as far as analgesia is concerned. Somewhat paradoxically these writers then also say that (3) above is of "immense help" in evaluating the relative potency of analgesics. Just how threshold effects can be at the same time of "minor importance" as far as analgesia is concerned, yet of "immense help" in evaluating analgesic potency is a mystery not explained.

Andrews (22) believes that simultaneous measurements of skin resistance and pain threshold are of value in differentiating some aspects of drug action. The action of morphine on that part of the autonomic nervous system which controls skin resistance appears to be comparable in normal subjects and post-addict subjects. Morphine reduces the skin response in both. He concludes from this that "The reduced skin resistance response is probably associated with a reduced pain appreciation, which offers an explanation of the clinical relief of pain in the post-addict," for he had reported earlier (21) that although normal subjects and post-addicts had comparable pre-drug pain thresholds, morphine had little pain threshold raising effect in post-addicts in comparison with normal subjects, yet the clinical relief of pain is accomplished in post-addicts with modest doses of morphine. He draws the interesting conclusion that measurements of pain threshold have little connection with the clinical relief of pain.

The same conclusion has been arrived at by others who have expressed the view that pain threshold elevation by pain-relieving agents is probably of only minor importance in regard to analgesic effectiveness (30). Batterman says that Wolff and his associates have emphasized this too. The "emphasis" comes out more strongly in their 1952 book (289). Surely this is somewhat paradoxical, for Hardy, Wolff and Goodell maintain that with their method they measure "original sensation" divorced from "reaction." They report great elevation of this pain threshold by analgesics yet believe that elevations of pain threshold are only one of the possible modes of action of analgesics and according to Andrews (21, 22) and Batterman (30) a minor one.

The finding just reported (22) that modest doses of morphine will relieve clinical pain in post-addicts, yet not produce, presumably the accustomed psychic effects sought after by addicts is considered to be evidence that morphine

does have action at the "lower integrating levels" (30). It may, but then it is not clear how Batterman can hold this view and yet, at the same time, conclude, as he did, that threshold-raising effects are probably of minor importance. Evidently he distinguishes between processes at "lower integrating levels" and threshold processes. There does not appear to be much evidence for such a distinction. It seems sounder, on the available evidence, to conclude that there is little, if any, relationship between analgesic action and threshold effects.

Cattell has said (124) "The rise in (pain) threshold which may accompany analgesia must be looked upon as incidental to the changes in mental function, with awareness of pain not necessarily altered." Others of the Cornell group have often insisted that the pain threshold findings are a measure of the original sensation, not complicated by the reaction component. Cattell (124) continues, "The available evidence points to changes in mentation and mood as the important elements in the analgesic action of drugs and we must regard pain threshold data as measurements of psychic reactions." Cattell's view evidently differs from that of his associates. He also repeats the thesis that the more the mental effects of analgesics the more their pain-relieving power. This does not appear to hold with dihydrocodeine, for it has been shown (262) that this analgesic agent, although less effective in a 30 mg dose than morphine in a 10 mg dose, has at that dose hardly any mental effects.

Also relevant to this section are the findings that fear and anxiety are related to the appearance of pain (see X, 13) and that their relief by morphine is related to the relief of pain (57, 316, 318, 319, 384, 439–445).

C. Evidence for a dependable relationship between analgesic action and experimental pain threshold in man

The investigators (notably 20, 116, 216, 219, 277, 435, 465, 466, 534, 666–669) have utilized three principal methods of producing experimental pain: radiant heat, electric shock, and the von Frey method of mechanical stimulation or a modification of it. Impressive as the number of studies is, on examination many of these studies are not so reliable as they seemed at first. (For a critical examination of experimental pain methods and analgesic agents with special attention to the radiant heat technique, see 197, 318, 319, 451.) In general the difficulties are as follows.

The design of the experiments has not been such as to permit the elimination of bias. For example, Hardy, Wolff and Goodell have used themselves as subjects for most of their significant drug studies. While they now accept the importance of using unknowns, this is of course quite impossible when the subjects are highly experienced and familiar with the effects of narcotics (50).

Although Wolff and Goodell (665), as mentioned above, showed early in their work on narcotics and pain which has been so often followed, that suggestion could have very great effects and that placebos could have as much effect as analgesic agents, neither they nor their followers have usually adequately safeguarded their work from the possible effects of suggestion, nor has it been customary to subtract placebo effects before concluding that a significant drug

result remained. While reliance on statistical methods to the exclusion of common sense is certainly undesirable, too few of these investigators have acted on the sure knowledge that common sense can in many cases be preserved only with some recourse to statistical methods. Miller (451) points out in conjunction with this same work—data were furnished to him by Goodell and Wolff—that while the standard deviation of a single observation is only about 5% of the average this is large in comparison with the threshold changes that may be produced by drugs.

Others have frankly eliminated subjects or data which did not come out as expected, that is, showing an elevation of pain threshold in response to the administration of powerful narcotics. Seevers and Pfeiffer (534) eliminated some subjects who showed a low pain threshold since they did not usually show an elevation with the use of the opiates. Lee (403) reported the same thing. Miller (451, p. 43) discusses the question of whether a low normal threshold signifies that the subject will have a low threshold after the medication. His finding was in the negative and this means that percentage increase of threshold is not an accurate measure of analgesia. Gaensler (229) reported that narcotic relief of pain (pain caused by increase in hydrostatic pressure in the biliary tree) was greater when the initial pain threshold was low than it was when the pain threshold was initially high. That is, narcotics are comparatively more effective when the area traumatized is sensitive (painful), when the pain is great, than when it is less. This fits in with Beecher's (55) observation that placebos are more effective when the pain is severe than when the pain is less severe, and, furthermore, supports the concept that analgesics effectively act on the reaction component of suffering (XII, C). Gaensler (229, p. 414) pointed out that it was never possible to abolish the pain of distention of the biliary tree however large the dose of morphine. He showed striking differences in pain threshold elevation by both morphine and meperidine. If the subject had not been alerted ahead of time the elevation was twice what it otherwise was. One would have supposed that the first painful stimulus would have produced a sufficient awakening to give comparable curves from then on, but this was not so. Before narcotics were administered the thresholds were identical whether "asleep" or awake, but not after. Perhaps one can conclude that the narcotics really alter pain perception very little but do produce a bemused state, comparable to distraction, which they can be "alerted out of" and will then report on the little altered pain perception (*cf.* lobotomy). This fits the view that it is the reaction which is chiefly altered, not the perception (see XII).

It was shown (see X) that a very great number of factors could cause pain thresholds to vary. In the studies presenting favorable results, as a consequence of analgesic action listed above, too few of these factors have been controlled.

D. Data which give rise to doubt as to a dependable relationship between analgesic action and the pain threshold in man

Macht *et al.* (435) make the puzzling statement "... the administration of some opium alkaloids produced a fall (electric shock method of stimulation)

and . . . others a rise in the threshold of pain sensation, thus affording a quantitative method of studying analgesia." It is also difficult to draw quantitative conclusions from their work because of the few subjects and inadequate dosage of the less potent analgesics used (534). They consider that a "crucial corroboration of the validity" of their method is the failure of saline placebos to alter the pain threshold. This observation perhaps merits less enthusiasm than that of the authors, since only the three authors were used as subjects and, considering the time required to test the six opium alkaloids studied, they must have become before long sophisticated subjects well able to differentiate between the aura of the narcotics used and a placebo. This fact plus their vested interest in the outcome leads to a less than "crucial corroboration" of their method. Unfortunately their error in this regard is a common one, indeed, one that threatens much work in this field. The only safeguards known to the reviewer, and it must be agreed these are only relatively reassuring, is to minimize the problem by using fresh subjects for only a relatively few observations, to use subjects that know nothing of the purpose of the experiments or the parameters at issue and, finally, who care nothing about the outcome.

The experiments of the Macht group are revealing. For example, they report that 10 mg morphine "produced quite marked lowering of the pain threshold" (judging by the context they meant elevation) in two of their subjects but not in the third where the pain threshold was essentially unchanged. The dose was increased to 12 mg and "instead of producing an analgesia" definite "hypersensibility" to pain was produced in this third subject, "as indicated by the rise in threshold." (Notwithstanding their odd error in the use of the term threshold, their meaning is clear.) Others might conclude that their method was not satisfactory. Later on they report that codeine has "very poor analgesic power . . . far inferior to that of morphine." This is not in accord with clinical observations when the agent in optimal dose is administered parenterally (395).

Straub (575) reports that, while narcotine is a practically inert drug, when it is administered with morphine a many-fold intensification of the morphine effect is produced. Macht *et al.* (435) believed they confirmed this statement. They reported that 5 mg morphine did not alter the pain threshold, produced no analgesia, yet 6 mg morphine in combination with narcotine "produced in each subject the highest degree of analgesia that we observed in our whole research." Yet narcotine in carefully controlled work appears to have little or no pharmacological effects in man. Indeed there is reason to believe it may be precipitated in the tissues and absorbed only exceedingly slowly over a period of days.

Jones and Chapman (353) report an elevation of pain threshold in man produced both by morphine and by monoacetylmorphine. This elevation was, however, far less than that reported by Hardy *et al.* (284) and similar to that reported by Slaughter. The studies of Jones and Chapman were not carried out as unknowns. It is puzzling to find that in none of the 24 subjects was the threshold lower after the use of morphine than before, yet in Denton and Beecher's (159) studies lowering was often found by Chapman who assisted in the

work. In the latter experiment the double unknowns technique was used. This is an illustration perhaps of the unconscious influence of the operator and is evidence for the use of the double unknowns technique. Jones and Chapman (353) report that monoacetylmorphine strikingly reduced the pain of ischaemic muscle contraction comparable to its reduction of radiant heat pain, notwithstanding the very different types of pain.

Others (373, 476) tried to use the radiant heat method to demonstrate the threshold-raising effects of parenteral procaine but without much success.

Ivy *et al.* (348) using electrical shocks to teeth observe in passing that 7 out of 16 human subjects, receiving 16 mg morphine subcutaneously, showed a lowering rather than a rise of threshold to dental pain; in one there was no change, and in 6 there was a rise. Two of the 16 subjects are unaccounted for and yet the workers consider the method useful! These data are very like those of Denton and Beecher (159) with the Hardy-Wolff-Goodell method which they considered notably unsatisfactory. It is surprising that Ivy *et al.* can have relied on their method.

It is highly questionable whether any real difference exists in Flodmark and Wramner's (216) data between the 30% elevation of pain threshold by 15 mg morphine and, a week later, 40% elevation by 8 mg morphine plus 0.5 mg prostigmine. Their own data (see their Figure 3) show that this variation and more is to be expected. In the experience of Denton and Beecher (159), Keats *et al.* (361) and Lasagna and Beecher (397) the 2 doses of morphine are only barely distinguishable when large numbers of patients and severe pain are used. Remarkably enough the investigators did not compare the effects of 8 mg morphine and 8 mg morphine plus 0.5 mg prostigmine. This "confirmation" of the Slaughter group's work must be dismissed.

Pfeiffer *et al.* (485) report a variety of threshold effects in man. For example, see Table 9.

It is to be observed that the nail bed and finger pad pain was produced by radiant heat whereas the tooth pulp was stimulated electrically to the point of pain. These authors do not appear to be concerned with their own data which show heroin, judging by their threshold changes, to be sixty times more effective on severe tooth pain than on nail bed pain whereas levomethadone is equally effective in the two circumstances. The reviewer is not aware of any

TABLE 9

Summary of mean per cent rise in pain thresholds with heroin (2 mg), dilaudid (2 mg), and l-Methadone (5 mg)

Drug	Nail Bed	Finger Pad	Tooth I	Tooth II
	%	%	%	%
Heroin (100 min)	1	8	26	60
Dilaudid (160 min)	15	9	26	50
l-Methadone (160 min)	20	17	21	24

other examples of powerful analgesic agents having such differentially specialized effects on the same types of pain.

Using the Hardy-Wolff-Goodell radiant heat method, Christensen and Gross (136) found methadone three times more potent than morphine. Denton and Beecher (160) found these two agents to be equal in analgesic power, milligram for milligram, when used to relieve pathological pain. Troxil (601) found 10 mg morphine equal to 15 mg methadone. The error arrived at with the radiant heat method is a commentary on the hazards of using experimental pain as it has been used for information applied to the clinic.

For all of Harris and Blockus' (292) care in designing and carrying out their experiments, apparently some important factors remained uncontrolled, for example, oral placebos elevated the pain threshold to a very highly significant level while parenteral placebos did not even show a positive trend. (If the significance levels had not been so far apart, one might have supposed that the explanation lay in inadequate number of subjects.) To the reviewer this merits attention. Surely the puzzle must be resolved before one can have confidence in the significant threshold changes that they have reported, for example, by 65 mg codeine administered parenterally.

