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TOWARD A THEORY OF PAIN:

RELIEF OF CHRONIC PAIN BY PREFRONTAL LEUCOTOMY, OPIATES, PLACEBOS, AND HYPNOSIS

THEODORE XENOPHON BARBER[1]
Department of Social Relations, Harvard University

The response to a nociceptive stimulus normally includes at least four components: "the sensation of pain"; discomfort; withdrawal movements; and *some* measurable physiological alteration, e.g., a transient or prolonged increase or decrease in blood pressure (Nafe & Wagoner, 1938; Goetzl, Bien, & Lu, 1951). This paper is concerned with the neurological correlates of this total response—hereafter termed *the pain response*—and how this total response or some components of this response can be mitigated or eliminated by prefrontal leucotomy, opiates, placebos, and hypnosis.

THE NEUROPHYSIOLOGICAL CORRELATES OF THE PAIN RESPONSE

Free Nerve Endings: The So-Called "Pain Receptors"

It has generally been assumed that the free nerve endings, which are found widely scattered near the cutaneous and visceral surfaces, are the *specific* receptors for noxious stimuli. However, Sinclair, Weddell, and Zander (1952) have shown that *S*s can discriminate cold, heat, touch, and prick just as well from the ear pinna, which contains only bare nerve endings and a basketlike network around the hair follicles, as they can from the skin of the forearm, which contains all of the encapsulated endings which have been described. Lele, Weddell, and Williams (1954) have demonstrated that the free nerve endings in the skin, when suitably stimulated, "give rise to a wide range of sensory experience which includes reports of 'cold,' 'touch,' 'warm,' 'prick,' 'itch,' and 'sharp pain.' " Lele and Weddell (1956) have confirmed earlier findings (e.g., Nafe & Wagoner, 1936) that *S*s report not only pain but also touch, warmth, and cold when appropriate stimuli are applied to the center of the cornea which contains only free endings. These and other investigations recently reviewed by Weddell (1955) and Sinclair (1955) indicate that a wide variety of sensory experiences can be evoked by suitable stimulation of the free nerve terminals and that theories of cutaneous sensibility postulating specific receptors for each sense modality are open to serious objection at the present time.[2]

Peripheral Conduction

A series of earlier investigations, reviewed by Bonica (1953, pp. 29–

[1] Postdoctoral research fellow, National Institute of Mental Health, Public Health Service. It is a pleasure to thank E. G. Boring, Asenath Petrie, H. K. Beecher, and D. R. Evans for the many hours they spent critically reading this manuscript. Although their valuable advice and suggestions led to the correction of many errors, responsibility for the remaining faults and the opinions expressed remain with the writer. At present the writer is a research associate at the Worcester Foundation for Experimental Biology and Medfield (Massachusetts) State Hospital.

[2] The possibility remains that the term *free nerve endings* does not refer to homogeneous units. If future investigations demonstrate specific biochemical differences between these endings, the question of specific receptors for the various sense modalities may require further investigations at the molecular level.

30), had apparently shown (*a*) that asphyxia or pressure applied to a peripheral nerve blocked the large, myelinated, fast-conducting A fibers first and abolished touch before pain and (*b*) that cocaine blocked the small, unmyelinated, slow-conducting C fibers first and abolished pain before touch. This appeared to be satisfactory evidence that touch is correlated with conduction in the larger A fibers and that pain is correlated with conduction in the small C fibers.[8] Other data, however, indicate that noxious stimuli applied to the cutaneous surface activate many, if not all, of the fiber types present in the cutaneous nerves, viz., the smaller A fibers and the C fibers. Since the large A fibers are present only in the muscle branches of the nerves and the Group B fibers consist of sympathetic preganglionic axones (Lloyd, 1955; Ruch, 1955, p. 334), they cannot be directly activated by cutaneous stimuli. Heinbecker, Bishop, and O'Leary (1933) demonstrated with a human subject that electric shock applied to an exposed nerve in such a manner as to stimulate the A-delta fibers consistently evoked a pain response. Zotterman (1939) reported that a burning stimulus applied to the skin of cat evoked a spike composition that included both the A-delta and C fibers. Brookhart, Livingston, and Haugen (1953) demonstrated that stimulation of the tooth pulp (which normally evokes a pain response) yields conduction characteristics of the A gamma-delta fibers. After reviewing these and other investigations attempting to relate the modalities of sensation to conduction in specific fibers, Livingston (1943), Bonica (1953), Sinclair (1955), and Schiller (1956) agree with Gasser (1943, p. 59) that "the fibers belonging to different modalities must be widely distributed throughout the various fiber sizes, and that there seems to be little possibility of associating any one sensation with an elevation in the electroneurogram."

If all cutaneous stimuli activate "fibers widely distributed throughout the various fiber sizes," what determines the differential response to each stimulus? To account for this differential response, investigators in this area (Bishop, 1946; Weddell, 1955; Sinclair, 1955) hypothesize that each cutaneous stimulus sets off a pattern of nerve impulses which differs from the pattern set off by other stimuli in that the *relative* number of activated fibers of various sizes differ, and the relatively different sizes carry impulses differing in energy value, frequency, and duration. A light touch, for example, preferentially activates the larger fibers. However, this does *not* mean that these large fibers are specific to light

[8] At the present time, extreme caution is necessary in drawing conclusions from the earlier experiments on reversible nerve blocks produced by asphyxia, compression, cocaine, etc. (Jones: 1956, 1958; Schiller, 1956). In a series of carefully controlled studies of nerve blocks produced by procaine, compression, and cooling, Sinclair and Hinshaw (Sinclair, 1955) have demonstrated that it is possible to obtain almost any order of sensory loss by using different *S*s, by varying the site stimulated, and by altering the nature of the stimulus.

The question of "double pain" and its relation to conduction in A-delta and C fibers has also been opened for further inquiry. "Double pain" may be due to inadequate control of the stimulus at the receptor level: Jones (1956) demonstrated that (physiologically normal) *S*s do *not* report double pain *if the stimulus is prevented from stimulating the same receptors more than once.* Sinclair (1955, p. 594) has also concluded from his own work and from earlier investigations in this area that "the question of second pain cannot be regarded as settled and the idea of two sets of pain fibres rests upon work which is not immune to criticism of the experimental findings as well as the interpretations placed upon them."

touch stimuli. The larger the fiber the lower its threshold. The slight disturbance caused by light touch, therefore, activates the largest fibers with the lowest threshold *more readily* than the smaller fibers with higher thresholds. Similarly, nociceptive stimuli applied to the cutaneous surface may more readily activate fibers in the C range, but this does not mean that these stimuli do not also activate other cutaneous fibers and it also does not mean that other stimuli cannot activate the C fibers.

Conduction in the Spinal Cord

Peripheral nerve fibers, which are both myelinated and unmyelinated and which may belong to either Class A or C, travel along the cranial, spinal, or sympathetic nerves to posterior root ganglia where they synapse with second order neurons. The generally accepted view is that noxious stimuli applied to the viscera and to subcutaneous and cutaneous structures activate those fibers in the spinal cord which cross through the anterior white commissure to the opposite lateral funiculus where they ascend cephalad, forming the lateral spinothalamic tract. However, this is by no means the complete story. True enough, in many cases, cutting the lateral spinothalamic tract prevents a response to many nociceptive stimuli applied to the contralateral side. However, in some cases, this loss is temporary; normal pain responsiveness may return after an intervening period (Ranson, 1943, p. 111). Also, this operation (anterolateral cordotomy) does not abolish pain discrimination while leaving temperature, touch, and pressure discrimination intact. As Schiller (1956, p. 208) points out, "One modality or two are never either completely spared or abolished to the absolute exclusion of the others . . . parts denervated by anterolateral cordotomy are reported as feeling 'numb,' discrimination of two points and texture of materials is diminished, and, in addition, there are thermanesthesia and analgesia." In addition, White and Sweet (1955, p. 45) demonstrated that a current at 100 or more volts applied to the "analgesic side" invariably produced a report of severe pain in all (40) patients examined. King (1957) confirmed this finding and, in addition, found that (after anterolateral cordotomy) the *maximum* elevation of the pain threshold on the "analgesic side" did not exceed 40 to 50%. Since, in the great majority of cases, the pain threshold elevation was much less than this maximum, and, in some cases, was not significantly different from the pain threshold on the normal side, King concluded that "a polysynaptic relay pathway for painful stimuli in man, aside from the spinothalamic system, seems probable."

Not only does anterolateral cordotomy consistently fail to abolish the response to more intense noxious stimuli, it also fails to affect the pain response to pinpricks in the majority of cases. White and Sweet (1955, p. 262) found that, after this operation, 60% of their patients consistently reported pain when multiple rapid pinpricks were applied to the "analgesic side."

French and Peyton (1948), Voris (1951), and White and Sweet (1955, p. 45) have presented additional evidence indicating that nociceptive stimuli activate fibers that do *not* cross to the opposite side in the spinal cord. Each of these investigators has reported cases in which the "analgesia" was *ipsilateral* following anterolateral cordotomy. From these re-

ports White and Sweet (1955, p. 275) conclude that the "pain fibres are diffused over a very wide area of the anterolateral quadrant, and that at times some centrally conducting fibres must run upwards in the ipsilateral as well as in the contralateral columns, at least for a considerable distance."

