column because of buoyancy, and so the generation floor is probably the production floor. Methane is thermodynamically stable to temperatures higher than those that exist in sedimentary rocks, but it can be oxidized in the presence of water and sulfur compounds (*1*). The No. 1 Bertha Rogers well drilled to 9.6 km in the Anadarko Basin of Oklahoma produced some molten sulfur at a bottom hole temperature of 260°C in Cambro-Ordovician sediments but no methane. Was its absence due to lack of generation or to chemical destruction?

Many more detailed studies are needed to clarify hydrocarbon migration within fine-grained sediments and across lithologic boundaries. Today the exploration geologist wants to know how much oil may be in the reservoirs of an unexplored area. We can make realistic estimates of the amount of oil generated, but estimates of the quantities expelled, trapped, and lost are still based on comparisons with heavily explored areas rather than on a complete understanding of the processes involved.

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Intrinsic Mechanisms of Pain Inhibition: Activation by Stress

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Our understanding of the neural and neurochemical mechanisms of pain perception has greatly increased since the time when Melzack and Wall presented their gate control theory of pain (*1*). One development presaged by that theory was the discovery of a central nervous system substrate whose normal function appears to be pain inhibition. This substrate includes cells of the medial brain stem and fibers descending from them to the spinal cord dorsal horn. In the cord, the transfer of nociceptive information from peripheral fibers to ascending paths is modulated by these descending controls.

Stimulation-Produced Analgesia

Until recently, most of the evidence for an intrinsic pain-suppressive system came from studies of stimulation-produced analgesia (SPA). Electrical stimulation of the midbrain periaqueductal gray and other portions of the medial brain stem in awake rats caused profound analgesia (*2, 3*) without consistently causing deficits in other sensory or motivational functions. These findings suggested a natural pain-inhibitory role for these brain regions (*3*). Such studies have been amply reviewed (*4, 5*), and need be only briefly summarized here as follows:

1) Pain inhibition appears to result from activation of centrifugal controls since even spinally mediated nociceptive reflexes are blocked by SPA (*3*). That nociceptive responding of dorsal horn cells is inhibited by stimulation at SPA sites supports this view (*6*). Also, lesions of the nucleus raphe magnus and spinal dorsolateral funiculus can disrupt SPA and block the inhibitory effect of SPA on dorsal horn cells, suggesting a bulbar relay and spinal path responsible for these descending effects (*7*).

2) SPA requires the integrity of certain neurotransmitters (*8*), suggesting an active process of inhibition in which the pain-inhibitory message is transmitted across synapses by means of those substances (*3*). Chemical activation of the periaqueductal gray with glutamate excites nucleus raphe magnus cells (*9*) and causes analgesia (*9, 10*). Morphine and enkephalin increase neuronal ("multiple unit") activity only or best in SPA areas, only in awake animals, and to a degree that is closely correlated with their analgesic action (*11, 12*). Supporting the view that this activation during SPA causes animals to feel less pain is the finding that rats self-administer electrical stimulation at certain SPA sites only when concomitant noxious stimuli are also being applied (*3, 13*). Also the results of neurosurgical trials indicate that valid pain suppression occurs with medial brain stem stimulation in man (*14*).

3) An idea of heuristic value was that SPA shared with opiate drugs both central sites and mechanisms of action (*3*). Thus, for example, brain areas supporting SPA and analgesia from opiate mi-

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croinjections overlap considerably (*5, 15*), and SPA areas are rich in opiate receptors and opioid peptides (*16*). SPA manifests tolerance and cross-tolerance with morphine (*17*). Morphine analgesia, like SPA, is disrupted by lesions of the nucleus raphe magnus and spinal dorsolateral funiculus (*7*). Morphine analgesia and SPA are similarly affected by many drugs (*8*), including opiate antagonists (*18*). This finding with opiate antagonists proved controversial (*19*). However, we have recently shown that, whereas SPA was equally well elicited from periaqueductal gray and dorsal raphe regions of the midbrain, only SPA from the dorsal raphe area was blocked by the opiate antagonist naloxone (*20*). Apparently, opioid (naloxone-sensitive) and nonopioid (naloxone-insensitive) substrates of SPA exist in close proximity within the mesencephalon. This finding can be added to a list of observations suggesting that multiple intrinsic analgesia systems exist, some opioid-mediated, some not.