Perhaps the key to the difficulty is a basic and possibly erroneous assumption, which strikes at the heart of experimental algesimetry in man. The reviewer has no wish to single out the work of Harris and Blockus (292) for special criticism. This work is used to illustrate certain points because it represents a generally careful study. Notwithstanding this fact, certain questions can be appropriately raised. They say, "To validate an algesimetric procedure it should be demonstrable that a compound generally acceptable as a clinical analgesic will cause the threshold of experimentally induced pain to become higher than it might otherwise be if no treatment or a placebo had been given." This states very clearly the assumption which is basic to *all* experimental algesimetry. Surely it is time to ask why experimental pain threshold elevation is essential "to validate an analgesic procedure." There is a very great deal of evidence at hand to indicate that it is not essential. First, there are discrepancies in even the best work, like that mentioned above, where placebos produced a significant change when administered orally but not at all when given parenterally. There is the widespread failure to confirm in man (see below) Hardy, Wolff and Goodell's reported threshold changes following the administration of analgesic agents. Since theirs is by far the most carefully and extensively studied method used in experimental algesimetry, these many carefully documented failures in man cannot be ignored.

Seevers and Pfeiffer (534), on the basis of studies of analgesic effectiveness using a modification of the von Frey hair technique, arrive at the arresting conclusion that morphine "is relatively impotent as concerns analgesia." (The study involved heroin hydrochloride (diacetylmorphine), 2 mg, morphine sulfate, 10 mg, dilaudid® hydrochloride (dihydromorphinone U.S.P.), 1 mg, and codeine phosphate, 64 mg.) This statement perhaps provides a commentary

on experimental pain methods in man for the evaluation of analgesic agents and emphasizes the wide gap between such experimental conclusions and clinical findings.

Only half (8) of the subjects were considered suitable for further study with a modification of the von Frey technique (534), some with a low pain threshold showed no effect from opiates, and those with a high threshold passed off the "hair" range before maximum analgesia had been produced. While the investigators can make any choice they wish, with such eliminations of subjects questions must be raised as to the meaning, the significance, of their results. It is curious to find in a given typical individual that morphine is essentially without effect on repeated testing, whereas heroin and dilaudid are much more effective. Can one conclude that, in given individuals, morphine is without effect, or, in reality, is something other than analgesia being measured?

Seevers and Pfeiffer (534) say, ". . . neither the degree nor the duration of analgesia is as great from intravenous as from hypodermic [subcutaneous] injection." One can understand how the duration of analgesia could be shorter on intravenous injection but it is certainly not clear how the *degree* could be less, in the light of all that is known concerning drug concentration and clinical effectiveness.

Several things in this study deserve emphasis. 1) Subjects with low pain thresholds had to be excluded since they "obtained no measurable analgesia from the opiates." 2) Nausea seemed to lower the pain threshold and prevented the analgesic action of all the drugs, yet one might have supposed from what is known from other studies that the emotion and distraction of nausea would have elevated the pain threshold. 3) Some presumably typical individuals persistently had essentially no analgesic effect from a clinically highly effective dose of morphine, but did from other narcotics (see 534, Figure 1), and one subject developed "not the slightest degree of analgesia from any of the (opiates)," even with larger than ordinary doses. (The reviewer knows of no clinical counterpart of this failure.) 4) The *degree* of analgesic effect on intravenous injection of the opiates was less than on subcutaneous administration. (However, notwithstanding their statement their own Figure 4 does not give good evidence of this.) Dilaudid, while strong subcutaneously, had a comparatively weak action on intravenous injection. These must be accepted as facts observed, but in toto they raise a question as to whether analgesia is what is really being measured.

In most cases narcotics failed in the study by Javert and Hardy (352) to raise the pain threshold in women in labor. This adds to the evidence that threshold changes sometimes produced by narcotics are neither dependable nor relevant to the real pain problem. They report, further, that morphine, heroin, or meperidine often reduced the pain intensity from 6 to 8 dols (severe) to 2 to 3 dols (comparatively slight) without a rise in pain threshold. They believe this was due to the action of the narcotics in reducing uterine activity. The fact remains that uterine activity was great enough to expel the baby. It seems doubtful that the reduction in uterine activity alone could account for the reduced pain. It would not be expected to account for the pain of cervical or peri-

neal dilatation. A more likely explanation is that pain threshold change, as measured, simply is not relevant to pain relief.

Hardy clearly considers the pain threshold-raising effect of an analgesic important; but he says it "is not the only important action of an analgesic in reducing pain" (282). Hardy and Javert (281) observed that while apomorphine greatly reduced the pain intensity of a woman in labor, it had no effect on pain threshold. It is evident that Hardy considers pain relief separable from threshold change.

With findings of this kind accepted by him, it is difficult to see how he can attribute importance to threshold change, since, as he agrees, pain relief can occur quite without threshold change.

Wolff *et al.* (289) say, "All agents known as analgesics raise the pain threshold . . ." This is not established for man. But then they say at once, ". . . the pain of a patient in labor is greatly reduced following the administration of an opiate, without alteration in pain threshold . . ." Here is contradiction within the same paragraph.

Houde *et al.* (330) describe a patient who, notwithstanding a great elevation in pain threshold by an analgesic agent, had a return of pain in the region of his disease at the height of the pain threshold reaction.

Parsons and Goetzl (479) "feel" that "a drug may possess analgesic properties in spite of its failure to raise the pain threshold in normal human subjects." This is heresy, for their whole series of papers is dedicated to the proposition that analgesic power *can* be revealed by pain threshold elevation in normal human subjects.

Slaughter (547) reports that both he and Chapman have independently ob-observed that some individuals appear to be "congenitally refractive" to 8 mg morphine. This reviewer knows of no clinical counterpart of this. It would be interesting to know just how common such "refractive" individuals are. It is surprising that neither Slaughter nor Chapman appears to consider that such failures challenge the adequacy of the method for the task undertaken.

While Wolff *et al.* (667) have, it is fair to say, emphasized that pain threshold elevation by analgesic drugs is less important than their effect on the reaction factor, the question arises as to whether pain threshold elevation is of *any* importance in man and whether in animals, when changes in its response to analgesics seem to be definite, it may not, in actuality, be so because of effects of these drugs on reaction. With the evidence of undependability of threshold change in man so great as it is, it is difficult to see how so many investigators can continue to place so much reliance on it in appraising analgesic agents in man.

Gold, in commenting on Cattell (124) said, "Several laboratories have now begun to compare analgesic agents by their power to raise the (pain) threshold. There should soon arise a classification of analgesic agents based on their power to raise thresholds." But then he continues with his usual wisdom, "I have the notion that such a classification, however, would not match the classification based on clinical experience in the relief of pain. A small dose of morphine which does not raise the threshold any more than a large dose of aspirin is much more effective in relieving pain than the large dose of aspirin."

It seems unlikely that elsewhere in science such a doubtful concept as the view that pain thresholds are generally and dependably sensitive to the effects of analgesic agents has had the attention and study of so many investigators over such a long time.

E. Failure to support the concept of a dependable relationship between pain threshold and analgesic action

It is apparent that many observers have never had the slightest doubt of a dependable relationship between analgesic action and pain threshold elevation in man. The design of the experiments of the originators or of those who have "confirmed" them have not in many cases been reassuring. The same can be said of several of those who have failed to confirm them, but in general the opponents have had better designed experiments than the advocates.

In the traditional pattern, noxious stimulation has been increased until minimal pain, the "pain threshold", appears. Algesimetric methods to be useful, so it is said (244), must permit the determination of pain thresholds in a quantitative way. It would seem, in view of the mass of evidence presented in foregoing sections, that the algesimetric methods based upon experimental pain in man hardly fulfill this "requirement." The data to be presented in this section cast further doubt on the usefulness of such methods for the experimental evaluation of analgesic agents in man. Nonetheless, it will be shown (see XII) that, when pathological pain is utilized, what amounts to a kind of threshold effect is determined in quantitative terms. In the latter case the labels have new meanings and the data referred to present a new kind of threshold in terms of dose-effect curves which demonstrate a given effect, *i.e.*, a given percentage of patients relieved by a given dose of drug under specified conditions. So, in essence, the above statement is supported, quantification of "threshold" is possible and useful.

Here is a partial list of those who have failed to confirm Hardy, Wolff and Goodell's observations in man of pain threshold rise as a consequence of analgesic action. Some only of the investigators used "trained" subjects so it is difficult to accept the view that trained subjects are useful whereas untrained are not. Even Hardy, Wolff and Goodell, as has been pointed out, are not consistent in requiring training as essential.

The following investigators were unsuccessful, using the radiant heat method of stimulation in man (19, 21, 75, 117, 118, 131, 159, 165, 215, 300, 350, 390, 591, 633, 636 experiments of Isbell and Frank). Slaughter (547), as mentioned, reported that both he and Chapman had found some individuals, judged by this experimental pain method, to be "congenitally refractive" to 8 mg morphine. Thorp (591) found no statistically significant rise in pain threshold in man even when 10 mg morphine was used (he worked with unknowns). He mentions the increasingly difficult endpoint determination with increasing doses of morphine and speaks of "a most uncertain method." He shows a decided elevation of pain threshold with the Hardy, Wolff and Goodell method when another pain is produced, *i.e.*, muscle ischaemia pain in the arm. Whyte (633) has extrapolated

Hardy, Wolff and Goodell's data and finds that pain ought to occur when the skin temperature reaches about 46°C. in a normal subject, 50°C. after acetylsalicylic acid, and 54°C. after morphine. Whyte found no such changes.

Hardy, Wolff and Goodell recognize that pain threshold varies with sweating and blood flow, for example, but give no evidence that these factors remained constant during drug studies. Severe pain certainly produces secretion of epinephrine and this has a profound effect on the peripheral circulation which can modify pain threshold. Conceivably severe pain may thus disturb subsequent threshold determinations for some time. Repeated testing in a given area is likely, as Whyte points out, to cause variations in vascularity and initial skin temperatures.

The following have failed with the method, using electric shocks to teeth in man to confirm Hardy, Wolff and Goodell's observations: Harris and Blockus (292), Harris and Brandel (293), Sonnenschein and Ivy (558), Ivy *et al.* (348).

The following have failed to support Hardy, Wolff and Goodell's observations with the von Frey hair method (or a modification of it) of stimulation in man: Mullin and Luckhardt (466) (data on acetylsalicylic acid), and Seevers and Pfeiffer (534). The latter reported that some individuals (with low pain thresholds) showed no effect from opiates.

In studies of ischaemic muscle pain Hewer *et al.* (314) conclude that analgesics act mainly by some mechanism other than that which raises pain thresholds. They base this on the observations of Hardy *et al.* (284) that the action of morphine on the threshold of pain from radiant energy is almost abolished when this drug is given to subjects suffering from ischaemic muscle pain. However, Hewer and Keele (313) have studied the effect of intravenously injected analgesics on existing ischaemic muscle pain. They found that with small doses of analgesics there is relief of such pain.

F. Pain threshold difficulties encountered with the acetylsalicylic acid class of analgesics in man

The "mild" analgesics such as those of the acetylsalicylic acid class have produced an inordinate amount of trouble for those who have tried to show a dependable relationship between analgesic action and pain threshold elevation. Here are some examples of difficulties with these agents in human experimentation.

Hardy *et al.* (284) reported that a large dose of acetylsalicylic acid raised the pain threshold 35 %, whereas the heat threshold was *lowered* 55 %, thus separating, they believed, the 2 types of sensation. They also showed that a constricting sphygmomanometer cuff could abolish most sensations in the hand but not pain. The pain threshold of the constricted hand and the forehead showed the same changes.

Wolff *et al.* (668) show great effects on radiant heat pain threshold in man from acetylsalicylic acid, with apparently clear-cut difference between doses increasing by as little as 0.03 g. It is remarkable that they could achieve such precision while many other careful investigators could not demonstrate *any* dependable effects in man with any dose of acetylsalicylic acid, with the same

method or with other methods. They have reported elsewhere (Wolff and Goodell, 665) however, that a placebo given in a setting where the subject believes it will raise his pain threshold does so equivalent to that of an active agent, acetylsalicylic acid. It is puzzling to this reviewer how they arrive at their conclusions as to the effectiveness of acetylsalicylic acid and similar agents in raising the pain threshold when they admit placebos can do as much. One would have supposed that for the threshold-raising effect of acetylsalicylic acid to be meaningful it would have to be elevated significantly above that of a placebo.

Hart (297), using a modification of the D'Amour-Smith method, found acetylsalicylic acid and salicylamide and its derivatives to have analgesic power in animals. Hart's modification of the D'Amour-Smith method consists in an arrangement whereby the animal is warmed up before it is subjected to the painful stimulus. While D'Amour and Smith (155) found response times from rat to rat negligibly low, Hart could not confirm this constant threshold in animals. Hart says, "Whatever the defects of our method may be, by its use we have not yet failed to detect analgetic action in a drug which has proven clinically useful for the relief of pain." This is quite a feat with the weaker analgesics he used. But, as Hart candidly points out, he has been unable to define the limitations of his method. Perhaps the approach deserves further examination.

How to explain the great differences between the Hardy, Wolff and Goodell group, on one hand, and other competent groups, on the other, is a question. Perhaps it is best to record the discrepancies and leave it at that.

The discrepancies may be a reflection of the hazard of the experimental design used by Hardy, Wolff and Goodell: Basing as much as they have on 3 subjects, themselves, is perilous, especially since the use of the double unknowns technique, it is generally agreed even by them, is essential although they did not attempt to use it in their early work. But one must also agree that such a design is impossible with drug-wise, sophisticated subjects who could not possibly be kept in ignorance of the use of powerful narcotics or even probably in many cases, acetylsalicylic acid. With a vested interest in the outcome (the hazard of not using disinterested subjects) it is clear that the essential elimination of bias could not be kept out of such work. The reviewer could not do it with their experimental design. He doubts that they could either.