Even the above account is incomplete; nociceptive stimuli can activate far more units in the cord than those found on both sides of the anterolateral quadrant. Livingston (1943) and White and Sweet (1955) have found that in many cases *bilateral* anterior cordotomy is insufficient to relieve a pain syndrome and Lhermitte and Puech (1946), Pool (1946), and Browder and Gallagher (1948) have demonstrated that some pain syndromes can be relieved by *posterior* cordotomy. Keele (1957, p. 164) has reviewed additional evidence which indicates that the "pain tracts" may be widely dispersed in the cord and concludes that "one is induced to look upon their anatomy as one of statistical probability, and to wonder how closely or how permanently the function of transmission of pain sense is attached to fixed neuronal paths in the cord." After summarizing the evidence in this area, Adey (1957) similarly concludes that the concept of localized fiber pathways in the spinal cord carrying particular types of sensory impulses is open to serious question and requires revision.

A number of investigators have interpreted their data as indicating that the same stimulus may activate different neural units in the cord at at different times. Gasser (1937) writes that "a given stream of afferent impulses over a peripheral nerve follows one pathway in the centers at one time and another pathway at another time. The direction of the switching is conditioned by the situation obtaining at the moment, and is always consonant with a coordinated reaction of the whole organism." Along similar lines, Livingston (1943, p. 25) interprets the evidence as indicating that "impulses, finding themselves blocked from their customary pathways, eventually find new or previously unused pathways." Bishop (1944) likewise suggests that when impulses along a neural pathway reach a certain critical frequency, they are "switched" to different conduction units from those into which they normally pass.

A number of other considerations should be emphasized. First of all, there is no need to hypothesize specific pathways for pain and other modalities to understand the alterations in sensibility which follow anterolateral cordotomy. As Sinclair (1955, p. 606) has pointed out, "Instead of cutting specific fibres, we may be so altering the sensory patterns the spinal cord is capable of conducting in such a way as to lead to a sensory dissociation." Furthermore, even if we assume a "segregation" of "pain-conducting fibers" at the cord level, we cannot relate this "segregation" to the "sensation of pain," to discomfort or suffering, or to other components of the pain response which appear to require higher neurological levels. Whatever "segregation" of fibers occurs at the cord level can be related only to reflex functions at this level and to nothing more (Bishop, 1946). It should also be noted that afferent impulses in the cord can be altered by impulses descending from the brain stem and cerebrum. Hagbarth and Kerr (1954) have demonstrated that afferent volleys in the anterior columns of the spinal cord are re-

duced in amplitude by electrical stimulation of the bulbar and midbrain reticular formation, of the precentral and postcentral gyri, and of various other forebrain structures.

Conduction at the Brain Stem Level

There seemed to be general agreement, just a few years ago, that spinothalamic pathways "carried pain" without interruption through the medulla, pons, and midbrain to the posterolateral ventral nucleus of the thalamus. Recent evidence indicates that this also is an incomplete account. First of all, there is little doubt that the great majority of the fibers from the anterolateral funiculus of the cord terminate at levels below the thalamus (Walker, 1940; Walker, 1943; Bowsher, 1957). Furthermore, an extensive series of investigations, recently summarized by Magoun (1958), indicate that the "classical sensory pathways" (including the "pain" pathways) give off collaterals to the reticular formation of the brain stem (and to the "diffusely" projecting thalamic nuclei) and that appropriate electrical stimulation of this zone of collateralization —"the reticular activating system" —causes a desynchronization of electrical activity throughout wide areas of the cortex such as is seen in the "arousal" reaction in the normal animal. In line with this evidence, it has been demonstrated that anesthetics exert their primary effect in blocking the response to noxious stimuli (as well as other stimuli) by preventing conduction through the reticular area of the brain stem (French & King, 1955). French, Verzeano, and Magoun (1953) reported that both sodium pentobarbital and ether depress conduction through the reticular formation while the direct afferent pathways continue to conduct impulses in normal manner. Similarly, Arduini and Arduini (1953), Peterson (1955), and Haugen and Melzack (1957) found that the potentials in the reticular formation were much more susceptible to procain, nitrous oxide, and other drugs than the potentials in the direct afferent pathways.

In summary, recent evidence seems to be consistent with Melzack, Stotler, and Livingston's (1958) conclusion from their study of brain stem lesions in the cat:

> Whatever the nature of pain perception may be, its neural substrates appear to be much more complex than that envisaged in a single ascending system. The patterns of impulses subserving pain appear to travel over multiple pathways at the brainstem level at least, and the ultimate perceptual event seems to depend upon activities occurring along all of these pathways (p. 365).

Conduction at the Thalamo-Cortical Level

It has generally been assumed that, after synapsing at the posterior ventral nucleus of the thalamus, "pain fibers" project to the postcentral convolution of the cortex. However, as Walker (1943) has pointed out, the posterior ventral nucleus has numerous connections with the adjacent thalamic nuclei and impulses can be conveyed to wide areas of the cerebral cortex in this indirect fashion.[4] Also, as pointed out above, nociceptive stimuli applied to visceral, somatic, and cutaneous structures also activate neurons in the reticular formation which sends impulses to many cortical areas over both thalamic and extrathalamic pathways. In line with these considerations,

[4] Murphy and Gellhorn (1945) report that strychninization of this thalamic nucleus also leads to firing in the ipsilateral and contralateral hypothalamus. Apparently, this is one of the pathways involved in the general hypothalamic excitation which follows peripheral noxious stimulation (Gellhorn & Ballin, 1946).

Gellhorn and Ballin (1946) report that noxious stimuli applied to the periphery of narcotized animals alter electrical activity throughout the entire cortex, and Benjamin and Ivy (1949) report that noxious stimuli applied to the extremities of human *Ss* evoke a nonspecific decrease in amplitude of the waves from the parietal, occipital, temporal, and frontal areas.[5]

In general, the evidence summarized below indicates that "adequate" stimulation of the cerebral cortex *may* elicit reports of pain; and that damage to a number of cortical areas *may* affect "the sensation of pain" and the withdrawal movements which normally follow noxious stimulation.

In *rare* instances, electrical stimulation of the cerebral cortex, especially of the precentral, postcentral, and superior parietal gyri, has been followed by "a sensation of pain" localized in the face, limbs, trunk, or other body area (Penfield & Boldrey, 1937; Horrax, 1946; Lewin & Phillips, 1952). Also, in a *few* patients, destruction of the postcentral, superior parietal, superior temporal, and insular convolutions (Davison & Schick, 1935); or tumors in the parietal lobe alone or in the parietal plus the frontal or occipital lobe (Michelson, 1943); or tumors in the right or left parietal, frontal, and temporal areas (Bender & Jaffe, 1958); have been reported to give rise to "spontaneous pain" referred to various body areas. However, we cannot conclude from these reports that the cerebral cortex "subserves" some special function in the "perception of pain." Electrical stimulation of many other neural tissues also, at times, evokes referred "pain sensations" (Sweet, White, Selverstone, & Nilges, 1950). Also, a series of investigations, summarized by Bonica (1953, p. 131), White and Sweet (1955, pp. 526–528), and Bender and Jaffe (1958), indicate that pathological processes in the spinal cord, the brain stem, and the thalamus may also produce "spontaneous pain" indistinguishable from that produced by lesions or tumors in the cortex. Furthermore, the pain response which follows electrical stimulation or pathological processes in the cortex could possibly be integrated by subcortical structures. Finally, it should be emphasized that reports of pain following electrical stimulation or lesions in the cerebral cortex are so rare that Penfield and Rasmussen (1950, p. 3) conclude that "the thalamus retains the problem of disposing of pain impulses without calling on the cortex for essential help."

In rare instances, cortical lesions have been reported to *prevent* "the sensation of pain" or "the recognition of the stimulus" without affecting other components of the pain response. Gilliatt and Pratt (1952) have reported that after a "right-sided cerebral thrombosis" a patient did not "consciously recognize" noxious stimuli applied to the left side of the body, even though the stimuli gave rise to general restlessness, increased blood pressure, tachycardia, deepening of respiration, and dilatation of the pupils. Marshall (1951) has also published 11 cases of left and right parietal lesions which were followed by a deficient "pain sensation" when pinprick, or intravenous injection of hypertonic sodium chloride,

[5] Although wide ares of the cerebral cortex are normally activated by peripheral nociceptive stimulation, it is quite certain that some of the components of the pain response can be carried out by animals lacking this structure. In pontile cats, for example, Bard and Macht (1958) report that a strong nociceptive stimulus elicits growl-like vocalizations, protrusion of claws, running movements, piloerection, and increased respiratory and cardiac activity.

was applied to areas contralateral to the lesion. These reports are exceptional; localized cortical lesions are *not* usually followed by alterations in "the sensation of pain." Penfield (cited by White & Sweet, 1955, p. 109), after wide experience with cortical ablations, states that he has "never seen a patient who had a parietal lesion lose sensation of pain excepting for a few hours or days following excision." White and Sweet (1955, p. 63) similarly conclude after reviewing the evidence that "studies in man following localized cortical extirpations reveal little reduction of pain sensation upon peripheral stimulation, and confirm the huge extent of the cortex concerned with sensation."