Summary. Portions of the brain stem seem normally to inhibit pain. In man and laboratory animals these brain areas and pathways from them to spinal sensory circuits can be activated by focal stimulation. Endogenous opioids appear to be implicated although separate nonopioid mechanisms are also evident. Stress seems to be a natural stimulus triggering pain suppression. Properties of electric footshock have been shown to determine the opioid or nonopioid basis of stress-induced analgesia. Two different opioid systems can be activated by different footshock paradigms. This dissection of stress analgesia has begun to integrate divergent findings concerning pain inhibition and also to account for some of the variance that has obscured the reliable measurement of the effects of stress on tumor growth and immune function.

Activation of Intrinsic Analgesia Systems by Stress

The most common approach today to the study of intrinsic pain-suppressive mechanisms is to investigate what environmental stimuli call them into play. We suggested (*21*) that the awareness of pain normally impels adaptive action essential for survival, and an analgesia system ought not, therefore, be activated trivially. In contrast, under emergency conditions, when pain perception could disrupt effective coping, pain inhibition would be more adaptive, a view supported by studies on the analgesic effect of certain stressors. However, the results of the earliest studies differed as to whether naloxone did (*22*) or did not (*23*) block this analgesia. Later reports did not resolve the question, although use of different stressors made comparison among these studies difficult (*24*). Some of our recent studies addressed this problem (*25*). Using rats and a single stressor, inescapable footshock with a fixed intensity and one of two temporal patterns, we found that both naloxone-sensitive and naloxone-insensitive stress analgesia can be reliably obtained. Thus, with a 60-hertz current of 2.5- or 3.0-milliampere intensity, 20 or 30 minutes of intermittent footshock (on for 1 of every 5 seconds) caused analgesia that was blocked by naloxone, whereas 3 minutes of the same footshock applied continuously caused equipotent analgesia unaffected by this drug (*25*). Other investigators also reported reliable elicitation of opioid and nonopioid forms of stress analgesia by manipulating the number of shock exposures (*26*) or the body region to which shock was applied (*27*). If stress is, as it seems, a physiological trigger for an intrinsic opioid-mediated analgesia system, it is equally apparent that a separate nonopioid mechanism also exists.

Subsequent studies confirmed the existence of opioid and nonopioid systems of stress analgesia by applying other criteria of opioid involvement. For example, tolerance developed with daily repetitions of the naloxone-sensitive form of stress analgesia but not the naloxone-insensitive form (*28*); and cross-tolerance was seen between morphine analgesia and only that form of stress analgesia blocked by naloxone (*27, 28*). The fact that cross-tolerance did not occur between the opioid and nonopioid forms of stress analgesia (*29*) confirms the separateness of their neurochemical substrates.

Because the pituitary-adrenal axis has a role in the adaptive response to stress, its involvement in stress analgesia seemed likely. We found that hypophysectomy attenuated only the opioid form of stress analgesia (*30*). However, hypophysectomy compromises the function of both adrenal cortex and medulla; and, because the adrenal medulla contains enkephalin-like peptides and secretes them in response to sympathetic activation (*31*), we next examined its role in stress analgesia. We showed that adrenalectomy, adrenal demedullation, and adrenal medullary denervation all blocked opioid but not nonopioid stress analgesia (*32*). Because demedullation and denervation had as great an effect as removal of the entire adrenal gland, because the three types of adrenal surgery had a greater effect on stress analgesia than did hypophysectomy, and because all these procedures affected only the opioid form of stress analgesia, we concluded that these effects resulted from the loss of adrenal medullary enkephalin-like peptides (*32*).