Several groups have failed to confirm Hardy, Wolff and Goodell's report of a pain threshold-raising effect of acetylsalicylic acid (75, 117, 118, 390, 479, 558).

Harrison and Bigelow (296) report a 25% elevation of threshold (with the muscle ischaemia method plus work) produced by acetylsalicylic acid and they say this effect is similar to the effects of this agent on cutaneous pain. The trouble is, a 30% elevation was produced by a placebo. How they can conclude from that that the cutaneous pain effects of acetylsalicylic acid were confirmed is not stated.

The failure of salicylates to elevate the experimental pain threshold in man has been reported by various authors (75, 277, 292, 293, 558). In an effort to square the experimental failure with the clinically observed fact of the effectiveness of acetylsalicylic acid, several explanations have been offered. It is said,

that the methods for testing are not sensitive enough, yet the methods are sufficiently sensitive to demonstrate the effectiveness of placebos, or to follow the changes produced by verbal suggestion, or to reflect moderate changes in temperature and so on; that experimentally induced pain is not the same thing as pathological pain; that the phenomenon is not explicable on the basis of the present concept of pain and analgesics (294). Perhaps the difficulty is that pain threshold measurements are irrelevant to the problem.

Although Harris and Blockus (292) are staunch advocates and defenders of the essentiality of pain threshold change in the appraisal of analgesic agents, their own evidence can be presented against this view. Despite their careful study, they were obliged to conclude that the effects of acetylsalicylic acid were not distinguishable from those of a placebo, as far as pain threshold change in man is concerned. Rather than facing this as evidence of inadequacy of the pain threshold change concept, they take refuge in the following statement. "Although we have often obtained relief from certain pains by taking aspirin . . . , in view of our experimental outcome, we are of the opinion that the causative mechanism of the pain was relieved rather than the perceptual thresholds being elevated." By implication, Harris and Blockus (292) are adding a further and elaborate requirement to algesimetry: When they know, or think they know (the reviewer is not prepared to grant that they do know in this instance), how an analgesic agent works, they will not require that it raise the pain threshold. When its action is mysterious as it is with morphine, then the pain threshold must be elevated. Not enough is known about the action of any analgesic agent at this time to permit such a dichotomy to be made. Nor is it permissible, in view of its well established pain-relieving power, to deny, as Harris and Blockus (292) do, that acetylsalicylic acid is an analgesic agent. These views have been presented in some detail as an example of the difficulty a good many observers have in facing the possibility that pain threshold change may really be unrelated to the action of analgesic agents.

Gaensler (229) found no pain threshold-elevating effects of acetylsalicylic acid (0.6 to 1.2 g by mouth in 12 patients), when he used increased pressure in the biliary duct to produce pain.

Mullin and Luckhardt (466) report that morphine, alcohol, trichlorethylene, all elevate the pain thresholds as judged by the von Frey hair technique without, apparently, appreciably affecting tactile sensitivity. They also report that acetylsalicylic acid, a barbiturate, a bromide and other agents affected neither pain nor tactile sensitivity.

Ercoli and Lewis (200, p. 311 *et seq.*) give a good summary of work by others on acetylsalicylic acid.

G. Relationship of the "pain"-reaction threshold of animals to the action of analgesic agents

There has been fairly general agreement to the present time that the reaction threshold changes (it is not permissible to call this pain threshold) produced in animals by analgesic agents are often useful in appraising analgesic power. The

usual failure in animals with the less powerful analgesic agents like acetylsalicylic acid is a point to consider, so also is the failure with the powerful narcotic N-allylnormorphine (396). But, generally speaking, threshold changes in animals have been more dependable than corresponding effects in man. It has been pointed out before by the reviewer that pain is pain to an animal, presumably, and all pain serious and significant. The threshold changes in animals which are elevated by analgesic agents may, and probably do, reflect changes in the reaction component, and this is far greater in the presence of significant pain than otherwise (see XII). It is no speculation, however, that the threshold changes which are depended on in animals are very different things from those in man. In animals (see VII) the threshold changes are indicated by reflex activity, and usually by spinal reflex activity at that (344). In man they are based upon cortical activity. A good many useful studies can be referred to in this connection (23, 155, 165, 184, 185, 186, 194, 200, 297, 349, 591, 651, 675).

Goetzl *et al.* (245), using the tail pressure method in mice, present smooth curves of effect increasing with morphine dosage. A considerably greater effect, judging by the appearance of the curves, was produced when d-amphetamine was given with the morphine. They state that the results obtained are in agreement with experiments in the dog.

Fleisch and Dolivo (212) found electrical stimulation of the rabbit tooth pulp to be the only satisfactory method of getting at threshold effects of analgesic drugs. They credit Ruckstuhl and Gordonoff with the shock to teeth method.

Andrews and Workman (23) report that acetylsalicylic acid has a threshold-raising effect in dogs. Cobra venom had no effect in raising the threshold, notwithstanding Macht (434).

Hougs-Olsen (338) finds, with radiant heat on the rat tail, methadone to be 1.3 times more active than morphine. Maximum rises of pain threshold at a given time cannot be used for comparison of two drugs, even when administered by the same route, since the maxima may occur at different times depending on dosage and agent. It may be better to use the area under the curve (see VI).

All has not been smooth sailing, however. Woolfe and Macdonald (675) concluded that meperidine is in the codeine rather than the morphine class, a misleading observation. Bliss and Sevringhaus (90) found a nine-fold variation of meperidine as compared with morphine when 6 laboratories attempted to determine analgesic potency in animals. (Table 10. See also Table 11.) This 900% spread with experimental animals can be contrasted with a 7% spread for morphine between the Houde and the Beecher groups and their 8% spread with a weak agent, a placebo (see Table 1). Most investigators have not, as mentioned, been able to evaluate weak analgesics, such as acetylsalicylic acid. There was a general failure to detect, in animals, that N-allylnormorphine was a powerful analgesic as was shown in man by Lasagna and Beecher (396) and confirmed by Keats (363).

Winder *et al.* (651) report a significant rise of "pain" threshold by acetylsalicylic acid in a small number of guinea pigs produced. Winder (648) found this agent to raise the "pain threshold" of guinea pigs more than meperidine did. This

TABLE 10

Variations in relative analgesic power as determined ('unknowns') in six laboratories in animals*

Laboratory	Methadone	Codeine	Meperidine	Aminopyrine
I	148	42.0	15.2	1.24
II	170	3.2	5.0	1.62
III**	102	8.1	12.2	2.67
IV**	133	33.0	45.5	5.89
V	114	9.5	5.1	1.30
VI	131	29.7	17.7	1.83

* Morphine = 100.

** Some log-dose response curves non-parallel; results valid only at ED50 or at mean response for standard.

These data were furnished through the courtesy of Dr. Bliss.

TABLE 11

*Analgesic power of methadone in relation to that of morphine**

Investigator	Species	Methadone Potency**	Method
Thorp *et al.* (1947)	rat	130	heat to tail
Hougs-Olsen (1949)	rat	130	heat to tail
Isbell *et al.* (1947)	man	400	experimental pain
Christensen and Gross (1948)	man	300	experimental pain
Troxil (1947)	man	150	pathological pain
Denton and Beecher (1949)	man	100	pathological pain

* The comparison shows better agreement between experimental pain in animals and pathological pain in man than between the former and experimental pain in man.

** Morphine = 100.

is an illustration of how misleading work with experimental pain as opposed to evaluation with pathological pain can be.

H. Ceiling effects

Approximate ceiling effectiveness of analgesic drugs must be recognized as a demonstrated fact in man. This is shown for the action of morphine and meperidine on visceral pain by Gaensler (229, Figure 3); 20 and 30 mg morphine were not more effective than 16 mg, and 200 mg or 100 mg meperidine were not appreciably more effective than 50 mg. Gaensler (229) found that the maximum *visceral* pain-relieving power of morphine appeared about 30 minutes following parenteral injection, *i.e.*, much earlier than with the Hardy-Wolff method or the von Frey method. A ceiling effect has been shown by Denton and Beecher (160) for morphine and the methadones, by Keats *et al.* (361) and by Lasagna and Beecher (397) for morphine and by Lasagna and Beecher (395) for meperidine and codeine.

Hardy *et al.* (283) found, on constructing dose-effect curves, that little in-

crease of the pain threshold occurred with doses of morphine above 15 mg, or of codeine above 60 mg. This agrees with the Beecher group findings of maximum effect.

Ercoli and Lewis (200) found ceiling effects: morphine 20 mg/kg produced the maximum duration of analgesia. They also report that enormous doses of morphine by mouth (25 to 40 mg base/kg) produced *no* effect in 15 rats. Seven rats were given 80 mg base/kg, but only 3 showed brief and moderate anesthesia. The average analgesic dose by mouth was 200 to 250 mg base/kg, about half the fatal dose.

Winder (647, 648) reports that, insofar as dosage can be pushed in his guinea pigs without interference from side effects, the analgesic effects appear to increase progressively for morphine and meperidine but not for acetylsalicylic acid. It seems unlikely that animals would be so different from man where powerful narcotics have a distinct ceiling effect. Winder's positive elevation of threshold with acetylsalicylic acid is not in agreement with Goetzl's (242) discouraging review on aspirin. If Winder is truly measuring analgesic effects, his work provides further evidence that man and animals differ.

Not only the ceiling effects of drugs but also ceiling pain has been discussed (289, 300).

XII. REACTION FACTORS OF THE PAIN EXPERIENCE[8]

There are many kinds of reactions to noxious stimulation. They generally fall into one of three groups: skeletal muscle responses, reactions mediated by the autonomic nervous system, and, finally, the most important one as far as suffering goes, the processing by the central nervous system of the original stimulation. This last response is more important than other forms of reaction for the simple reason that it can determine the presence or absence of suffering; it is an intimate part of the pain experience. The other reactions are not a component of pain but *consequences* of it.

In section II the general problems of defining pain were discussed with a brief reference to the "operational approach." As pointed out there, it is the reviewer's belief that true operationism embraces the use of questions and answers, and that the Beecher group's techniques, for example, are operational. Extreme operationists have gone so far as to deny that one can depend upon what the subject says about his pain. To the reviewer this is a kind of nihilism. If this extreme view is accepted, then even when dealing with man one would have to depend upon reactions to pain. As already made clear, these reactions may be quite far removed from the pain threshold. Others agree with the inaccuracy of reaction as a basis for judgment (80, 227, 244). (See VII, 2.)

A. Psychic reaction or processing component

It is important to state as exactly as possible what is meant by "original sensation" and reaction (54). The output from the sensory receptors is the pri-

[8] "Peut-on avoir une sensation sans avoir l'idée, la conscience, le témoignage interne qu'on éprouve cette sensation?"

(Voltaire: Oeuvres Complètes, Physique; 1768.)

mary phenomenon and is derived from stimulation. The resulting afferent nerve impulses emerge finally in the central nervous system and become there a recognized sensation or perception. (The two terms evidently refer to exactly the same thing [see IX].) Presumably in all normal individuals the primary, the initial events, are the same for a given stimulus. Also there can be little doubt that the secondary response, the reaction to, or the processing of, the primary events, is different for each individual. Cleavage between primary and secondary response has to be an arbitrary matter. From a neurophysiological view it would seem better to place the end of the primary response just before any processing has begun; but in practical terms this is impossible. It seems necessary to call the events including the eruption of the sensation into consciousness as primary, "the original sensation," and the succeeding events as secondary, as reaction, as processing. One must face the fact that processing doubtless begins before awareness has been achieved. (See IX.)

The existence of the sensation and its recognition are then the stimuli which precipitate the important psychic reaction, presumably the major part of the processing. In the sense in which the term reaction is used here the reference is not to physical activity such as the withdrawal of a burned finger from a flame, but rather to the mental process set up by the original stimulation. It seems hardly questionable that this perception and process of recognition are influenced by the subject's concept of the sensation, by its significance, by its importance and degree of seriousness. An ache beneath the sternum, in connoting the possibility of sudden death from heart failure, can be a wholly unsettling experience, whereas the same intensity and duration of ache in a finger is a trivial annoyance easily disregarded. It seems unquestionable too that the meaning of a sensation depends upon, is governed in large part by past experience as well as by present consideration; thus discrimination, memory and judgment enter into this process of reaction. One can suppose that in physical terms, "association paths," "long circuiting," "reverberation" of nerve impulses and thus internuncial neurones are involved. This working hypothesis can reasonably be extended to suppose that, when one can reduce or eliminate a subjective response by the use of drugs, drugs are effective either by virtue of (a) lessening or blocking the original sensation or (b) by reducing or impeding the process of recognition or (c) by altering the processes of discrimination, memory and judgment which follow recognition.

The basic reason for the choice of the dichotomy, original sensation-reaction, has a rather long history; it goes back 60 years to a book by Marshall (446), for it was there that the concept of the reaction as important began to emerge. Marshall said,". . . I cannot bring myself to believe that . . . pains can be revived apart from any content to which they are attached." According to Marshall's theory, " . . . pleasure and pain are not independent mental contents, capable of existing in consciousness alone, but [are] . . . a sort of modification or coloring of sensations and ideas" (578). While Marshall did not clearly formulate the crucial assumption, Strong (578) did, stimulated by Marshall. Strong said, "Whenever we feel a pain, there we have a sensation or idea, distinct from the pain, with reference to which pain is felt, . . . in every actual state of mind we are able to distinguish these two sides, the cognitive and affective."