Damage to a number of cortical areas *may* affect the purposive withdrawal movements which normally follow nociceptive stimulation. Schilder and Stengel (1931) published a study of 3 patients with tumors or lesions of the left parietal lobe (with additional lesions, in two of the cases, in the frontal or temporal lobe) who did not withdraw from noxious stimuli, threatening gestures, loud noises, or sudden flashes of light. Similarly, Hemphill and Stengel (1940) reported that a patient with a probable lesion of the left labyrinth failed to show withdrawal responses to noxious stimuli and to unexpected sounds. Although the patient "admitted that he could feel the painful stimulus" and that he could hear an automobile horn, he failed to show withdrawal or defense reactions when a match was struck close to his eyes and when an automobile horn threatened his life. Rubins and Friedman (1948) have published a similar study of four patients with lesions in or around the supramarginal gyrus of the dominant hemisphere who showed a lack of withdrawal to noxious stimuli and to threatening gestures even though they "felt" pain and were aware of the threatening character of the gestures. The latter investigators emphasize that only certain motor withdrawal reactions appear to be normally integrated in or around the damaged areas.

Although specific unilateral lesions, in some instances, result in deficiencies in pain responsiveness, it by no means follows that the more extensive the unilateral lesion, the more deficient the response. On the contrary, removing either the right or left cerebral hemisphere either does not seriously affect the response to a noxious stimulus or alters only the response to lower intensities of stimulation. Dandy (1933) reported two cases of extirpation of the right cerebral hemisphere; in both patients the response to a pinprick on the contralateral side was seriously deficient, but movements of joints and compression of muscles on either side of the body brought forth a pain reaction with an intense "feeling" component. Gardner (1933) found that 20 months after right hemispherectomy firm pressure with a pin (on the contralateral or ipsilateral side) was recognized as "painful." Zollinger (1935) reported that after removal of the left cerebral hemisphere (in a right-handed woman), the patient showed "acute pain with motion of the joints or compression of the deep muscles." Rowe (1937) stated that, after removal of the right hemisphere, his patient responded normally to nociceptive stimuli applied anywhere on the ipsilateral side and to scattered areas on the contralateral side. Somewhat in contrast to the above are the later reports of Evans (cited by Walker, 1943), Bell and Karnosh (1949), Krynauw (1950) —12 patients—, and Marshall and Walker (1950)—4 patients: a few

months after hemispherectomy, most of their patients showed normal pain responses and accurate localization of pinprick applied on either side of the body.

From our current neurological concepts we might assume that after hemispherectomy the ipsilateral thalamus integrates the response to a nociceptive stimulus on the contralateral side. This is by no means the case. The hemispherectomized chimpanzee shows practically complete degeneration of all the ipsilateral thalamic nuclei which project to the cortex (Walker, 1943). There is no reason to suspect that the same retrograde thalamic degeneration does not occur in man. Apparently, the remaining cerebral hemisphere and the thalamic nuclei on the same side are sufficient to integrate the response to nociceptive stimuli on either side of the body.

The above studies appear to indicate the following:

1. Noxious stimulation in the periphery alters electrical activity in many cortical areas.

2. Referred "pain sensations" are at times evoked by electrical stimulation or pathological processes at any level of the neuraxis, *including the cerebral cortex.*

3. In rare instances, localized cortical lesions abolish "the sensation of pain," i.e., the ability to discriminate a noxious stimulus and to differentiate it from other stimuli, without affecting other components of the pain response. Also, in rare instances, localized cortical lesions abolish the avoidance movements which normally follow noxious stimulation.

4. Removal of either the right or left cerebral hemisphere either does not seriously affect the response to nociceptive stimuli or alters only the response to relatively nonintense stimuli applied to the contralateral side.

5. Although the decorticate animal shows *some* components of the pain response—e.g., running movements and increased respiratory and vasomotor activity—, the *intact* organism probably utilizes a variety of cortical neuronal mechanisms when carrying out the *total* response to a noxious stimulus. This is further exemplified in the following discussion on the mitigation of the discomfort-suffering component of the pain response by prefrontal leucotomy.

"Relief of Pain" by Prefrontal Leucotomy

During recent years an extensive group of patients has undergone prefrontal leucotomy (or "lobotomy") for the relief of severe, intractable pain syndromes such as causalgia, postherpetic neuralgia, metastatic carcinoma, thalamic syndrome, etc. (e.g., Van Wagenen, cited by Walker, 1943; Dynes & Poppen, 1949; Freeman & Watts, 1950). Although some patients died soon after the operation and others were not "relieved of pain," others were "relieved" (at least for an extended time period) and further analysis of this effect may give us an increased understanding of the pain phenomenon.

First of all, it is necessary to point out that intractable pain has been alleviated in *some* patients not only by bilateral frontal leucotomy, which supposedly destroys the thalamofrontal projections, but also by unilateral frontal leucotomy; by bilateral lower quadrant frontal leucotomy; by topectomy (i.e., by removing limited areas, such as Brodmann's Areas 9 and 10, from the frontal lobes); and by a number of other operations on the frontal areas which have been summarized by Sargant and Slater (1954). Secondly, the "pain relief" which may follow these operations does *not* appear to be related to the *specific* prefrontal areas affected; on the contrary, the degree of "relief" appears to be a nonspecific effect, closely related to the *extent* of the prefrontal damage (Petrie, 1951; Hardy, Wolff, & Goodell, 1952; Petrie, 1958; Elithorn, Glithero, & Slater, 1958).

It must be further emphasized that only *some* patients have been helped

by these procedures. Walker (1950) estimates that at least one third of the patients receiving these operations have not had any "pain relief." A representative report is Hardy, Wolff, and Goodell's (1952) analysis of 38 prefrontal leucotomies (25 unilateral and 13 bilateral) performed by Dr. Bronson Ray at the New York Hospital for the relief of pain syndromes related to metastatic cancer, Hodgkin's disease, radiculitis, tabes, etc. Of the 25 patients receiving unilateral leucotomy, 10 were relieved of pain and 15 showed no alteration in their pain syndrome. Of the 13 patients receiving the bilateral operation, 11 were relieved and 2 were not helped. The term *relief of pain*, as used by these investigators, implies that when the patient was directly asked if he had pain, he replied either that he no longer had it, or that it was still present but of lower intensity than before, or that it was still present but no longer "bothered" him. Although some investigators use an additional criterion—viz., that the patient no longer asked for drugs—most investigators also use the above criteria.

A further point should be emphasized: postmortem examinations of leucotomized patients indicate that in some cases the prefrontal areas are *not* damaged and the thalamofrontal projections are *not* severed. In a postmortem study of 15 patients who had undergone transorbital lobotomy for pain of malignant disease, Freeman and Williams (1951) found that 3 cases were characterized by massive hemorrhage, 2 cases failed to involve the thalamofrontal projections, and the other cases apparently showed destruction of the thalamofrontal radiations with retrograde degeneration of the dorsomedial nucleus of the thalamus. Meyer and Beck (1945) also report from postmortem studies that the prefrontal lobe is at times entirely untouched and that severance of the thalamofrontal fibers is often incomplete.

When prefrontal leucotomy alleviates intractable pain it does not necessarily elevate the pain threshold or alter "the sensation of pain." Chapman, Solomon, and Rose (1950) found a lowering of the pain threshold immediately after the bilateral operation followed by a return to preoperative levels after an intervening time period. Hardy et al. (1952) reported that the pain threshold in 10 postleucotomy patients, who were relieved of their pain syndrome, showed no significant difference from the preoperative level. King, Clausen, and Scarff (1950) noted a slight lowering or no change in the pain threshold after successful unilateral leucotomy for intractable pain. Also, with few, if any, exceptions, investigators report that the "sensation" or "perception" of pain is practically unaltered by any of these procedures: e.g., "Prefrontal lobotomy changes the attitude of the individual toward his pain, but does not alter the perception of pain" (Freeman & Watts, 1950, p. 354).

The evidence available at present also indicates that, if and when prefrontal leucotomy relieves a pain syndrome, the relief is secondary to a more generalized effect of the operation which, at times, can be conceptualized as *apathy*, i.e., as a decreased responsiveness to all stimuli —including nociceptive stimuli. Hardy et al. (1952, p. 317) emphasize that postleucotomy patients who were either partially or totally relieved of pain "exhibited in many ways . . . a flattened affect if not actual apathy. . . . They failed not only to complain of their spontaneous pain but also of their needs, such

as personal nursing care, need of urine bottle, bedpan, or the adjustment of an uncomfortable dressing. When incontinent of feces they were indifferent to the odor it spread about their persons and beds." Bonner, Cobb, Sweet, and White (1952) have also emphasized that apathy characterized their patients immediately following bilateral lower quadrant frontal leucotomy. Although the apathy tended to lessen with the passage of time, it was still a characteristic feature in patients followed up to 36 months postoperatively.

Although many patients who are relieved of intractable pain by prefrontal operations do not show the extreme apathy described above, the evidence indicates that all patients who are helped by these operations show a characteristic personality alteration (Krayenbühl & Stoll, 1950; Petrie, 1952; Petit-Dutaillis, Messimy, & Berges, 1953; Elithorn, Glithero, & Slater, 1958); and that patients who are *not* helped and patients who have undergone other operations which do *not* mitigate intractable pain, e.g., temporal lobotomy, cingulectomy, and orbital undercutting, do *not* show the same change in personality (Petrie, 1958). This characteristic alteration has received a wide variety of formulations: Dynes and Poppen (1949) conceptualize it as a decrease in "worry" and "concern"; Le Beau (1950) terms it the relief of "anxiety"; Elithorn et al. (1958) formulate it as an "impaired ability to elaborate a persisting attitude or mood." These formulations are not necessarily in basic disagreement; they appear to be referring to a common behavioral matrix, viz., to a mitigated "readiness to respond" to external and internal stimuli. Summarizing the investigations in this area, Walsh (1957, p. 474) writes: "The patient suffering from pain complains less of his discomfort than before. Not . . . a failure to appreciate the situation but a failure to respond to it. . . . This failure to react is seen when stimuli that arise within the body itself are considered; but there may also be a dimished response to external situations."

It should be emphasized that the leucotomized patient is *able* to respond normally to nociceptive stimulation. Hardy et al. (1952, p. 316) have reported that "some patients, although ostensibly tranquil before being asked about their pain, overreacted with a show of grimacing and fears *when their attention was focused upon it* by a direct question concerning its quality and its intensity" (emphasis added). The same theme is repeated by other investigators; for example, Hawkes and Gotten (1948, p. 209) report that "when questioned [the leucotomized patients] all indicated that they realized some pain was present *when they thought about it*" (emphasis added). Apparently, when the leucotomized patient is *directly asked* to report on his pain, he "focuses his attention" on and "thinks about" the ever-present nociceptive stimulus in his body and, when thus reacting to it, often shows discomfort or suffering and almost always reports a "sensation of pain." However, when the patient is not directly asked to report on the noxious tissue condition, he does not "attend" to it or "think" about it *to the same extent* as before the operation and, when not thus reacting to it, does not appear to be "in pain," i.e., does not show discomfort.

Apparently, discomfort and suffering can be minimized or eliminated by preventing a "secondary reaction" to the noxious stimulus. Neurosurgeons have used somewhat different terms to describe this effect: Freeman

(1949, p. 18) writes after extensive experience with prefrontal operations that "when the emotion is done away with, the pain either becomes no longer significant or actually disappears"; Otenasek (1948, p. 234) similarly suggests that "when the fear of pain is abolished, the perception of pain is not intolerable."

Neurophysiological Correlates of Postleucotomy "Pain Relief"

Since prefrontal leucotomy mitigates the discomfort-suffering component of the pain response in some patients and fails to do so in others, since this effect is often temporary, and since we are rarely certain in any one such operation which fiber tracts were destroyed, to what extent scar formation and vascular damage occurred, and to what extent the operation resulted in physiological disturbances in other cerebral areas, it is extremely difficult to formulate any hypothesis concerning the "pain relief" which may follow this operation. Also, as Koskoff, Dennis, Lazovik, and Wheeler (1948) have pointed out:

> The relief of suffering in such a wide variety of patients suggests that the mechanism does not involve the interruption of specific pain pathways, despite the evidence of thalamic degeneration following frontal lobotomy. Preservation of the response to painful stimulation noted in such patients also suggests that the interruption of specific afferent pain tracts is not responsible for the relief of suffering (p. 740).

Nevertheless, a number of investigators have proposed a variety of mechanisms which may be directly or indirectly related to postleucotomy "pain relief." Starzl and Whitlock (1952) have presented evidence that the "diffuse" thalamic projection system, which exerts a general cortical "arousal" effect, projects primarily, but not exclusively, to the frontal cortex in monkey. From this evidence they hypothesize that "pain relief" following leucotomy is due to the destruction of the afferent fibers from this system. Fulton (1951, p. 127) has suggested that frontal leucotomy relieves pain by removing "large numbers of visceral pain projections from the sphere of consciousness," specifically, by destroying visceral afferent pathways to the orbitofrontal cortex. However, as White and Sweet (1955, p. 64) point out, "We know of no evidence . . . that stimulus to the central end of any visceral nerve carrying many nerve fibers, such as the great splanchnic nerve, will cause synchronous bursts of change of potential within this part of the brain in mammals." Also, Fulton's suggestion does not explain why the leucotomized patient appears to have a diminished responsiveness to many other stimuli besides noxious stimuli nor does it explain why the patient may state, when directly asked, that the "pain feeling" is the "same" but does not matter any more.

The above investigators have emphasized the destruction of the afferent projections to the frontal areas and have neglected the probable extensive destruction of corticofugal fibers. In a postmortem investigation of six lobotomized patients, Yakovlev, Hamlin, and Sweet (1950, p. 328) found that the frontopontine tracts were bilaterally and symetrically degenerated and that "the great frontal corticofugal pathway descending from the entire anterior pre-Rolandic half of the cerebral hemisphere was deprived of a large and important component." They conclude with a statement that cannot be too much overemphasized:

> On the basis of this study it seems to us that in the attempts made thus far to correlate the

behavioral changes following frontal lobotomy with anatomy . . . the degeneration of anterior thalamic radiations and nuclei has been stressed to the exclusion of the obvious degeneration of the far greater mass of efferent projections which connect frontal lobes to all the levels of the neuraxis . . . (p. 328).

In line with this suggestion, a few workers have attempted to formulate the effects of leucotomy in terms of the destruction of efferent projections. Bonner et al. (1952) speculate that if the connections between neocortex and archicortex are severed by prefrontal leucotomy "there would be less activation of the archicortical circuits which probably subserve emotional reactions and thus perpetuate suffering." Arnold (1955, p. 154) hypothesizes that since the dorsomedial nucleus of the thalamus degenerates after prefrontal leucotomy and since the frontal lobes activate the sympathetic centers in the posterior hypothalamus by connections through this nucleus, "Anxiety is reduced because the excitation of sympathetic effectors is now prevented and with it a prolongation and intensification of the emotion." However, since sympathectomized animals (Cannon, Newton, Bright, Menkin, & Moore, 1929) and sympathectomized human patients (Ray & Console, 1949; Grimson, Orgain, Anderson, Broome, & Longino, 1949) apparently respond with normal "emotion" and "anxiety" to many stimuli, it is doubtful that the prevention of sympathetic excitation is the mechanism involved in the reduced "anxiety" or diminished reactivity of the leucotomized patient.

In summary, although a number of neurophysiological mechanisms are apparently nonfunctional after prefrontal leucotomy, we cannot state with any degree of certainty which of these mechanisms are necessary for the maintenance of intractable pain. Nor are we certain that destruction of one or more specific nuclei or nerve pathways is closely correlated with the effects of this operation. In fact, the evidence at present suggests that prefrontal leucotomy has different effects on different patients even when apparently similar neural tissue is destroyed. To account for these differential effects we must have not only (*a*) much more preoperative data on each patient (e.g., the patient's personality characteristics, his general level of reactivity, the duration of his pain syndrome) but also (*b*) much more specific postoperative data such as the specific tracts destroyed and the extent of postoperative hemorrhage, and (*c*) a better understanding of a number of phenomena which at present are not well understood, such as the "reintegration" of function which may occur after destruction of neural tissue, the specific functions of the afferent and efferent fibers from the frontal areas, etc. When such specific data are available, we may be able to account both for the patient who is *not* helped by this operation and for the patient who is not only relieved of pain but also of worry and concern about many situations including, in many cases, forthcoming death.

The Problem of Congenital Insensitivity to Pain

A theory of pain must account for the "normal" response to noxious stimulation, for the alterations in this response by analgesics, placebos, hypnosis, neurosurgical and other procedures, and for the antithesis of "normal" pain responsiveness, i.e., the problem of "congenital insensitivity to pain." At the present time we are far from a complete understanding of the latter phenomenon. Nevertheless, within the limits of the

evidence as it now stands, certain significant factors stand out that should be emphasized.

McMurray (1955) and Critchley (1956) have recently reviewed the handful (ca. 16) of well-documented cases of "congenital insensitivity." McMurray's (1950) case can be briefly summarized to indicate the more or less typical findings in these patients:

A 22-year-old female college student, IQ 128, with no apparent personality disorders. A history of consistent lack of pain responsiveness dating at least since early childhood. Extensive burns, frostbite, deep cuts, and other serious tissue damage "had gone unnoticed or been looked on indifferently." Her medical history included the incision of a large abscess over the occipital bone, osteomyelitis of the right calcaneus and of the left femur, tonsillectomy and adenoidectomy, and acute pyelitis, with no complaints of pain or tenderness. When subjected in the laboratory to such noxious stimuli as cold water at a temperature of 0° to 2° C., hot water at 49° to 51° C., and electric shock from an inductorium, she did not report pain, did not show wincing, withdrawal, or other indications of discomfort, and did not show any significant alterations in blood pressure, heart rate, or respiration. Extensive neurological examination did not reveal any evidence of organic neurological disease.

Although the other reported cases generally follow the above pattern, there are some differences: 2 patients (Ford & Wilkins, 1938, Case 2; Kunkle & Chapman, 1943) showed epileptic tendencies; 3 patients (Kunkle & Chapman, 1943; Arbuse, Cantor, & Barenberg, 1949; Cohen, Kipnis, Kunkle, & Kubzansky, 1955) showed increased diastolic and systolic blood pressure and increased heart rate when their hands were immersed in water at 0° C.; and at least 4 patients were of borderline normal or below normal intelligence (Ford & Wilkins, 1938, Case 2; Arbuse et al., 1949; Farquhar & Sutton, 1951; Madonick, 1954).