The great confusion as to whether pain is a separate modality (see III) has been due, Bishop (77) believes, to failure to recognize that pain has two aspects: (a) it is a sensation with its own sense organs and fibers and (b) it is an unpleasant psychological experience, which leads to an attempt to escape the stimulus. Pain may be experienced as a sensation without its "dolorous affect" Bishop says, but his evidence for the practical demonstration of this is not clear. It seems most unlikely that this is possible (see IX). In the above remarks Bishop has restated Strong's (578) hypothesis of original sensation *versus* the psychological reaction to it. How to separate pain sensation from its dolorous affect is the problem. The confusion referred to by Bishop is derived from an attempt to deal with the two categories at once, "one a psychological category of unpleasant experience, the other a physiological category of neurological pathway, to a complex set of events" (77).

Forbes (218a) has discussed the pre-pain results of stimulating pain receptors.

He says, one must recognize "the difference between pain viewed psychologically as unpleasant, and pain as excitation of pain receptors. The latter, even well above threshold, can be actually pleasant, and therefore not recognized as pain by the average subject. This can best be illustrated by pressing gently on a skin surface with a moderately sharp edge, *e.g.* a finger nail. The most gentle contact evokes only touch sensation; a slight increase in pressure evokes a sharply defined change in the quality of sensation, but at threshold this sensation is not unpleasant. Further increase of pressure causes a gradual increase in the new sensation till it becomes unpleasant and is thus recognized as pain. The first onset (threshold) of the new (pain) sensation is very definite,—an easily recognized end point. The transition to a degree of stimulation which is unpleasant, and therefore called 'pain', is gradual and ill-defined, therefore subject to great individual variation. I am convinced that the pleasurable sensation enjoyed in a hot bath is due to *moderate* stimulation of the pain receptors. The threshold of excitation of those receptors is definite; the threshold for an unpleasant excess, popularly called 'painful,' is very fuzzy, and probably varies enormously between individuals,—probably far more than the threshold for the pain receptor modality.

"When I do a similar experiment, concentrating sunlight on my finger with a lens, I note a similar transition from the pure sensation of warmth to the added pain sensation, but the difference between the two is not as clear and definite as it is with tactile pressure; even in this case the change in modality as the pain receptors are first stimulated occurs before the intensity of pain sensation becomes unpleasant.

"The moral is that in defining what you are measuring, it is important to differentiate between the threshold of what 'hurts' (*i.e.* is unpleasant) and the far more definite threshold of excitation of pain receptors, which hardly anyone calls 'pain'. I find no evidence that you or any of the authors quoted has recognized this distinction. The nearest approach to it seems to be Bishop's 'painless prick.' "

Professor Forbes' comments are interesting and deserve recording, but to the reviewer there are two difficulties here: First, how to tell whether in a mixed receptor field the sensations mentioned truly arise from the pain receptors and not from touch or pressure or warmth receptors and, second, by common agreement the pain threshold has been defined (VII, 1) as the first barely perceptible *pain*. While many sensory thresholds have their own special interest, the pain threshold is of primary interest in these studies.

Bishop has been able to stimulate the pain-inducing mechanism so as to pro-

duce a painless "prick." Increase in frequency of the same stimulation evokes pain. He "suggests that a rational and unequivocal definition of modality could be based upon physiological mechanisms, more objectively than upon psychological reactions, even though psychological experience is involved in the identification of sensory mechanisms." This of course amounts to defining pain as the adequate stimulation of "pain" endings. Bishop goes on to say "Its justification will depend on the ability of the subject to discriminate between stimulation of these endings and of any others whether or not the stimulus and the emotional state of the subject is appropriate to the arousal of a dolorous reaction." To the reviewer this falls considerably short of an "unequivocal definition." For example, how is one to reconcile with this Beecher's observation (38) that a very high percentage of men wounded in battle experience little, and in many cases no pain (men not in shock, clear mentally, having received no morphine recently and none in many cases)? It cannot be doubted that their pain-inducing mechanism has been stimulated to an even greater degree than was the case with the civilian undergoing surgery who, with much less extensive wounds, reported pain of sufficient degree to require narcotics several times as often as the wounded soldiers (57). It is common observation that emotion can block pain. Such block doubtless occurs centrally; it seems extremely unlikely that the "pain-inducing mechanism" fails in the periphery. If the failure, then, is central, how and where is one to separate the two confusing categories of "sensation" and "unpleasant psychological experience?"

Wolff and Goodell (665) make a great point that "The reaction pattern is, however, independent of perception and may be dissociated from it." They offer as examples of the dissociation of pain perception from the reaction pattern, indifference to injury sustained during excitement of games, combat or sexual arousal; during injury the absence of reactions to pain effected by suggestion, hypnosis or catalepsy; the apathy to injury accompanying autosuggestion or religious or mystical rites; painless childbirth. They agree that this dissociation may be of varying degree. It should be observed that all of these examples are derived, insofar as the cause of the pain is specified, from pathological or traumatic situations. Another type of approach to the separation of the two components is shown in the work of Keats and Beecher (357) on the dissociation of pain and comfort by a barbiturate and by morphine. They compared this with the results of frontal lobotomy or leukotomy. This work with drugs showed that a change in attitude toward the pain could be similarly effected by the drugs and by lobotomy. This is evidence that pain perception and attitude to pain can be separated, that the reaction component is the important factor from the patients' point of view, and that suffering is largely dependent on the reaction (attitude) rather than the original sensation. ("I have my pain unchanged but it doesn't hurt me now.") (For a further discussion of lobotomy or leukotomy and reaction see XII, F, 1, c.)

There seems to be some separation of perception and reaction in the differences encountered between normal subjects and psychoneurotics (see XII, F, 1, b).

Evidence was presented (X, 20) that suggestion can affect the experimental

pain threshold. Such an effect does not demonstrate a separation as referred to here. This so-called separation of reaction pattern and perception appears to be not so much a separation as domination, even obliteration, of perception by the reaction. Doubtless one could argue that the elimination of one factor by another is a kind of separation, but this is hardly what is implied by the term separation.

B. Experimental vs. pathological pain and the psychic reaction component

It is an assumption, not more, that all pain experience in man consists of the original sensation plus the psychic reaction to that stimulus, and one assumes further that in various situations there are great quantitative differences in the rôle of each component. There is much to support this hypothesis. It is Beecher's view (54) that this assumption can be extended probably to include all subjective responses, especially those that arise in disease or trauma. It is also his view that, because of the difficulty of reproducing in the laboratory pathological *reaction* to the original stimulus, the choice of "real" as opposed to contrived sensation is a good one. Hardy *et al.* (291) say that "*pain sensation must be separated from associated reaction pattern* if progress is to be made." One can easily agree that this separation is desirable, but there is doubt that it has been made as yet, clearly and unequivocally, in work with experimental pain. Not much imagination is needed to suppose that the sickbed of the patient in pain with its ominous threat against his happiness, his security, his very life, provides a milieu *and reaction* entirely different from the laboratory. Some anxiety and some fear can be contrived in the laboratory and associated with experimental pain (57, 316, 318, 319, 384, 439, 440). It is not likely that this contrived situation can ever be made to approximate closely the real situation which arises in pathology or trauma.

After this section was written, it was of interest to find the following statement by Bishop (80): "A comparison of the attitude of the subject undergoing pain stimulation as an experimental procedure with that of the sick and anxious patient whose pain is mysterious, unpredictable and of unknown causation, not to mention the factor of persistence of the pain, indicates that in casual experience the reaction to pain may be of more significance to the animal than its mere perception."

Of course the importance of the assumption hinges on the question of how great the reaction element actually is. It will presently be shown that it can dominate the situation. Consider, for example, the curative power of placebos (53, 55).

Hardy, Wolff and Goodell appear to believe they have in their experimental pain a pure original sensation, for they often write of their data as providing access to study of sensations without reaction, and yet they go on to describe their own rather elaborate response (reaction) to their experiments (see 667, pp. 664 and 677; 673, pp. 10 and 14). It is evident that they have had a decided reaction to the total situation. They seem to dismiss a pleasant reaction as no reaction at all, and in reaction appear to include only unpleasant responses.

While a good many different approaches to the study of subjective responses are possible, some appear more promising than others in terms of probable results. It has been a continuing source of surprise to the writer that the dichotomy mentioned earlier, experimental *versus* pathological source of sensations, has not been an obvious distinction to make. It has not been to some. The matter is pertinent to the theme of this review. Since a fundamental and, in the writer's view at least, a most important assumption is involved, that, perhaps, throws some light on the phenomenon of perception, it may be well to summarize the reasons for this distinction. If in the end this assumption is found to be full of faults, it will be easily discarded. As long as it is as productive as at present, it will be retained. (One can successfully differentiate between powerful and weak analgesics and placebos as unknowns using pathological pain, but not if experimental pain in man is used. See V, B, 2, XI.)

Szasz (585) considers "organic," "psychogenic," and "experimental" pain. He avers that within the framework of concepts he has elaborated, "organic" and "psychogenic" are meaningless, but he proposes to retain the terms "not as descriptions of the pain experience, but as *judgments* of an observer. The difference between 'organic' and 'psychogenic' pain is (in his view) similar to that between 'realistic' fear and 'neurotic' anxiety." He says further, "The designation 'experimental' . . . refers to the opinion and intention of the observer and not to the ego experience." Szasz has not understood the meaning of the reaction component as the great differentiating factor between experimental and pathological pain. The overwhelming importance, at times, of the significance of a wound (57), of the cause of the pain cannot so easily be disregarded. The casual discomfort of experimental pain contrasts sharply with a pain that means or implies disease or even impending death. There is more here than the "opinion and intention of the observer." Szasz, notwithstanding, the ego experience is inevitably involved. According to Seevers and Pfeiffer (534) there is no reason to believe that the pain stimuli used in experimental and pathological pain are different. It was shown in V, B, 2 and XI that a very different response to analgesic drugs was found under the two circumstances. It is agreed that, when an experimental pain is contrived in such a way as to contain a large element of anxiety or fear, the difference lessens between pain of the two origins. It will be shown in this section on psychic reaction that experimental pain as usually produced differs very greatly from pathological pain.

A large dose of morphine is not capable of consistently and significantly altering the brief jabs of experimental pain, even in properly set up and controlled experiments in man. Compare this with the fact that much smaller doses of morphine consistently reduce, often check completely, the severe pain of an operative incision or a great wound. It seems that the sensible conclusion is that, significantly, the two situations are not comparable, and that something more than stimulation of nerve endings is involved, believed here to be reaction. *Great wounds with great significance and presumably great reaction are made painless by small doses of morphine, whereas fleeting experimental pains with no serious significance are not blocked by morphine. The difference in the two situations would*

seem to be in difference of significance of the two wounds. Morphine acts on the significant pain, not on the other (54, 57, 316, 318, 319, 384, 439, 440).

Also related to this discussion is the question of why some wounds are painless and others are not (38, 57). Adrian (4) says, ". . . pain messages are clearly more potent than any others in rousing the brain from sleep, and in capturing the attention." If this be true, one can only wonder how it is that the majority of the seriously wounded soldiers studied by Beecher (38) at Anzio often had their expected wound pain blocked. These men were clear mentally, and not in shock; they had not had narcotics recently and none at all in many cases. It seems from this that the reaction, or processing, component can dominate the pain experience. It is more potent than the noxious stimuli in determining the presence or absence of suffering. The total situation has of course great influence on the reaction that develops in it. Thus after removal from battle badly wounded men were often euphoric, their reaction to their wounds, to removal from the battlefield (a milieu of destruction and death) to the relative safety of the forward hospital, was a reaction of satisfaction, nonetheless a reaction (38, 57). This probably is an example of a pleasant reaction having practical importance, for a very high percentage of the wounded soldiers, although in good general condition, entirely denied pain from their extensive wounds or had so little they did not want any medication to relieve it.

In a comparative study of wound pain (57) a group of male civilian patients undergoing major surgery was asked the same questions as those put to the wounded soldiers. Of the wounded soldiers about one third (for the types of wounds compared in the present instance) wanted medication to relieve their pain and two thirds did not. Of the civilians suffering from far less tissue trauma four fifths wanted medication to relieve their pain and one fifth did not. Thus the figures are reversed. While the details are discussed elsewhere (57), the important difference in the 2 groups seems to lie in their responses to the wounds. In the wounded soldier it was relief, thankfulness at his escape alive from the battlefield, even euphoria (his wound was a good thing); to the civilian his major surgery even though essential was a depressing, calamitous event. The civilian group's pain was strikingly more frequent and more severe than that of the soldiers. *These data state in numerical terms what is known to all thoughtful clinical observers: There is no simple, direct relationship between the wound* PER SE *and the pain experienced. The pain is in very large part determined by other factors, and of great importance here is the significance of the wound, i.e., reaction to the wound.*

A factor not taken into account in work with experimental pain is that the natural function of pain endings and nerve fibers is to produce reactions to lessen the pain and protect the body from damage (4). Insofar as such deep seated reactions are skeletal they are frustrated by the experimental requirements. What effect this abnormal state of affairs has, if any, is not known. It seems likely that it has an effect on the "central" or "mental" reactions.