In many of the reported cases, the insensitivity to pain is not an all-or-none phenomenon. Many, and possibly all, of these *S*s have at some time in their life responded *in the normal manner* to some noxious stimuli. Three of Jewesbury's (1951) cases illustrate this exceptionally well. His first case showed no response to pinprick or to laboratory pain tests such as muscle ischemia and histamine injection, he was able to pick up glowing coals without discomfort, and he had teeth drilled and extracted without any report of pain; however, the patient did, at times, show the normal response to noxious stimulation, for example, when he had smashed his fingernail and when he had been kicked on the testicles. Jewesbury's second and third cases also did not show pain responses in the laboratory tests of muscle ischemia, histamine injection, and electric shock at 40 milliamperes (the maximum available); however, the second patient had frequent frontal headaches and showed normal pain responsiveness during appendicitis and pyelitis and the third patient had reported pain from headaches and from retention of urine due to an enlarged prostate. Similarly, Kunkle and Chapman's (1943) patient had complained of "moderate toothache"; Rose's (1953) patient complained of pain after a vascular accident in his right leg; Madonick's (1954) patient and two of Ford and Wilkins' (1938) patients had "abdominal pain"; the patient of Cohen's et al. (1955) had reported

a "throbbing headache" after spinal anesthesia; and Jéquier and Deller's (1956) patient reported "a little pain" when stimulated with a very hot object.

As Critchley (1956) has noted, these *S*s are not actually "insensitive" to noxious stimulation; they can detect, identify, and localize noxious stimuli and can easily differentiate them from other stimuli. McMurray's (1950) *S* states that, when a hypodermic needle is inserted into her skin, she feels it penetrating the tissue layers but does not "feel pain." Stimuli such as pinprick and cutaneous shock and heat produce the report of a pricking or sharp quality, but she does not describe this quality as "painful." In fact, since this *S* can discriminate the sharp quality of heat stimulation, McMurray was able to establish in the patient a "threshold" close to the normal heat pain threshold. Similarly, Ford and Wilkins (1938), Kunkle and Chapman (1943), Boyd and Nie (1949), Jewesbury (1951), Westlake (1952), and Jéquier and Deller (1956) have reported that their *S*s had no difficulty differentiating and localizing a nociceptive stimulus; they could, for example, easily discriminate between the blunt and pointed end of a pin and had no difficulty localizing the pinprick.

The available evidence indicates that many, if not all, of these *S*s have normal peripheral neural apparatus. Biopsy specimens from McMurray's patient showed "nerve fibers and free nerve endings present. . . . No morphological features that would distinguish them from the pain endings of normal subjects" (Feindel, 1953, p. 402). Other investigators who attempted histological studies (Girard, Devic, & Garin, 1953; Madonick, 1954; Cohen et al., 1955) also found nerve fibers in apparently normal pattern.

In many, if not all, of these cases, the evidence indicates that no distinct localized damage exists in the central nervous system. Investigators who performed extensive neurological examination of their *S*s (Boyd & Nie, 1949; Arbuse et al., 1949; McMurray, 1950; Jewesbury, 1951; Rose, 1953; Madonick, 1954; Jéquier & Deller, 1956) report that all tests were essentially normal—normal reflexes, normal skull and spine X ray, normal pneumoencephalogram, normal electroencephalogram, etc. Arbuse et al. (1949) have emphasized that there is no indication in their case, or in any other reported case, of a lesion in any specific part of the brain. Most investigators who have examined these *S*s appear to be in agreement with De Jong's (1949, p. 411) conclusion that the defective reaction is more likely due to a "generalized or diffuse developmental anomaly" and that it is highly doubtful that any "local lesions" exist.

In at least three of the reported cases the pain insensitivity was *not* due to an *irreversible* "anomaly." Ford and Wilkins' (1938) first case appeared to be insensitive to pain and readily submitted to many serious noxious stimuli in the laboratory without signs of discomfort; later, however, he seemed to be afraid of "getting hurt," refused to have a tooth extracted without an anesthetic, and generally appeared to be becoming more concerned about potentially pain-producing stimuli. Similarly, during the first 2½ years of life, Jewesbury's (1951) fourth case did not show any signs of pain responsiveness to a wide variety of injuries—serious burns, bruises, bleeding fingers, etc. At two years of age

he had been reported in the press as "the child who knows no pain." However, when examined at 3½ years of age he showed *normal* pain responses to *all* nociceptive stimuli. Rose's (1953) case also followed a similar pattern; Rose reports that "his sensitivity to pain is becoming progressively nearer the normal and he now feels the minor injuries of boy's life as well as any other child."

Since each of the reported cases appears to differ in some way from every other reported case, we cannot generalize from the above data. However, we are probably safe in tentatively concluding that *some* of these *Ss are able* to respond to at least some nociceptive stimuli in the normal manner, i.e., with the "sensation of pain," discomfort, and alterations in some physiological functions, even though they almost always fail to do so. Also, many, if not all, of these *Ss* can discriminate and localize noxious stimuli and easily differentiate these stimuli from heat, warm, pressure, and touch stimuli. But this "sensing" of a noxious stimulus is not "painful"; very rarely is it associated with unpleasantness or discomfort. As Critchley (1956, p. 742) has pointed out: "The most remarkable feature in this syndrome is a typical lack of conformity between the feeling of pain as a discriminative quality of sensation, and the registration of distress, either overtly or automatically." In fact, the available evidence suggests that *some*, if not many, of these *Ss* resemble in their pain responsiveness the hypnotic "analgesic" *S* and the restricted and isolated animals studied by Melzack and Scott (1957) more than they resemble those rare patients with lesions of the afferent apparatus who are unable to discriminate a nociceptive stimulus. The former phenomena, summarized below, also indicate that "pain" in the sense of discomfort and suffering is not necessarily present when noxious stimuli are discriminated, differentiated, and localized.

The Effect of Early Isolation on the Pain Response in the Adult

Melzack and Scott (1957) have provided much needed data concerning the effect of early isolation on pain responsiveness in the mature organism. These investigators reared 10 dogs in isolation from puppyhood to maturity in special cages which drastically limited both their over-all experience and their specific experience with nociceptive stimuli. Comparing the behavior of these restricted dogs with the behavior of 12 normally reared dogs, they report the following:

(*a*) In general, the 10 restricted dogs failed to show adaptive and intelligent responses to noxious stimuli. Many of the dogs made no attempt to avoid a pinprick, a flame, or an electric shock stimulus. Although some of the restricted dogs did learn to avoid these stimuli, they required many more trials than the control animals. As long as two years after release from isolation, many of the restricted dogs continued to show maladaptive behavior when given noxious stimuli. The investigators conclude that "it appears that the requisite experience must come at the correct time in the young organism's life. During later stages of development, the experience necessary for adaptive, well-organized responses to pain may never be properly acquired" (p. 159).

(*b*) The restricted animals appeared to be unable to localize the source of the noxious stimulus. Not

only were the stimuli "not 'perceived' as coming from the experimenter" but the dogs also appeared to be "unaware that they were being stimulated by *something in the environment*" (p. 158).

(*c*) Although the restricted animals may have "felt" the nociceptive stimuli "in some way," they rarely showed discomfort or suffering:

> Their reflexive jerks and movements during pinprick and contact with fire suggest that they may have "felt something" during stimulation; but the lack of any observable emotional disturbance apart from these reflex movements in at least 4 of the dogs following pinprick and in 7 of them after nose-burning indicates that the *perception* of the event was highly abnormal in comparison with the behavior of the normally reared control dogs. . . . The results suggest that the restricted dogs lacked awareness of a necessary aspect of normal pain perception; the "meaning" of physical damage or at least *threat* to the physical well-being (p. 159).

Additional investigations are needed to determine the validity of the following hypothesis suggested by this study: some components of the normal pain response (local reflex movements and "the sensation of pain") do not require prior experience with noxious stimuli; other components of the pain response (localizing the stimulus, purposive withdrawal movements, and discomfort-suffering) require previous experience with such stimuli.

Hypnotically-Induced "Analgesia"

The experimental evidence, summarized by Weitzenhoffer (1953), indicates that, when given appropriate suggestions to induce "analgesia," *some* "good" hypnotic *S*s do not show a pain response to *some* noxious stimuli, that is, they do not give a verbal report of pain, they do not withdraw from the stimulus, they do not show discomfort by wincing, tremor, or restlessness, and they do not show significant alterations in blood pressure, heart rate, pulse rate, or respiration. Dynes (1932) reported that following pinprick during hypnotically-induced "anesthesia" seven "trained" hypnotic *S*s denied that the stimuli were painful, did not show withdrawal or facial flinch, and showed little or no disturbance in the normal rate and rhythm of respiratory and cardiac activity. Subsequently, Dynes' *S*s were asked (by someone other than the experimenter) to "fake a trance" during the following experiment but not to "enter hypnosis." In this situation, pretending they were in trance, they showed all of the normal responses to the nociceptive stimuli. In a similar study, Sears (1932) recorded the responses of seven "good" hypnotic *S*s to a sharp steel point pressed against the leg for 1 sec. with a pressure of 20 oz. Suggestions of analgesia were given for the left leg and the right leg was employed as a control. When the stimulus was applied to the "analgesic" left leg, the *S*s did not show facial flinch or variations in respiration and the increased pulse rate, which normally follows nociceptive stimulation, was significantly decreased. However, they did show these responses when the stimulus was applied to the "normal" right leg. In further control experiments, when the *S*s were asked to inhibit all reactions to the noxious stimulation, all *S*s showed alterations in pulse and respiration. Doupe, Miller, and Keller (1939) have in general confirmed these findings, reporting that their hypnotic *S*s showed a slight alteration in respiratory rhythm, no significant change in pulse rate, and no facial grimace when multiple pinpricks were applied to the "anal-

gesic" arm.[6] Brown and Vogel (1938) also found that three *S*s showed less variability in blood pressure, pulse, and respiration when nociceptive stimuli (lancet, thumb tack, and water at 49° C.) were applied to the "anesthetic" limb than when the same stimuli were applied to the "normal control" limb. Although they conclude that "physiological reactions to moderate and mild sensory stimuli may be affected by suggestion in the hypnotic state and by imagination in the waking state," it is not clear from their report to what degree these responses were affected.