There is, moreover, the fact, widely reported and fairly generally agreed upon, that experimental pain can be useful in appraising analgesic power in animals (XI, G). In man, experimental pain has so far proved useless in the

hands of many careful workers (XI, D, E, F), but pathological pain is highly useful for this purpose (V, B). Presumably pain is pain to an animal, and all pain serious and significant of danger. In man only pathological pain is significant and serious. Thus in both instances *narcotics are effective but chiefly effective (probably) only in the presence of significant meaning of the pain involved. This looks as though narcotics are effective through their relationship to the meaning of the pain, i.e., to the reaction to it.*

Consider also, as recorded earlier (38), that the majority of men freshly and grievously wounded in warfare, but clear mentally, not in shock and with normal blood pressure, having had no narcotics for a period of 4 hours or more and some not at all, state that they do not have wound pain great enough to require medication on direct questioning. *They complain as vigorously as normal men at an inept venipuncture; so there is no total pain block.* There is every reason to suppose that the wounds they have received stimulate sensory nerves, that the original stimulation starts out, but the usual end result is somehow prevented. The usual response to a severe wound, pain, does not occur in the majority of these cases. *Thus emotion can block pain; that is common experience. It is difficult to understand how emotion can affect the basic pain apparatus other than by affecting the reaction to the original sensation.* Certainly psychological effects have great influence on subjective responses, not only pain but other responses as well. Every small boy has learned, knows, even though he does not consciously recognize the fact, that emotion can block the pain of a wound received during fighting but not perceived until the fight and the emotion have subsided.

Thus it seems reasonable to separate pain on the basis of its origin and significance to the subject, experimental or pathologic (this includes traumatic, of course). Presumably this applies to other subjective responses that have powerful connotations; this assumption needs further testing.

One cannot know whether in the above instances the pain sensation or the reaction to pain is blocked; however, since the conscious man badly wounded in warfare often does not suffer at all from his great wound, yet is annoyed by, and suffers apparently normally from, a venipuncture, one can conclude that the nervous system can transmit pain sensations but that somehow the reaction to them is the altered element. This conclusion is strengthened by the observations (see XI) that there is no dependable relationship between pain threshold in man and the effect of analgesics.

The fact that powerful analgesics have not clearly been shown to produce a dependable elevation of experimental pain threshold in man, yet are universally found to be effective in treating pain of pathological origin, indicates a difference between experimental pain and pain of pathological origin. The concept developed in this section provides a possible explanation of this difference.

C. Further evidence for the importance of the psychic reaction component

Still another type of evidence supports the view that the most important factor in suffering is the psychic reaction: It was found (357) that it was possible to differentiate between comfort and pain relief. Soon after initiation of the study

referred to, 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 difficult. Two types of puzzling reactions were observed. One was in those subjects who claimed that their pain had not, or had only slightly, changed, and yet, who did not want further medication. They appeared comfortable (here, of course, the judgment is based upon objective data), content, and divorced from any "painful" experience in contrast to their pre-drug state. Despite the fact that their pain was said to be still present, it was impossible to 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. Here it was impossible to believe that the medication had been very successful, 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, *viz*: (a) no comfort, no pain relief, (b) no comfort, pain relief, (c) comfort, no pain relief, and (d) comfort, pain relief. The latter categories of response were considered to represent the therapeutic or desired effect, both from the physician's and the patient's viewpoint.

Hill *et al.* (316) administered 250 mg pentobarbital sodium intramuscularly to post-addict subjects and found that this failed to reduce the disruption of performance presumably caused by anxiety which accompanies painful self-penalization, although morphine had reduced such disruption. They conclude, therefore, that the barbiturate does not relieve severe experimental anxiety whereas morphine does. They also recall the wellknown fact that pentobarbital is not a powerful analgesic agent whereas morphine is. The inference is that the barbiturate is not very effective as an analgesic because it does not relieve the experimental anxiety associated with the pain that was employed. There are many hazards in such a syllogistic approach to this problem. The investigators are aware of this fact and have not drawn any sweeping conclusions.

Barbiturates in small dose do appear to relieve "spontaneous" anxiety (as opposed to the "contrived" anxiety of the experiments just referred to) and have a wide clinical acceptance and usefulness for this purpose. A 100 mg dose of pentobarbital sodium administered intravenously (41) to healthy young volunteers was found to lead usually to a brief period of happy drunkenness during which time inhibitions were relieved and highly charged areas spontaneously and incautiously brought into the conversation. For years such procedures have been utilized to relieve pathological anxiety in "narcoanalysis." In short, it is common experience that barbiturates are highly effective in relieving clinical anxiety.

While the use of post-narcotic addicts as subjects leads to interesting information concerning this special group, a great difficulty is that narcotics cannot be administered to them as unknowns and their reaction to opiates as far as euphoria and dysphoria are concerned is opposite to that of normal individuals (399).

In 143 postoperative patients receiving intravenously 8 mg morphine per 70 kg

body weight, 27 obtained neither comfort nor pain relief, 7 had pain relief but no comfort, 9 had comfort but no pain relief and 100 obtained both comfort and pain relief from the medication. It appears to be possible and feasible to separate comfort and pain relief.

Somewhat comparable data were obtained following the intravenous injection of 60 or 90 mg pentobarbital sodium per 70 kg body weight. Here in 146 postoperative patients in pain, 5 had pain relief without comfort and 16 comfort without pain relief. Presumably the comfort is established by the reaction. These "comfort" data offer suggestive support. This support appears somewhat stronger when it is recalled that the state produced by the intravenous use of these doses of barbiturate is like that caused by frontal lobotomy or leukotomy. Keats and Beecher (357) suggested that a kind of pharmacological lobotomy is produced which may interfere with long circuiting of nerve impulses, association paths.

Several (95, 385, 615) have held the view that relief of suffering may result from interruption of activity in association paths which is part of a vicious cycle. Presumably irritants, both organic and psychic, activate long-circuiting afferent impulses which involve internuncial pools at fronto-thalamic levels. The hypothesis is that, when the wide-spreading impulses reach the cortex, various conditioned states are aroused; impulses spread to the motor cortex; the more widespread the long-circuiting is through association areas, the greater is the conditioning of the response. Frontal lobotomy physically interrupts the association pathways and stops the reverberations. It does not seem unreasonable to suppose that the reaction to pain requires the functioning of association paths, "long circuiting" of nerve impulses (357). It is difficult to explain in any other way how frontal lobotomy or barbiturate can relieve pain (and this they have been shown to do) other than by altering the reaction to pain sensation (see XII, F). *Comfort and pain relief can be separated by a barbiturate, by morphine, and by frontal lobotomy. In the presence of apparently persisting pain ("my pain is the same, but it doesn't hurt me now") comfort can be established. The pain apparatus functions, but the disturbing element can be blocked in these three ways; evidently the processing, the reaction, is the altered factor.*

Further support for the importance of the reaction can be found in the use of antitussive drugs which seem (261) to be principally effective in altering the patient's state of mind and not his cough frequency (chronic cough). This work also supports the view that pathological sources are essential for the appraisal of drugs designed to modify subjective responses arising there. While the effectiveness of antitussive agents is very slight in their effect on cough frequency (chronic cough), a suppressing trend seems to be present. This was not the case with experimental cough produced by the inhalation of ammonia gas or citric acid mist in the study referred to. On the other hand, Bickerman and Barach (73) appear to show a significant effect of antitussive agents on cough frequency in man. Evidently a considerable number (75%) of their subjects were eliminated if they did not show the desired tussive effect over a rather long time. It is apparent, however, that failure to show desired tussive effect was not the only reason subjects were eliminated from the Bickerman-Barach study. Bickerman

has said it was his impression that 3 out of 4 persons tested coughed in response to the citric acid aerosol. This also agrees with his statement (73) that a presumably typical sample (2 out of 10 subjects) failed to cough. This is in agreement with the reviewer's experience (261), *i.e.*, three quarters or more coughed on the 5% citric acid aerosol. Notwithstanding this high eligibility percentage, Bickerman and Barach excluded 75% (115 out of 153 subjects). They excluded two thirds of the eligible subjects. It is difficult to know what these selected data represent.

It is interesting that experimental cough produced by the intravenous injection of paraldehyde (although not a satisfactory technique for reasons mentioned, 261) is associated with pain and fear (the other techniques are not), and heroin was effective in reducing the number of paraldehyde induced coughs (261). This fits in with the picture presented above. *Study of cough shows that antitussive agents in patients with cough of pathological origin do not usually significantly reduce the number of coughs, but the patients think they cough less. They can sometimes differentiate, when tested with unknowns, between an "effective" antitussive, codeine, and a placebo. In such cases the reaction, not the cough frequency, is modified by the antitussive agent.*

Stronger support for the importance of the reaction aspect of suffering than that in the immediately foregoing two paragraphs can be found in the repeated demonstration of the importance of placebos in relieving subjective responses. Over the years this placebo effect has been shown (by others in 8 studies and by the reviewer's laboratory in 7 studies) to average 35% of subjects relieved (53). Since only some 75% of patients in severe pain can be satisfactorily relieved (397) by even large doses of morphine (15 mg per 70 kg body weight), this placebo effect amounts to about 50% of the "drug" effectiveness. The only effect the placebo can have is on the reaction to pain. Certainly it would be impossible to believe that 1 ml of 0.9% sodium chloride solution had any physical effect on the anatomical apparatus of pain. *Placebos, organically ineffective as they are, can only affect reaction.*

In the work just referred to, the average effectiveness of placebos was mentioned as 35%. In a study recently completed (55) and referred to above, it has been possible to show that the effectiveness of placebos is greater when stress (pain) is greater than when it is less. It was found that, when postoperative wound pain was at its greatest, a standard dose of morphine relieved 52% of a group of subjects in pain; a placebo relieved 40% of the same subjects, *i.e.*, 77% of those relieved by morphine. (Half of the population was given morphine first and half a placebo; at the second administration the order was reversed.) Later on, when the pain was much less in the same group of patients, the same dose of morphine relieved 89% and the placebo 26%. Cleghorn and his associates (see 55), in dealing with objective studies of the power of a placebo to fire the adrenals in anxiety states, reported that the effectiveness of a placebo increases, as measured by objective changes, with the degree of anxiety.

In these observations it appears that the greatest significance for the patient, whether pain or anxiety, is associated with the greatest placebo effect. *The in-*

creased effectiveness of placebos with increased stress can seemingly only be explained by the importance of the reaction, or processing, component of suffering.

Thus a considerable quantity of factual data has been presented here to support the 60-year old speculations of Marshall and of Strong as to the existence (and importance) of the reaction, or processing, component in suffering. In whichever way one looks at the problem of subjective responses, the reaction component looms larger in the stimulation-suffering-relief sequence than the original sensation. All of this leads to the practical conclusion that in treating subjective responses more attention might with profit be given to a search for therapy designed to alter reaction.

Irwin (343a), however, points out that ". . . studies with spinal cord reflexes, in both animals and man, show morphine to possess an unusually selective depressant action on pain reflexes. In addition, along the lines of our own studies in the rat, morphine appears to enhance supra-spinal inhibitory mechanisms on pain reflexes (tail-flick and skin-twitch). This must mean something. It is an electrophysiological fact that sensory impulses to the cortex can be damped by inhibitory mechanisms operating at a spinal cord level. If one is dealing with a spreading central excitatory state in the spinal cord or brain stem, initiated by a pathological pain focus, which tends to enhance the intensity of pain perceived—I fail to see why a spinal cord depressant such as morphine which selectively influences pain pathways (reflexes) should not reduce the pain by damping down the central excitatory state (which is facilitatory in nature) and even constricting its area of spread in the spinal cord. This would not only reduce the intensity of pain, but also may modify the quality of the pain perceived. We have the experimental evidence pointing to this mode of action of morphine, but investigators have failed to give it the emphasis which I feel it deserves. It should be apparent that a mechanism such as this, considering the doses of morphine used, would have least influence on sudden induced pain and most influence on chronic (pathological) pain. In this respect, the concept harmonizes with known clinical facts."

These remarks are interesting and pertinent to the discussion at hand and possibly describe in part *how* the reaction component is modified by analgesics. Irwin's view does not appear to be at variance with the thesis under discussion but rather relates to possible mechanism.

D. Cumulative central effects of pain summation and the psychic reaction component

It has been assumed that all neurones from the pain end organs enter a neurone pool in the dorsal horn of the spinal cord. Synaptic connections are made there with a network of internuncial neurones which maintain an excitatory state based upon impulses from the peripheral end organs (289, 634, 635).

Lewis (412) proposed an arrangement very like this in his "nocifensor" system, but he believed the skin is the controlling site of the excitatory state rather than the spinal cord and that these nocifensor nerves are capable of effecting changes in the skin without reference to the spinal cord, yet possibly are susceptible to influence from the central nervous system.

Walshe (617) objected to the postulation of special nerves to supply the nocifensor system. Livingston speaks of the wide spread of the pain process (see 132). (Even the anticipation of pain causes blood vessels to dilate.) He believes that a central process underlies the wide spreading consequences of pain or anticipation of pain and that this central process proceeds with increas-

ing momentum. He believes that if one can reduce the input of harmful impulses, the central process will get a chance to subside. Morrison and Spiegel (458) present evidence that, with pain accompanying proved organic visceral disease, there is an increase of skin potentials in the respective dermatomes, compared with the remainder of the body, by 10 mV or more.

It has been postulated that referred pain requires the existence of branching and interconnected sensory pathways (543). This arrangement leads to misinterpretation of the true origin of the pain sensations by the central nervous system and secondarily to the liberation of metabolites by the nerve endings where the pain is felt, and these give rise to secondary pain impulses which originate at the periphery.

If the stimulation of the pool is intense enough impulses will pass out over various primary pathways and give rise to secondary hyperalgesia. It has been shown experimentally that continuous stimulation from the wound area is not necessary for the production and maintenance of secondary hyperalgesia (289).

In Sherrington's classic studies (149), it was shown that stimulation of a few fibers of two afferent nerves, each inadequate to evoke a reflex, can together do so if the time interval is not great; the longer the interval the less the response. Summation occurs within the spinal cord. Other work showed that an excitatory state in the reflex centers was produced by a subliminal volley of impulses, made evident only when a second centripetal volley reveals that facilitation has occurred. There is no space to deal in this review with the fascinating phenomena of the central excitatory state. The matter is mentioned here since it is pertinent to several observations on pain reactions. Likewise there is no space to deal with the interesting phenomenon of central pain, variously called "spontaneous" pain or "thalamic" pain. This is doubtless related to a central excitatory state and depends probably on external stimuli to get it going and perhaps keep it going. [See Kendall (369) for a discussion of it and for references to original work of Head and Holmes and others; see also (615).]

Bishop (81) points out that pain is followed by slight adaptation, the less completely the stronger the stimulus (see also X, 17). Important is the cumulative central effect of pain summation. A pain intensity that can be readily borne for a short time becomes intolerable if long continued. This central factor of cumulative effect (Bishop says this is what Wolff refers to as "reaction" in contrast to discrimination; but this is open to question) "more than compensates for the slight adaptation shown by sense organs and becomes the factor of major importance in pathological states."

Causalgic pain, as Gerard (238) has put it, ". . . tends to increase in time and to spread in space. It has a devastating ability to leak around any kind of surgical block interposed in its path. The pain exhibits the tendency, seen in the course of evolution of the nervous system itself, of progressive centralization and cephalization of its site. Central pain is common only when pathologic change involves the grey matter proper. . . ."

Artificial synapses, "cross-talk," (238) can occur between fibers that have become oversensitive to the electrical fields of their neighbors. Such breakdown

of isolated conduction, so that sympathetic efferent impulses excite somatic afferents, has been used to explain causalgia. As Gerard (238) points out, this can hardly be the whole explanation or even the most important explanation, for surgical operations on the periphery, after such pain has persisted for a time, will not cure the pain. The disturbance which may have been initiated in the periphery has now moved into the central nervous system. This is an example of a persistent reaction.

Central reinforcement is probable in the increased pain with emotion (238). Peripheral factors, such as increased muscle tension, may also operate to increase the pain (673). Central reinforcement and irradiation are general occurrences. Spread of deep pain from one cooled finger to an adjacent *blocked* finger has to be central (673). Some (618) believe it is this central process that lobotomy affects. "Pain then becomes a sensation rather than a threat and the individual is no longer dominated by pain." (See also 670.)

Another type of evidence, supporting the view that causalgic type pain results from central overactivity maintained by peripheral stimulation, is that a single nerve block in the periphery will at times cure the pain permanently. Gerard (238) has summarized the evidence for (a) causalgic pain being continued by an overexcitatory state in the spinal cord and for an opposite view (b) that causalgia appears as a result of defective innervation rather than excesses. Reconciling evidence is provided.

When noxious impulses from injured tissue are blocked (procaine) from entering the central nervous system, hyperalgesia will be eliminated whether caused by nerve stimulation or skin injury (288). It is concluded that "the barrage of noxious impulses from the site of injury develops in the cord a central excitatory state," and that, when the flow of noxious impulses into the cord is interrupted, there is "a rapid discharge of the excitatory state." This latter statement might imply a termination of the abnormal state in the cord. This does not seem to be the case, for, when the procaine block has worn off, the hyperalgesia returns.

It is interesting to observe that pin pricking in the hyperalgesic area causes the area of hyperalgesia to recede. This is interpreted as causing an immediate but temporary discharge of a part of the central excitatory state (288).

Critchley (151) has written in detail on how to distinguish between psychogenic pain and organic pain. Since the evidence presented in this review indicates how little of suffering is attributable to the original sensation and how much to the reaction or psychic component, it seems unsafe to distinguish between pains according to various kinds of spontaneous origins. All pains are in some part psychogenic, *i.e.*, amplified by the psyche at least. It seems of little importance in suffering whether pains are induced peripherally or not. Even if all pains have a peripheral beginning, they are amplified or minimized by central modification.

Sides, quoted by Critchley (151) said, ". . . a sensation is not an intense idea, nor is an idea a weak sensation." This all seems much too neat. An idea can *produce* a sensation; a disgusting idea can evoke a sensation of nausea.

E. "Negative" support for the importance of the psychic reaction component

A central necessity in discussion of measurement of pain is to recognize the two principal components of the pain experience, perception (the original sensation) and reaction (the psychic processing of the original sensation). It is easy but hazardous to conclude that one deals with one of these components rather than the other when a mixture may be involved. Hardy *et al.* (285) say "The age-old linkage between perception of pain and reaction to it has filled the vast literature on the subject, especially that based on animal experiments, with irrelevancies and contradictions. It is this natural but unfortunate identification that makes it necessary to interpret with caution the great body of observation available from clinical sources and animal experimentation." The problem confronting this reviewer could scarcely have been better stated. It is ironic that these very authors have added so much to this problem by their demonstrably erroneous assumptions that they deal with a "pure culture" of perception when they refer to pain threshold determinations made by themselves on themselves. The pain threshold is not dependably elevated by narcotics in man but generally is in animals (XI, E, F, G). The lack of a dependable response of the pain threshold to analgesic agents in man (XI) leaves the reaction component of suffering as of principal importance in the relief of suffering by narcotics. The failure to alter pain threshold in man is evidence against narcotics acting on the peripheral pain apparatus, whether in man or in animals. It seems hardly likely that at such an elemental level man and animals would differ. Presumably, then, the threshold rise in animals is effected by central mechanisms, just as "must" be the case in man with pathological pain which is subdued, that is, the threshold is elevated, not only by narcotics but also by placebos.

There is no evidence for separate fibers or sense organs for itch, but there are, on the other hand, many "correspondences" among the members of the series, prick, itch, pain (81). It is highly probable that itch belongs to the pain modality rather than to the tactile. Itch, Bishop believes, results from the temporal summation of repeated mild pricks. Now if, as dermatologists claim, morphine does not relieve itch, then this might be construed as further evidence that morphine relieves pain by acting on the reaction component to pain rather than the original pain sensation. If its action were on the original sensation, seemingly morphine should relieve itch, if Bishop is correct.

The lack of constancy of the pain threshold (VIII) weakens the Hardy-Wolff thesis that they are measuring original sensation with their method divorced from reaction. Reasons were presented (VIII and IX) for believing that variations in the reaction component are responsible for the inconstancy of the pain threshold.

"It is a foregone conclusion that laboratory methods for algesimetry must be designed to prevent or ameliorate pain induced artificially" (Miller, 451). Since the reaction component in suffering is so great (see below), and since this has not usually been accurately contrived in the laboratory, perhaps Miller's conclusion had better be reconsidered, for there is much evidence that artificial pain in man has failed in its purpose as a testing ground for analgesic agents.

In fairness to Miller it must be pointed out that his review was written eight years before this one. It is chiefly during this period that the difficulties with the earlier data have become apparent. One can suppose, in general, that, where the the reaction component is small in the test situation, contrived symptoms are treacherous things to lean on, but that, where objective change, such as smooth muscle spasm, is concerned, one can deal more surely with it experimentally than one can with pain, unless, as sometimes happens, subjective factors are at the back of the muscle spasm.

In post-addicts the threshold-raising effects of analgesics are greatly reduced in comparison with their effects in normals, yet modest doses of morphine will relieve the clinical pain of post-addicts (21, 22). *If* the threshold in man is dependably elevated by analgesics and *if* such elevation is a measure of reduced original sensation, as Hardy, Wolff and Goodell believe, then the above can be construed as supporting the importance of the reaction component in suffering; for the modest doses of morphine in post-addicts have relieved pain without changing essentially the pain threshold level. By elimination one can suppose that the morphine affects the reaction component. Even so, the concept may seem a little shaky. The modest doses of morphine which relieve clinical pain in post-addicts presumably are too small to give much of a psychic change, at least less than usually required. Either the "reaction" process is more sensitive in the post-addict than are other psychic processes which are influenced by morphine, or the "reaction" process is something not akin to the psychic processes referred to.

"Those drugs which possess a marked psychic effect on the individual are the most potent as regards analgesia" (30). [Dihydrocodeine does not fit with this statement (262).] Batterman uses this explanation to account for the observed fact (see 21, 22) that, in addicts although morphine has lost its threshold-raising effects, even small doses still relieve clinical pain. (How then can one account for the effectiveness of dihydrocodeine with its scarcity of psychic effects?)

Haugen and Livingston (300), using the Hardy-Wolff-Goodell dolorimeter, have attacked the question of the pain threshold, to determine under what conditions it is constant. They do not believe that the threshold is a measure of perception, while tolerance is a measure of "reaction" (667). Haugen and Livingston aver that "reaction" is certainly a factor in interpretation of any sensory experience. The fact that many persons do agree better as to how much heat barely causes pain than they do as to how much heat they can stand is not a matter for surprise. The fact that distraction, suggestion, placebos apparently can all greatly modify the pain threshold, shows that it is highly subject to psychological factors.

F. Various other forms of reaction to stimulation

There are of course many kinds of reactions other than the psychic processing of the original stimulation just referred to. These reactions are nearly all of the automatic or reflex variety. Reactions, other than the psychic or processing reaction described in the foregoing sections, perhaps better called the *conse-*

quences of pain; they are directed chiefly to the end of escaping pain. They vary all the way from a spinal reflex, to a visit to the doctor, or the building of hospitals (4), or research activities in order that pain might be better treated or escaped. There are still other forms of reaction which do not fit into the three major categories, skeletal muscle reactions, autonomic responses or the psychic processing described above. An example is headache resulting from the electrical stimulation of a tooth (507).

1. Skeletal muscle reactions. a. General. Individual nerve fibers have wide ramifications and the conducting apparatus is of vast extent. Any stimulus of the body surface can set up impulses in a large number of different fibers. "A 'touch spot', a hair or a 'pain spot' is not innervated by one fiber but by several and these fibers supply other spots as well" (4). As Sherrington has shown, the spinal cord controls the immediate skeletal reactions to pain. Such flexion and withdrawal movements are not very precise. As afferent discharge is increased, activity in the spinal cord spreads widely and may continue as after-discharge when the original stimulation has stopped. The widely connected neurones provide for summation effects. Pain, the danger signal, leads to reactions to minimize it. Increased muscle tension, a wince of the outer canthus of the eye, the reflex withdrawal of a burned finger from a flame, a cry, motions of rejection, flight, escape, all of these are instances of skeletal muscle reactions to pain with the purpose of escaping from an unpleasant environment.

> "The immediate reactions to an urgent signal are managed by the spinal cord and the higher centres may be unable to control them, for we are dealing with a mechanism which must act automatically and at once, whatever the cerebral hemispheres may have planned for the general direction of behaviour. But clearly, the reactions to pain signals cannot proceed entirely at the spinal level. They must reach the cerebrum and enter into consciousness if the organism is to face the danger effectively, and they must retain their urgency and power of overriding less important reactions. We are dealing, however, with a mechanism for use in emergencies when widespread and violent action may be of more value than exact control and when more and more of the body may have to take part in avoiding the danger and bringing the signals to an end." Adrian (4).

Pain reactions involve a "three neurone arc," with at least one neurone in the grey matter. Great possibilities for spread of stimulus are opened up through internuncial neurones. This with summation can lead to extensive activity. "Thus an intense pain stimulus may come to dominate the whole executive apparatus of the cord" (4). In the brain the effects of pain are diffuse and generalized, not confined to definite channels and special centers in the brain as they are for signals of touch, hearing or sight.

b. Psychoneurotic individuals compared with normals. Numerous studies have indicated that the radiant heat pain thresholds are about the same in psychoneurotic as in normal subjects; but the motor reaction level is lower in the psychoneurotics than in the normals (126, 128, 129, 519). It was found that 22 women with the "menopausal syndrome" were comparable to psychoneurotics in the above comparisons and so also were a group of peptic ulcer patients (521).

c. Effects of lobotomy. Some interesting side lights thrown on the pain experience by lobotomy were discussed in XII, A and C. Further information provided

by lobotomy or leukotomy comes from the work of several investigators (132, 133, 442) where it was stated that the pain perception level for a given individual was about the same following lobotomy or leukotomy, yet the skeletal muscle reaction threshold was lowered following the operation. Evidence that this lowering is not a permanent effect is shown in the work of Chapman *et al.* (133) who carried out follow-up studies on reaction to heat stimuli in 13 patients out of the original 23, who had been subjected to lobotomy. This check-up one to two years after the first testing indicated that the decreased tolerance to heat found in the first studies probably represented only a temporary change after lobotomy. The motor reaction levels in response to heat stimuli had a tendency to return to the preoperative level during the second postoperative year. Presumably the damaged brain adjusts to the injury of lobotomy and some new mechanism restores the normal reaction. Improvement with the passage of time in psychomotor function following lobotomy has also been reported by others (385).