Although the experimental studies generally report either a complete lack or a significant decrease in vasomotor and respiratory alterations following nociceptive stimulation during hypnotically-induced "analgesia," they report completely contradictory results with the galvanic skin response (GSR). Some investigators (Georgi, 1921) found that the GSR to noxious stimulation was completely eliminated during hypnotic "anesthesia"; others (West, Niell, & Hardy, 1952) concluded that it is at times significantly decreased over the normal and at other times completely eliminated; and still others (Levine, 1930; Barber & Coules, 1959) reported that the GSR to noxious stimuli is not significantly altered after hypnotic suggestions of analgesia. However, an extensive group of investigations indicate that the GSR is *the least specific* of all the physiological responses which may follow noxious stimulation. Although blood pressure alterations, for example, are at times present when *S* is responding to nonpainful stimuli, *some* variation in blood pressure appears to be always present when *S* does "feel pain" (Nafe & Wagoner, 1938; Goetzl, Bien, & Lu, 1951). This is not true of the GSR, however. An *S* may show a GSR when he does *not* "feel pain" and he may *not* show a GSR when he *does* "feel pain." Brown and Vogel (1938) demonstrated that hypnotic *S*s often showed a GSR when there was no doubt that they did not "feel pain," that is, when noxious stimuli were applied to an area made insensitive by novocain block. They write that "light application of the pin point [to the area in which novocain had been injected] . . . appreciated as touch, caused large galvanometer deflections" (p. 419). Along similar lines, Levine (1930) and Barber and Coules (1959), using hypnotic *S*s, and Sattler (1943), using nonhypnotic *S*s, found that *S*s often show a GSR when they are told they are to be given a painful stimulus *but are not given the stimulus*. West et al. (1952) found that (*a*) the GSR showed a significant decrease over the control levels for all seven of their hypnotic *S*s even when "there was no alteration in pain perception, according to subjective reports," and (*b*) during the control periods a stimulus "evoking a pain of 6 or 7 dols" at times failed to produce a GSR. After a careful, long-term investigation designed to determine the relationship of the GSR to the pain response, Furer and Hardy (1950) concluded that the GSR is directly related to the "threat-content" of the stimulus and is not related to the "sensation of pain" as such. Following Furer and Hardy's interpretation, we can con-

[6] Doupe et al. also found that, in comparison with the normal limb, the hypnotically "anesthetic" limb showed a reduced vasoconstrictor response to pinprick. They are uncertain, however, whether this "residual response" is "of the nature of a spinal reflex" or due to "sub-conscious or co-conscious activities" on the part of the *S*.

clude that studies which have recorded the GSR during hypnotically-induced "analgesia" indicate that to some hypnotic "analgesic" *S*s the noxious stimuli are "threatening," to others they are less "threatening" than during the control period, and to still others they are not "threatening" at all.

However, we cannot draw any conclusions from the above studies as to the effectiveness of hypnotic procedures when the stimuli are more severe and of longer duration. For this type of report we must turn to the clinical investigations. In general, the clinical reports suggest that hypnotic methods, *with some patients*, may be as effective as morphine and other opiates in minimizing pathological pain syndromes and in mitigating or totally eliminating the discomfort-suffering component of the pain response during a variety of surgical procedures. A typical report of the surgical use of hypnotic techniques is Mason's (1955) discussion of a case of mammaplasty: during the operation, which consisted of excision of breast tissue, skin, fat, and complete reshaping of the breast, the patient "never showed signs of pain or seemed distressed" and the pulse and blood pressure showed very little, if any, alteration. Kroger (1957) has also reported four cases which are more or less typical of the surgical findings. The first case, a 20-yr.-old female, had "a fairly large tumor" removed from the right breast without preoperative or operative medication. She showed "no indication of a pain reflex at any time" and she was "fully aware of the entire surgical procedure." Another patient, who underwent Caesarean section and hysterectomy with hypnotic "anesthesia," "experienced no subjective discomfort and conversed with everybody in the operating room. She was fully conscious and was able to watch the birth of her baby. There was no discomfort when the baby was delivered by forceps, or when the uterus was extirpated." Other studies, recently summarized by Barber (1958b), also report that hypnotic methods are successful with *some* patients in minimizing or completely eliminating the discomfort-suffering component of the pain response during childbirth, terminal cancer, fatal burns, dysmenorrhea, and other pain syndromes.

It should be emphasized, however, that in the more severe and intractable pain syndromes, such as terminal cancer and spinal cord injuries, hypnotic methods are reported to *minimize discomfort and suffering;* rarely, if ever, are these procedures reported to completely eliminate the total pain response to the ever-present noxious stimulus in the patient's body. Dorcus and Kirkner (1948) found that although hypnotic methods could minimize discomfort in five cases of spinal cord injury—i.e., the patients reported less pain and requested a smaller amount of drugs—these methods were by no means effective in entirely eliminating the pain response. Similarly, Butler (1954) reported that hypnotic methods were effective with some patients in minimizing discomfort during terminal cancer—the patients either required half of their usual amount of morphine or, in a few cases, did not require any drugs for a period of time.

The evidence available at present indicates that two objections which have been raised concerning the effectiveness of hypnotic procedures in "relieving pain" are not valid. Hull (1933) was of the opinion that hypnotic *S*s may state, after the experiment, that they did not "feel pain"

during the experiment because amnesia has been suggested and they simply do not remember. However, in a number of recent studies (Rosen, 1951; Mason, 1955; Kroger, 1957) posthypnotic amnesia was not suggested and the patients continued to insist that they had not "felt pain" even when they were perfectly able to recall the entire procedure. Others have objected that hypnotic *S*s actually "feel pain" but deny it (when questioned by the hypnotist) because of their *rapport* or strong "transference" relationship with the hypnotist. This also seems doubtful. Whenever any of the above patients were questioned afterwards by disinterested observers, they continued to vehemently deny "feeling pain" during the procedure (Marcuse & Phipps, 1956; Kroger, 1957).

Before we can state what are the necessary and sufficient conditions for hypnotic "analgesia," we need more extensive, controlled experiments utilizing a wide variety of noxious stimuli applied to visceral, somatic, and cutaneous structures. Recent investigators, however, have emphasized three conditions which may be among the necessary conditions for this phenomenon.

First of all, it seems that the *S* must be a certain type of person who is *able* to become "deeply hypnotized." With few, if any, exceptions, investitors agree that these individuals (usually termed *somnambulists*) are a small minority—5 to 25%—of the population, at least in our culture (Weitzenhoffer, 1953, p. 59; Butler, 1954; Mason, 1955; Kroger, 1957). The limited evidence available at present suggests that these individuals are characterized by a number of distinct "abilities." Young (1928, p. 372) found that one or more of the following characteristics showed themselves in all of his "best" *S*s long *before* they were "hypnotized": "deep abstraction, reverie amounting almost to ecstasy, putting oneself to sleep at will, actually hypnotizing one's self." Similarly, Barber (1958b, 1958c) found that all of his somnambulistic *S*s had been able since childhood to go to sleep easily and quickly at anytime—day or night—and to concentrate on their work or studies by "blocking-out" irrelevant stimuli.

What appears to be a second necessary condition for hypnotic "analgesia" has been formulated by Leuba (1957) as follows:

> "There must be concentration on the ideas presented by the hypnotist and with a minimum of counter or critical thoughts; and a belief that what the hypnotist says will happen, can actually happen, and will happen. In other words, there must be a set or attitude to accept the hypnotist's statements completely and uncritically" (p. 37).

Along similar lines, Kroger (1957, p. xi) has concluded from his extensive experience with hypnotic procedures that "when one wishes to perform major surgery under hypnoanesthesia . . . it is very important to get the patient to believe in the actuality of the trance state." Recent evidence indicates that these statements may be valid. Barber (1957b) reported that a somnambulistic hypnotic *S* (who quickly and easily carries out all of the "complex" hypnotic behaviors such as analgesia, age-regression, negative and positive hallucinations, etc.) becomes "unhypnotizable" when he no longer "believes" in hypnosis, i.e., when he concludes from his own reading, or from training in autohypnosis,[7] that the hypnotist does not possess any special power or ability and that whatever occurs dur-

[7] Shor, R. E. Personal communication. October, 1957.

ing the hypnotic situation is brought about primarily by the subject himself. A number of investigators have also reported that somnambulistic *S*s (in the "deepest stage of hypnosis") do *not* carry out "complex" hypnotic behaviors such as color blindness (Erickson, 1939), age-regression (Orne, 1951), immoral or dangerous behavior (Young, 1952), and negative hallucinations (Barber, 1958a) when the hypnotist simply gives them the appropriate suggestions; however, they do carry out such behavior when the hypnotist manipulates the situation in such a way as to lead the *S*s to "believe" that the suggestions are *literally* true statements.