Leukotomy and morphine, these two dissimilar agents, both appear to have the power to distract. Perhaps therein lies their power to relieve pain. The fact that pain is relieved by frontal lobotomy without changing pain thresholds while actually lowering the motor reaction thresholds is evidence that *this* reaction is not important in pain relief (641). The psychic reaction as a component of the pain experience is modified by frontal lobotomy advantageously, however, even though emotionality may be greater following frontal lobotomy than it was before. This is evidence that the reaction of easily triggered emotions, such as quick anger and impatience, are not the important psychic reactions, affected by frontal lobotomy, as far as pain relief goes. The meaning of the pain seems to be the changed psychic reaction of importance.

It is believed that frontal lobotomy "does not relieve pain, but rather the disabling reaction to pain, the fear of pain" (223). A similar action has been postulated for morphine (318, 319, 384, 439, 440, 442, 443, 444). (See also X, 13.)

2. Reactions effected by the autonomic nervous system. a. The skin resistance, galvanic skin response. A painful stimulus is followed by a change in skin resistance. (See VII, D and X, D, E, F.) The physical factors involved in skin resistance are: the electrical resistance of the skin and action potentials from the sweat glands. These observations were made in 1911 by Wells and Forbes. More recently Deane and Forbes have found evidence that the "basket cells" are involved (218a). Evidence was presented to indicate that the galvanic skin reaction could not of itself soundly be used as a determinant of pain threshold, for with the passage of time and increasing use of the determination the galvanic skin response diminished. It was postulated that the galvanic skin response was a fair measure of the threat content of the situation (60, 227) and that as this lessened so also the changes in skin resistance lessened. Adaptation was rapid. In short, the skin resistance varies independently of the pain threshold (197, 227).

In studies of the galvanic skin response as a reaction to the pain of thermal stimulation, it was found (670) that the amount of heat necessary to evoke this "alarm reaction" was widely variable from day to day in the same individual and from individual to individual (3 persons). It was also reported that the effect

of alcohol on the galvanic skin response outlasts its effect on the pain threshold.

One may question whether the galvanic skin response in response to radiant heat stimulation measures an important reaction effect of analgesic agents, since Isbell (unpublished work referred to by Wikler (636)) found that pentobarbital sodium in modest doses would affect it as much as powerful narcotics. Isbell's heat stimuli were below the pain level, but Wikler (636) infers that the finding would apply if the stimulation had been painful. Further evidence of the unrelatedness of pain relief and the galvanic skin response can be seen in the finding that lobotomy relieves pathological pain, yet a pain stimulus produces, after lobotomy, a greater galvanic skin response than before the operation was performed (442). It was also found that the amplitude of the galvanic skin response decreased when suprathreshold pain intensities were used (60). Wikler (641) mentions that it has been shown that analgesics reduce the skin resistance changes in response to pain and so also do barbiturates in small dose and atropine.

b. Other autonomic reactions, physical changes. A wide variety of reactions to pain, chiefly mediated through the autonomic nervous system, affect the circulation resulting in tachycardia (60, 146, 248, 666), cardiac arrhythmias (673), electrocardiographic changes (as a secondary phenomenon). (Severe muscle ischaemia pain will affect the heart; T-waves may be higher or lower, a positive wave may become negative or a negative one positive. A normal electrocardiogram may become abnormal, or an abnormal one normal in response to severe pain. These findings were made in individuals with heart disease in which the electrocardiogram is known to be more susceptible to change than normal). (248), elevation of blood pressure (243, 673), fall of blood pressure, syncope, prostration, pallor, flushing, decreased volume of legs, spleen, kidney (243), diminution in renal function, apparently through vasoconstriction (655). Other evidence of autonomic effects are seen in the "alarm" reaction (289) with spatial summation (666), sweating (124, 528), dilatation of pupils, lachrymation (673), nausea, cardiospasm, increased peristalsis, disturbance of gastric and colonic function (673), and increased skeletal muscle tension (as a secondary phenomenon) (289, 414).

c. Other autonomic reactions, mental changes, emotions. It is evident that the mental activity that leads to emotional reactions as a consequence of the original sensation must be part of the psychic reaction process. Emotions generated in this way can influence the situation to the point of increasing or of eliminating suffering and thus fulfill the criteria set down to characterize the psychic reaction component (for details see X, 1, 2, 3, 13, 20). The emotions of principal importance here are anxiety, fear, terror, rage and sometimes pleasure (60). For example, the pain experienced is related not only to the intensity of the noxious stimulus, but also to the threat value of the stimulus and ". . . patients with pathological anxiety respond at lower levels of stimulus intensity, with greater disturbance, and for a longer time than do relatively anxiety free control subjects" (60). The greater the anxiety of the patients studied, the greater is the over-reaction to painful stimuli (227, 439, 440, 582).

Anticipation of pain appears to be an important part of the pain experience.

Hill *et al.* (319) appear to equate anticipation of pain with one of the reactions to pain. They suggest that one of the primary actions of potent analgesic agents is reduction of anticipation of pain. A stimulus which precedes an unpleasant stimulus soon acquires the power to produce anticipatory fear reactions (202, 436). The conditioned unpleasant stimulus may produce more disturbances in behavior than the unconditioned unpleasant stimulus. Frontal lobotomy greatly reduces motor responses which are anticipatory of pain in comparison with the effect of frontal lobotomy on direct responses to painful stimuli (132, 442). (See also XII, F, 1, c.)

Evidence has been obtained (318) that morphine reduces anticipation of pain. It was shown that experimental conditions which lead to the enhancement of anxiety, that is, fear of pain, also lead to over-estimation of the intensity of painful stimuli. Morphine reduced or abolished this error but did not significantly affect the subjects' ability to estimate intensity of painful stimuli under experimental conditions when anxiety was largely relieved. This work is interesting for another reason: it provides objective evidence of the influence of both anxiety and morphine on one aspect of the subjective experience of pain.

Another study (319) was designed to test this same matter without depending on the patient's report but rather on overt performance. The underlying hypothesis is that efficiency of performance, as indicated by reaction time to visual stimuli, is dependent on motivation. With optimal motivation, minimum reaction times are expected, where motivation is low, longer reaction times would obtain. If motivation is excessive, performance will be disrupted, with long or variable reaction times. The subjects were former opiate addicts. The shortest reaction times were found in the non-morphinized subjects, when they were not penalized for long reaction times. Morphine alone significantly increased reaction times. Electric shock penalties significantly increased reaction times in non-morphinized subjects, but penalties in morphinized subjects did not increase the reaction times above that of morphine alone. The conclusion was reached that "morphine reduces the disruptive effects on performance which are associated with anxiety produced by anticipation of pain."

Kornetsky (384) repeated the earlier studies (318, 319) using a radiant heat stimulus instead of electrical as the earlier group had used. Kornetsky also wished to see if a reduction of the subject's anticipatory anxiety by a reassuring attitude on the part of the experimenter could be observed and determined by specific measures of anticipation. He found that morphine is most effective in raising the differential pain threshold when anxiety is present. When anxiety is relieved morphine does not significantly raise the differential pain threshold. Morphine reduces the anticipatory responses to pain when anxiety is present. He suggests that morphine may only be effective as an analgesic agent when anxiety is present. These studies are supported by work in animals (315a).

Hill *et al.* (316) set out to determine whether barbiturates have an effect like morphine in relieving anxiety associated with anticipation of pain. Apparently, as judged by their particular experimental set-up, they do not. It should perhaps be emphasized (these authors mention it but do not emphasize it) that the sub-

jects used in this study were postaddicts to narcotics and probably in many cases to barbiturates as well. How this would affect the results is not certain. In any case it is difficult to reconcile the failure of pentobarbital to relieve anxiety in this experimental study with (a) the bland, often silly state of recently anxious patients, facing an operation, who have been premedicated with a small dose of pentobarbital sodium (0.1 g, intramuscularly), (b) the euphoretic qualities of pentobarbital (399), and (c) the silly, somewhat drunken state and incautious discussion of highly charged subjects who got 0.1 g pentobarbital intravenously (41). But most of all it is difficult to reconcile this failure of a barbiturate to relieve anxiety in this experimental work with the observation of Beecher (38) in World War II, amply confirmed by others, that a manic, wounded soldier screaming with pain could be quieted at once with a very small intravenous dose of a barbiturate (0.2 g amobarbital sodium). These observations made during combat were not an adequately controlled scientific experiment; possibly they represent nothing more than a placebo effect in a highly charged atmosphere. As Beecher (55) has shown, placebos appear to be more effective where stress is greater than they are when it is less. On the other hand, the findings of Keats and Beecher (357), in a controlled study, that barbiturates have power to relieve pain significantly above a placebo is evidence that more than a placebo effect may have been involved in the battle injuries just mentioned. The question merits further study.

The following work may not basically be in conflict with the foregoing, however, there is some suggestion that this is the case. With a pain of given intensity ("dol" pain technique) the galvanic skin response was studied (227) under several conditions of skin temperature (cold, neutral, hot). Peak reactions occurred near the comfort zone with diminishing responses as the extremes were approached. Perhaps this is an example of the usefulness of counter-irritation in diminishing the reaction to pain. Furer and Hardy (227) make the following statement.

> "It is clear that the addition of the strong environmental threat to the threat from the painful stimuli had the effect of reducing rather than enhancing the threat of the pains. It is possible therefore that wherever certain types of stressful situations may summate in so far as their threat content is concerned, there are others whose effects cancel. In this instance the strong sensations of heat or cold cancelled the effects of the pains in causing a generalized sympathetic reaction. The broad implication of this finding is that intensely preoccupying situations, even though stressful in themselves, may reduce or eliminate the effects of reactions to another anxiety-producing situation. It is possible that a principal characteristic of the cancelling type of stress is intense sensory stimulation."

Hardy *et al.* (279) have presented the view that "the adequate stimulus for pain is tissue injury." Against this view is the observation of Beecher (38) that the majority (75%) of men severely wounded in battle (who were clear mentally, not in shock, and who had had no morphine for hours and none at all in many cases) did not have enough pain to want or need anything to relieve it. In civilians having far less tissue trauma, the figures were reversed (57). As Beecher points out, the factor determining the appearance (that is, even the presence or absence

of pain in many cases) of pain seems to be the significance of the wound not the tissue trauma. To the wounded soldier who had been under unremitting shell fire for weeks, his wound was a good thing (it meant the end of the war for him) and was associated with far less pain than was the case of the civilians who considered their need for surgery a disaster. Also pertinent are the following observations (57, 129, 315a, 316, 318, 319, 439, 440, 442, 443, 444) that anxiety increases pain and relief of anxiety is associated with relief of pain. Beecher (57) presented evidence that the emotional meaning, the significance of the wound, was of much greater importance than the wound itself in determining the presence and degree of pain the victim would experience.[9]

Caster (123) has taken advantage of the rhythmic nature of functional activities of the autonomic nervous system to study the response to emotion. His hypothesis is that emotions are "chaotic disturbances of visceral toxicity" and as such are bound to disturb the normal rhythms under the control of the autonomic nervous system. To this end he has studied particularly skin resistance, the pulse and the respiration.

d. Substitution symptoms and signs as reactions to pain. These may be mediated in large part through the autonomic nervous system and accordingly are placed in this section. To be included in this category as *symptoms* are burning, numbness, pressure sense, tingling, prickling and other forms of paresthesia. Substitution *signs* are aerophagia, eructation, coughing and sneezing. Possibly hiccoughs, yawning and hysterical choking should be included, but the role of the autonomic nervous system in their production is not so clear as in the other cases (417, 535).

3. Miscellaneous reactions. Other kinds of reaction to the original sensation are the alteration of judgment of pain intensity (see 318) and disruption of performance (319).

It was found (278) following a study in 7 patients with hyperalgesic areas of referred pain, that the pain threshold values were normal in hyperalgesic areas and did not differ from the values found when radiant heat was applied to the corresponding area on the opposite side of the body. Thus the hyperalgesia is not to be explained by locally lowered perception, but rather to "change in the reaction to the afferent impulses initiated in the periphery at the usual threshold."

4. Reaction as influenced by hypnotism. There are two interesting facets to the relationship of drugs to hypnotism (the term hypnotism is used instead of hypnosis to avoid confusion with the effects of ordinary sleep-producing drugs). There are drugs which facilitate the onset and increase the depth of hypnotism on the one hand and on the other there are drugs whose effects can be altered by

[9] Dubos (172) summarized a long series of impressive data to demonstrate that the 19th century doctrine of Pasteur and Koch as to the specificity of etiology of disease is no longer tenable in any inclusive sense. The reviewer pointed out to Dr. Dubos that the newer doctrine of non-specificity of etiology of disease could be extended to a symptom of disease, pain, where the pain experienced bears great relationship to the significance of the wound but little or none to the extent of the wound. Dubos (173) replied that it was his "conviction that 'specificity', while an essential concept in the formulation of scientific medicine during the 19th century, often tends to prevent us from gaining a comprehensive view of the problem of disease."

hypnotic suggestion. It seems probable that both phenomena are closely related, indeed, operate through, the reaction or processing component which is under discussion. Hypnotism is not sleep (325). The hypnotized subject has an intense contact with the operator, whereas in sleep contact with the outside world is lost.