A third factor which seems to be closely related to the above, has been recently emphasized by physicians attempting to relieve the pain of terminal cancer or childbirth by hypnotic methods; the patient must have confidence in his physician-hypnotist and the hypnotist must "give of himself" to the patient. In treating the pain of terminal cancer by hypnotic procedures, Butler (1954) saw his patients at least daily and often two to four times a day. Whenever hypnotherapy was terminated for any length of time, the patients all showed a return of the original pain syndrome. However, in the few cases when hypnotic procedures were discontinued *but the patient received the same amount of personal attention from the physician*, the patients did just as well for one or two days as they did during "hypnosis." Butler emphasizes that in treating the pain of terminal cancer by hypnotic methods the hypnotist-physician "gives of himself to the patients. . . . Even an hour's treatment with a very sick patient can produce an appreciable tiring of the hypnologist, and, as the sympathetic bond between the two grows stronger, the hypnologist may even 'feel' the symptoms he is trying to eradicate from the patient" (p. 6). Along similar lines, Winkelstein (1958, p. 154) concluded, after using hypnotic methods over a 2-yr. period with 200 of his obstetrical patients, that "the mental attitude of the patient, the patient-obstetrician rapport, and the confidence of the patient in the procedure as well as in the accoucheur, seemed to be as important factors as was the hypnosuggestion itself."

In summary, the evidence available at the present time indicates that when the hypnotist properly manipulates the situation *some* "good" hypnotic *S*s show a mitigated pain response to *some* noxious stimuli,[8] that is, (*a*) they do not show withdrawal or avoidance, (*b*) they report that the stimuli are not painful, (*c*) they do not show discomfort and (*d*) they do not show physiological responses such as vasomotor and respiratory alterations (although they may or may not show galvanic skin responses). The evidence also suggests that *S*s who are able to carry out the above are "set" to accept the hypnotist's suggestions as literally true statements and have complete confidence in the hypnotist and in the efficacy of hypnotic procedures.[9]

[8] It should be emphasized that the hypnotic "analgesic" *S*, like the leucotomized, narcotized, or congenitally insensitive patient, is able to discriminate, differentiate, and localize the noxious stimulus when asked to do so (Rosen, 1951). Although he can "sense" the stimulus, it does not arouse discomfort.

[9] As will be pointed out below, the "pain relief" which at times follows the administration of a placebo is also closely related to the *S*'s belief or conviction that the "drug" has curative properties.. Apparently, at least some of the effectiveness of hypnotic "analgesia" is due to a "placebo effect."

However, the hypnotic "analgesic" *S* also resembles the patient who has received mor-

THE INCONSTANT PAIN THREHSOLD

Recent studies indicate that both morphine and placebos can eliminate discomfort and suffering without altering the pain threshold and without affecting "the sensation of pain." Since many of the studies on placebos and analgesic drugs are intimately related with the pain threshold studies, we shall first review the latter investigations.

When the subject of pain was last reviewed in this journal (Edwards, 1950) it appeared that Hardy, Wolff, and Goodell (1940) had established that the pain threshold was relatively constant in the same *S* at different times. Using what was later to become known as the Hardy-Wolff-Goodell radiant heat technique[10] and using themselves as *S*s, these investigators reported that when pain threshold measurements were taken almost daily for nearly a year, the average threshold value was 232 mc./sec./cm.^{2} with a standard deviation of only ± 9 millicalories. In addition, they reported that all observations were within $\pm 12\%$ of the mean. It also appeared that the same workers (Schumacher, Goodell, Hardy, & Wolff, 1940) had established that a large group of *untrained* *S*s had approximately the same pain threshold. They reported that the average threshold for 150 untrained *S*s was 206 mc./sec./cm.^{2} with a standard deviation of only ± 21 millicalories and a range extending only from 173 to 232 millicalories. Subsequent investigations, however, have failed to confirm both of the above conclusions; it now appears that there is a wide variation in pain threshold among a group of *S*s and that the threshold is by no means consistent in the same *S* over time.

Using the Hardy-Wolff-Goodell radiant heat technique, Chapman and Jones (1944) found that the pain thresholds of 200 *S*s varied between -40 to $+50\%$ of the mean and Kuhn and Bromiley (1951) reported that the pain thresholds of 37 *S*s ranged from 169 to 296 millicalories with a standard deviation of 31.9. Hall and Stride (1954), using a modified Hardy-Wolff-Goodell technique, found that the pain threshold of 400 psychiatric patients (neurotics, depressives, and schizophrenics) extended "over almost the whole range of stimulus intensity" with the mean at 260 millicalories and a standard deviation of 72 ± 45. The depressives and schizophrenics reported pain at a uniformly high level of stimulus intensity while the anxiety neurotics consistently reported pain at low stimulus intensities. Since the pain threshold, but not the warmth threshold, could be easily altered by varying the instructions, Hall and Stride suggest that pain threshold variations are due to "central attitude or pain-conceptualization and not to differences in peripheral sensitivity." Five additional studies, using the Hardy-Wolff-Goodell technique, which also failed to find consistency in the pain threshold have been recently reviewed by Beecher (1957).

Other workers using other methods have also found wide variability in the

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phine or other opiates. As pointed out below, morphine apparently gives "pain relief" by bringing about "freedom from anxiety" or "a bemused state." These terms also appear applicable to the "good" hypnotic *S* who becomes relatively unconcerned about and "relatively inattentive to all stimuli *except* the words of the operator and stimuli to which the operator specifically directs his attention" (Barber, 1957a).

To what extent hypnotic "analgesia" is due to each of these seemingly different mechanisms is a subject for further research.

[10] For a detailed descrption of this method see Hardy et al. (1952, pp. 67–85).

pain threshold. Although Hardy et al. (1940) had reported that all threshold measurements of their 3 *S*s (themselves) fell within ±12% of the mean, Lanier (1943), using an electric shock stimulus, found that the threshold of 15 college women showed a variation around the mean of −80 to +300%. He also found that some *S*s showed a relatively constant threshold while others showed wide variations in their pain threshold at different times. Clark and Bindra (1956), using thermal, electrical, and mechanical stimuli, have demonstrated wide individual differences in the pain threshold of 46 untrained *S*s. They attribute these variations to "attitudinal" variables such as the definition of pain, set, anxiety, and timidity.

After reviewing the many investigations in this area, Beecher (1957, p. 128) writes that "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." Similarly, Kutscher and Kutscher (1957) conclude, after reviewing the literature, that the pain threshold varies widely among human beings, provided that a sufficiently large group of *S*s is tested.

The second conclusion that appears to have been established by these investigations is that the pain threshold can be easily influenced by varying the instructions (Hall & Stride, 1954), by a wide variety of "distractions," and by placebos, analgesics, and hypnosis. Wolff and Goodell (1943) had earlier demonstrated that placebos, in some cases, elevated the pain threshold as much as 95%, that the distraction caused by retaining and repeating from 5 to 9 digits raised the threshold as much as 45% and that "shallow hypnosis" elevated the pain threshold by 40%. Subsequent work on the effects of analgesics and placebos on pain threshold will be discussed in the following section of this paper.

Kutscher and Kutscher (1957) have noted that the pain threshold can be significantly influenced by the operator administering the test. A report by Denton and Beecher (1949) indicates that this observation may be valid. Having failed to find any consistent effect of analgesic agents on pain threshold in trained subjects, these investigators requested the service of an individual who had had wide experience with the Hardy-Wolff-Goodell method. They found that this operator reported consistent elevations in the threshold, after the administration of an analgesic drug, when he knew which drug—a placebo or an analgesic—had been administered; however, when he did not know whether an effective drug or a placebo had been administered, he was unable to report any consistent threshold elevation.

That the pain threshold can be readily influenced by a wide variety of factors is not surprising if we stop to consider that determination of the human pain threshold does not even remotely resemble the determination of threshold responses of nerve fibers, nerve trunks, or other isolated physiological units; determination of the human pain threshold obviously requires judgment or interpretation on the part of the *S*. The *S* must interpret the stimulus in accordance with his concept of pain and interpretation clearly depends on *S*'s previous life-history and especially his specific history in responding to similar or related stimuli. In fact, the Hardy-

Wolff-Goodell method requires more than that *S* simply judge when he first becomes aware of a stimulus; he is required to determine when the stimulus first undergoes a qualitative change. Operationally, the Hardy-Wolff-Goodell "pricking pain threshold" refers to the *S*'s judgment that the feeling of warmth and heat has "swelled" and "drawn together" into a "very small" and "barely perceptible prick" at the "*exact end* of the 3-sec. exposure to the stimulus" (Hardy et al., 1952, p. 81). This "pricking" feeling must be interpreted by *S* as different not only from the warmth and heat which precede it but also from the "burning" which may be simultaneously present. It would indeed be suprising if such an intricate judgment could not be influenced by a wide variety of factors.

The Effect of Opiates on the Pain Response

As pointed out above, morphine and other opiates give "pain relief" without necessarily altering the pain threshold. Although Wolff, Hardy, and Goodell (1940) reported that the pain threshold is consistently elevated after morphine, subsequent investigations failed to confirm this conclusion. Andrews (1943), Chapman and Jones (1944), Denton and Beecher (1949), Isbell (cited by Wikler, 1950), Javert and Hardy (1951), and Kuhn and Bromiley (1951) found that after an analgesic dose of morphine the pain threshold may be elevated, may be lowered, or may remain unchanged.