In 1943 Kubie (see also Kubie and Margolin, 389) reviewed the drugs used to produce hypnagogic states and thus permit the uncovering of subconscious aspects of personality, subconscious thought processes, recovery of buried memories and forgotten experiences. A relationship exists between hypnotism induced by "verbal means and the twilight states of consciousness" produced by the barbiturates and scopolamine (257, 258). Subjects difficult to hypnotize can be made more susceptible by the agents just mentioned (653, 654). Specifically, it was found that the influence of alcohol on suggestion, as measured by the postural sway technique, was slight (342). Scopolamine heightened suggestibility in 8 normal subjects studied (25). (See also 39.) Nitrous oxide inhalation produces a state of suggestibility without loss of consciousness (645).

There is evidence that hypnotism can influence drug effects. Alcohol, chloral hydrate, morphine, and barbital were found to have stronger effects when used in conjunction with hypnotism (581, see 377). It is also claimed, however, that hypnotism can counteract the effects of barbital, chloral hydrate, and alcohol. Mental performance tests on 2 normal subjects when they were intoxicated and then when they were hypnotized showed scores much lower than normal under the alcohol, but the scores returned to normal as a result of hypnotism (488). The same investigators gave normally intoxicating doses of alcohol while their subjects were hypnotized. They were told they were drinking water. No signs of intoxication became evident and they performed at their normal levels. Otherwise the effects of alcohol, chloral hydrate, morphine, and barbiturates were all much stronger when used in conjunction with hypnotism.

It is well known that the British surgeon Esdaile carried out many surgical operations in India under hypnotism. This was in 1845, before the clinical establishment of anesthesia had become general (*cf.* "painless childbirth" of today, 499). Abolition of pain or block of it in this way must be attributed to the reaction component. Hollander (325, p. 598) gives a picturesque and fine account of a very early operation under hypnotism. The pain apparatus was unimpaired. The reference given provides extensive documentation of the successful use of hypnotism for "painless" surgery in many countries.

Hollander advances the idea that hypnotism is not all suggestion, for analgesia can be produced by physical means without the patient knowing what is expected of him. It is true in hypnotism that "suggestions operate as they do at no other time, and that through them functions are affected which ordinarily elude the action of the waking will" (*cf.* the calm acceptance of surgery under hypnotism without pulse rate change, *etc.*).

Hollander believes hypnotism is largely a condition of profound abstraction or absentmindedness, perhaps dissociation, akin to reverie or deep meditation, so the individual does not notice his sensations, and the external world is obliterated (except the operator). This is similar to the ecstasy sometimes produced by

work: Marini while writing "Adore" did not notice a serious burn of his foot (325) (*cf.* the effects of this emotion with that of anger in fighting when there is no pain). Hollander believes the mystics of the Middle Ages possessed the gift of self-hypnosis.

A gas mask without anesthetic can be a placebo (325): teeth are painlessly pulled. Hypnotism can be aided by the smell of chloroform used in surgery (325, pp. 604, 605). Beecher (53) has summarized his own and the data of others to indicate the profound effectiveness of placebos, a form of suggestion.

The sick are said to be more suggestible than normal individuals (325); they are more readily hypnotized. If this is so then placebos would be expected to be more effective in the ill than in others, and perhaps the degree of illness (stress) would also be a factor (55). Then there is hysterical anesthesia which is pertinent to the present considerations.

Studies of pain in normal subjects, awake and hypnotized, showed that the wholly voluntary (verbal report) or partially voluntary (facial grimace, variability of respiration) responses were much more reduced by hypnotism than were the non-voluntary responses to pain (pulse changes, galvanic skin reaction) (532). These findings were interpreted (257, 258) as in line with the hypothesis that hypnotic suggestion operates on the volitional level; but, as pointed out, the fact that both pulse and galvanic skin response (179) show definite effects points to a deeper lying mechanism than the volitional. Sears (532) carried out additional experiments in which the subjects in a normal waking condition were instructed to repress or conceal, insofar as this was possible, all reactions to the painful stimuli used. There was no remote resemblance between these data and those obtained under hypnotism. Thus the "volitional" hypothesis is of itself not adequate to explain the phenomena of hypnotism. Others (169) report that hypnotically induced anesthesia is capable of reducing the vasoconstrictor response to painful stimuli to about the same extent as reported (532).

Brown and Vogel (106) alone of all investigators offer conflicting data. They base their observations on studies, in man, of blood pressure, pulse rate, skin potential, respiratory changes, and movements of the hands. Sharp pain was produced by stabs of a 4 mm spring lancet. Continuous pain was produced by a thumb tack held down with weighted leather strap. Suggestion and hypnosis were compared. They report failure to get dependable quantitative physiological reactions to pain. They were not able to confirm Sears' and Dynes' observations of the effects of hypnotism on physiological variables. Gorton (257, 258) finds much to criticize in the study of Brown and Vogel, for example, the statistical handling of the data was inadequate.

Light hypnotism raised the radiant heat pain threshold 40%, while waking suggestion in the form of placebos raised the pain threshold some 30% (665).

Some apparently were able by suggesting an infantile state ("You are five months old") to elicit dorsiflexion of the great toe on plantar stimulation (239). The authors say, "Unlike other physiologic changes brought about in hypnosis these were not elicited by direct suggestion nor were they produced by the hypnotic state itself." They were the result of chronological suggestions. This

"functional ablation of certain cortical fields" as a result of age-regression with profound neurophysiologic changes will provide remarkable evidence, if confirmed, that hypnotic suggestion in suitable individuals can bring about "psychobiologic" changes of immense importance in the total organism.

Hypnotism reduces the reaction to painful stimuli whether facial flinch or galvanic skin response (532). This latter point indicates that hypnotism can modify reactions that are effected through the autonomic nervous system as well as through the central nervous system.

This reviewer is obliged to conclude, as Hollander (325) did, perhaps overelegantly: "The fundamental process by which mind influences mind, and the mind influences bodily states and functions, is still wrapped in mystery." But, it might be added, progress in understanding has been made, and it is evident from the material in this section on reaction that the psychic reaction to external stimuli, whether physical or mental, has far reaching effects on human behavior.

5. Reaction as influenced by analgesics. The psychic reaction component as an important site for drug action has been discussed in detail by Beecher (54). The use of drugs to aid in establishing the existence and importance of the psychic reaction component has been dealt with extensively above (XII, A to E). As pointed out all pain has been assumed to consist of the original sensation and the psychic reaction to it. This applies to experimentally contrived pain as well as to pain of pathological origin. It has already been made evident in the sections referred to that there are wide differences in pain from the two origins. Factual material and other reasons have been presented for believing that the two types of pain differ in the psychic reaction component, in its character, intensity, magnitude and significance. The influence of analgesics on the reaction component appears to be of paramount importance in the relief of pain. This is the inescapable conclusion derived from the material of this review. There is no need to repeat here the documentation for these ideas; it is important to refer to them, however, in view of the heading of this section where additional material must be included.

The importance of the reaction component in the relief of pain by analgesic agents has been emphasized by others (124). In discussion of Cattell's views, Gold concurs and says he believes that change in the psychic reaction to pain is the essential, the primary, part of analgesic action.

Hardy *et al.* (285) recall that, when morphine sulfate is administered during experimental pain, pain continues to be perceived. One can ask, is it at the original level? They seem to assume so, but on what evidence is not clear. The "characteristic fight-flight-anxiety reaction pattern of pain no longer obtains. In other words, perception has been dissociated from reaction." There may be something of a contradiction here: Perception persists, but the reaction is the factor altered by morphine, yet at the same time they insist that morphine produces elevation of the pain threshold, yet change of pain threshold is taken as a measure of "pure" perception. They argue that morphine dissociates reaction from perception; the former disappears while perception persists; yet on plenty of other occasions they argue that morphine elevates the pain threshold which

is according to them a measure of perception. It seems highly probable that insofar as their threshold data contain a reaction component this reaction component would be diminished by the morphine and in such circumstance the threshold would rise after morphine. In actual practice other factors apparently often obscure this in man, when it occurs. (See VIII, IX, X.) If morphine does indeed produce a threshold elevation in man it does so probably only because the threshold as they elicit it is not pure but is dependent on both original sensation and reaction components. The first sentence in this paragraph points to a difference between experimentally contrived and pathological pain. In the former, when morphine was administered during the pain, it was, they reported, ineffective. This is certainly unlike the clinical situation where morphine is nearly always administered *during* pain and is almost invariably effective.

They (283) report further, "when the painful period [experimental pain] immediately preceded the injection of morphine (15 mg) or codeine (120 mg) the analgesic effect of the agent was almost wiped out. If the agent were given at the beginning of the period of pain 30% of normal analgesia was observed. If the beginning of the pain period were delayed until 40 minutes after the injection, 65% of normal analgesia was realized. Delaying the onset of pain until the maximum effect of the drug had been reached showed that pain then caused little change in the time action curve." But, as mentioned, this does not agree with clinical experience: analgesics given in the presence of well established pain are promptly effective.

Beecher (38) showed in a wounded soldier (this observation was widely confirmed by others in the battle area) that a small dose of a barbiturate stopped his writhing in "pain" and produced a light sleep. Here is the use of a sedative to modify several types of reaction to pain. (See also 39, 298.)

The effect of nitrous oxide, in 10 to 40% concentrations in oxygen, on pain threshold has been studied in man and judged by electric shocks to tooth pulp (560). Psychomotor activity was studied before and during the nitrous oxide analgesia. [Unfortunately the investigators used the inaccurate voltage as the parameter of stimulation (see 317).] They concluded that "it appears likely" the analgesic action reported is secondary to a diminution in psychomotor activity. This brief report is interesting in that it provides objective evidence (change in psychomotor response) of an influence on the reaction component by an analgesic agent, if one is not reading too much into this meager account.

The Harvard group have for some years also been interested in determining the effects of analgesic agents upon the reaction factors as judged by psychomotor performance (101, 254, 261, 262, 607).

XIII. CONCLUSIONS

This review covers 106 years of experimental work. Hardly an item has been mentioned for which there have not been opposing data to be considered. This fact has required a rather formidable length of presentation of data. Every effort has been made to give opposing views fairly. But where it is possible to do so, conclusions must be drawn if progress is to be made. The reviewer has set

down the conclusions he believes are warranted by the data, but references to the text and, in the text, numerous references to original sources are given, so that the reader can consult the basis for the conclusions stated and arrive at better ones if he can.

1) Pain cannot be satisfactorily defined, except as every man defines it introspectively for himself (II).

2) Pain sensations and pain perceptions are identical. Neither represents the "original sensation" alone but represents also an indefinite amount of psychic processing or reaction component (IX).

3) No convincing demonstration has yet been given that the pain threshold is a constant from man to man, or from one time to another in a given man (VIII).

4) More than a score of factors are said to produce variations in the pain threshold. Not a single experimental study has controlled even the majority of these factors. Conclusions concerning pain threshold must therefore be tentative (X).

5) "Experimental" pain and "pathological" pain are both composed of "original sensation" and the psychic processing of the original sensation (XII, B). The results of this processing are synonymous with the psychic reaction component (XII). The two components have not yet been satisfactorily separated experimentally (XII, B). Pain from the two origins differs greatly in the quantitative representation of the two components (XII, B). It is essential that these differences be taken into account when scientific study of pain or pain relief is undertaken.

6) The experimental pain techniques at present generally employed in man, while useful for some purposes, are probably useless for the appraisal of the analgesic agents (XI, D, E, F). The same techniques in animals have definite usefulness with the powerful narcotics (XI, G), but none apparently with the acetylsalicylic acid class of compounds (XI, F).

7) Assay of analgesic power can be carried on with less than a 10% error when pathological pain is employed in man provided one works in the steep part of the dose response curve (V, B, 2, a, 3).

8) Techniques for the appraisal of side action liability in sick individuals have not yet been satisfactorily developed and established (V, B, 2, g).

9) No dependable relationship has been established between the action of analgesic agents and the experimental pain threshold in man (XI). The record is better for animals but still far from perfect (XI, G). Uncritical acceptance of the view that a dependable relationship exists in man has done much to confuse and mislead work on pain.

10) Analgesic agents appear to exert their principal, if not entire, effect on the "reaction component" rather than on the "original sensation" (XII). This is perhaps at once the most striking and most surprising concept to come out of this long study. If this view can be further substantiated and if it applies also to other subjective responses as well as to pain, and this appears to be the case, then acceptance of this concept will require a wide shift in therapeutic planning. Heretofore the goal has been to dull the "original sensation." Strong evidence

has been presented to direct future therapeutic research to modification of the psychic reaction to the original sensation. Here is a promising area for further experimental attack.

11) Quantitative work with pain is possible and rewarding. Experience in this area has already served as a prototype to guide work with other subjective responses. Quantitative study of the psychological effects of drugs is an urgent need; such work is properly a part of pharmacology. The possibility of accurate quantitative work in this field has been demonstrated; but even so, accomplishments to date constitute no more than a beginning in what promises to be a great development in pharmacology. Successful pursuit of studies in this field is basic to the sound growth of the behavioral sciences.

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