A related line of research comparing placebos and analgesic drugs arrived at similar results. Denton and Beecher (1949) found, using the Hardy-Wolff-Goodell method, that a placebo had the same effect on pain threshold as an analgesic dose of morphine. Similarly, Birren, Schapiro, and Miller (1950) reported that a placebo (lactose) had the same effect on pain threshold as 0.6 gm. of acetylsalicylic acid and sodium phenobarbital. Isbell (cited by Wikler, 1950) also found no significant difference in the effect on the pain threshold when *S*s received morphine and when they received a placebo but were told they were being given morphine. Beecher (1957) has reviewed 10 additional investigations which also indicate that morphine and other opiates (*a*) do not necessarily elevate the pain threshold when they give "pain relief" and (*b*) if and when they do elevate the pain threshold, they do so to the same extent and possibly in the same way as placebos.

The evidence also indicates that opiates can give "pain relief" without altering "the awareness of pain" or "the pain sensation." Cattell (1943) has summarized the data indicating that "awareness of pain" is not necessarily altered by narcotics. Wolff et al. (1940, p. 677) have emphasized that after morphine administration "the pain sensation is perceived and is recognized as pain with no difficulties." Apparently, "the sensation of pain," in itself, is not necessarily "painful." "The sensation of pain" may be completely unaffected by morphine (and placebos, hypnosis, prefrontal leucotomy, etc.) and yet discomfort and suffering are no longer present.

The "pain relief," i.e., the mitigation of discomfort and suffering, which follows the administration of morphine and other opiates appears to be one component of a more generalized effect on the patient which has been variously conceptualized as "freedom from anxiety," "content-

ment," and "a bemused state." This viewpoint is perhaps best epitomized by Beecher (1957, p. 152) who writes after extensive clinical and experimental experience with analgesic drugs that "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." Along similar lines, Hill, Kornetsky, Flanary, and Wikler (1952a) have hypothesized that the "pain relief" following morphine administration is a consequence of a more generalized effect which they term relief of "anxiety" or "fear of pain." They tested this hypothesis by studying the effect of subcutaneous injection of 15 mg. of morphine on *S*'s ability to judge the intensity of electric shock stimuli under two conditions: (*a*) when *S*s were made "anxious" by not "familiarizing them with the potentially fear inspiring experimental situation," and (*b*) when "anxiety" was allayed by "reassurance, demonstration, and explanation." They reported the following:

> (*a*) Under conditions which promote anxiety or fear of pain, subjects tend to overestimate the intensities of painful stimuli; (*b*) morphine reduces such anxiety; (*c*) under conditions in which anxiety is largely eliminated, little if any overestimation of the intensities of painful stimuli occurs; (*d*) morphine does not affect the ability of subjects to accurately estimate the intensities of painful stimuli when anxiety is dissipated (p. 479).

Corroborative data were obtained in another study by the same group of investigators (Hill, Kornetsky, Flanary, & Wikler, 1952b). In an additional follow-up experiment, using thermal stimuli, Kornetsky (1954) also confirmed these results and concluded that morphine appears to be effective as an analgesic agent only when "anxiety" is present.

In summary, the investigations on narcotics suggest a similar conclusion as the investigations on prefrontal leucotomy and hypnosis which were summarized in an earlier section of this paper: discomfort and suffering are not inevitably associated with noxious stimulation; they appear to be components of a secondary "reaction to" the stimulus (which has been conceptualized as "anxiety" or "fear of pain") which can be minimized or eliminated by opiates hypnosis, placebos, prefrontal leucotomy, and other procedures.

The Placebo Effect

The effect of placebos on the pain response deserves further comment. Jellinek (1946) reported that 60% of 199 patients with chronic headaches received "relief" from a placebo on one or more occasions. In extensive studies of severe, steady, postoperative wound pain, Beecher (1955) and his collaborators (Lasagna, Mosteller, von Felsinger, & Beecher, 1954) found that about 35% of their patients received "satisfactory" relief from a placebo.[11] ("Satisfactory relief" is defined by these workers as "50 per cent or more relief of pain at 45 and 90 minutes after the administration of the agent.") Houde and Wallenstein (1953) and Keats (1956) have carried out similar studies and have confirmed the findings of the Beecher group.

How does a placebo relieve chronic headache or minimize the suffering

[11] This finding does not indicate that placebos are only 35% as effective as morphine. Morphine, in maximum safe dosages, results in "satisfactory" postoperative pain relief in only 75% of the same group of patients (Lasagna & Beecher, 1954). The placebo, therefore, is about half as effective as morphine in the same situation and among the same patients.

associated with a postoperative wound? As a first approximation to an answer, it seems difficult to disagree with Wolf's (1950, pp. 106–108) conclusion:

> The above "placebo" actions depended for their force on the conviction of the patient that this or that effect would result. . . . The fact that "placebo effects" occur depends, of course, on the generalization established repeatedly by numerous workers that the mechanisms of the human body are capable of reacting not only to direct physical and chemical stimulation but also to symbolic stimuli, words and events which have somehow aquired special meaning for the individual.

In general, the above studies and the many other studies on the effects of placebos on physiological functions and in psychotherapeutic situations, reviewed by Beecher (1955), Rosenthal and Frank (1956), and Kurland (1957) indicate that the placebo reactor is responding to a "drug" which he believes has curative properties. This belief appears to be a function of many factors: what the physician specifically tells the patient about the "drug," the patient's previous experience with drugs, his previous experience with physicians, his specific experience with the physician giving him the "drug," etc. The placebo response may be viewed as a direct function of "the stimulus"; however, "the stimulus" is not the ineffective, inert compound but the entire situation which includes the "drug," the words of the physician, and the patient's previous experience with physicians and drugs.

Placebo research is still in its infancy. As Kurland (1957) has pointed out, the effect of the placebo is usually stated in general terms, the duration of reactivity is usually not specified, and specific physiological measures are rarely reported. Studies of the differential effect of placebos are also rare. Are some individuals more prone to respond to placebos? Lasagna et al. (1954) studied 27 postoperative patients with the Rorschach, the TAT, the Wechsler-Bellevue Vocabulary Subtest, and a questionnaire filled out by the nurses on the wards. The 11 consistent placebo reactors differed from the 16 patients who never received pain relief from a placebo in a number of characteristics, among which were the following:

> The reactors were more productive of responses, more anxious, more self-centered and preoccupied with internal bodily processes, and more emotionally labile. They are individuals who seem more dependent on outside stimulation than on their own mental processes. These processes tend to be less mature than in the case of the non-reactors. The reactors are in general individuals whose instinctual needs are greater and whose control over the social expression of these needs is less strongly defined and developed than in the non-reactors . . . (p. 775).

However, Wolf, Doering, Clark, and Hagens (1957) contradict these conclusions: finding that intra-individual variations in response to placebos are as great as interindividual variations, they conclude that the placebo reactor cannot be predicted from a knowledge of the *S*'s characteristics. An interesting field of research has been opened for further inquiry.

Conclusions

The investigations summarized above suggest the following conclusions which may be significant for a theory of pain:

1. The generally accepted view, that "pain" has its "own" peripheral receptors and its "own" pathways in the central nervous system, is misleading. Nociceptive stimuli activate various types of nerve fibers which travel in more than one pathway in

the spinal cord and brain stem and which project by thalamic and extrathalamic pathways to wide areas of the cortex.

2. The response to a nociceptive stimulus is apparently brought about when a spatiotemporal pattern of neural activity set off by the noxious stimulus reaches segmental and suprasegmental centers. The pattern of neural impulses set off by noxious stimuli differs from the neural pattern set off by other stimuli in that the *relative* number of fibers of different sizes activated differ, and the relatively different fibers activated carry impulses of different energy value, of different frequency, and of different duration.

3. "Pain" in the sense of discomfort and suffering is *not* necessarily present when noxious stimuli are discriminated, differentiated, and localized. The few cases which have been reported of "congenital insensitivity to pain" suggest that an individual may be able to "sense" a noxious stimulus—i.e., may be able to discriminate and localize the stimulus and differentiate it from other stimuli—and yet not show withdrawal movements, physiological alterations, or discomfort. Also, discomfort and suffering can be minimized or totally eliminated in some *S*s by placebos, opiates, prefrontal leucotomy, and hypnotic procedures *without* necessarily altering the "sensation of pain" or elevating the pain threshold.

4. The mitigation of discomfort-suffering by prefrontal leucotomy, opiates, and, to some extent, hypnosis, appears to be secondary to a more generalized effect of these procedures. Prefrontal leucotomy "alleviates worry and concern" and "relieves anxiety"; morphine gives "freedom from anxiety" and brings about "contentment" and "a bemused state"; the hypnotic *S* is relieved of pain when he becomes "relatively inattentive and unconcerned about all stimuli to which the hypnotist does not specifically direct his attention." These terms appear to refer to a common behavioral matrix: a mitigated "readiness to respond" to stimulation. Apparently, discomfort and suffering follow nociceptive stimulation when the *S* "attends to" and "reacts to" the stimulus. Minimize this readiness to respond and "the sensation of pain" is no longer "painful"; it can become an isolated "sensation" unaccompanied by discomfort.

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