Subsequently we compared the brief (continuous) and longer duration (intermittent) parameters of footshock yielding nonopioid and opioid stress analgesia, respectively. We found that scopolamine, the muscarinic cholinergic antagonist, reduced only the opioid form of stress analgesia, whereas centrally inactive methylscopolamine was without effect (*33*). Moreover, the muscarinic agonist, oxotremorine, caused an analgesia that was sensitive to opiate antagonist blockade (*33*). It appears that central cholinergic and opioid systems interact in mediating this type of stress analgesia. Both opioid and nonopioid stress analgesia are disrupted by spinal dorsolateral funiculus lesions (*34, 35*), although lesions of nucleus raphe magnus whose neurons contribute importantly to this spinal path reduced only the nonopioid form [(*36*); see, however, (*37*)].

The specific neurochemistry of nonopioid stress analgesia has remained elusive. Mixed results have been obtained in attempts to alter nonopioid stress analgesia with various serotonin, norepinephrine, and dopamine agonists, antagonists, and depletors (*38–40*). We have suggested a role for histamine in mediating nonopioid stress analgesia, finding that H_1 but not H_2 antihistamines reduce stress analgesia from brief, continuous footshock (*39, 40*). Moreover, the fact that the histamine depletor, α-fluoromethylhistidine, also reduces this analgesia, whereas a mast cell degranulator compound 48/80 does not, suggests that neuronal stores of histamine are most important in this regard (*39, 41*).

Multiple Opioid Systems of Stress Analgesia

Analgesia from brief continuous footshock is itself not a unitary phenomenon. Both opioid and nonopioid mechanisms of stress analgesia can be reliably triggered by continuous footshock depending on relatively small differences in du-

ration or intensity. Although the opioid analgesia induced by brief continuous footshock and the opioid analgesia induced by the longer duration intermittent footshock stress (described above) equally satisfy various criteria of opioid involvement, they differ in several other neural and neurohumoral characteristics (*42*).

In an initial study in this series, we compared rats (*43*) divided into 48 groups (n = 8) consisting of 12 sets of footshock parameters (see Fig. 1) and four drug regimens. Footshock resulted from constant current 60-Hz sine waves delivered through a scrambler to the grid floor of a Plexiglas chamber (22 by 23 by 20 cm). All rats received two injections: (i) either sodium pentobarbital (55 mg/kg, intraperitoneally) or saline given 40 minutes before stress analgesia testing; (ii) either the long-lasting opiate antagonist, naltrexone (5 mg/kg, subcutaneously), or saline, given 20 minutes before stress. Pain responsiveness was assessed with the tail-flick test (*44*). Tail-flick latencies to radiant heat were measured at 1-minute intervals for 5 minutes before stress, the mean of the last three trials defining the baseline latency. Testing was resumed 1 minute after footshock and continued at 1-minute intervals for 10 minutes. A 7-second limit of exposure to the heat was used to minimize tissue damage to the tail.

First, the results from unanesthetized animals should be considered. Rats exposed to the same kind of footshock as that used in our earlier work showed comparable results since 3-minute continuous footshock (2.5 mA) produced analgesia not significantly (*45*) affected by naltrexone (Fig. 1B, center), and 20-minute intermittent footshock (2.5 mA) produced similar analgesia that was significantly reduced by this drug (Fig. 1D). As duration of continuous footshock was varied (Fig. 1B), analgesia in saline-treated rats did not vary in potency or duration for all values above 30 seconds (Fig. 1C). However, although naltrexone had no effect on analgesia from 4 or 5 minutes of continuous footshock, it significantly reduced analgesia in the 1- and 2-minute groups, just as it did in the 20-minute intermittent group (Fig. 1D). Similarly, holding footshock duration constant (3 minutes), but varying its intensity, resulted in analgesia that was significantly reduced by naltrexone at 1.5 and 2.0 mA and analgesia that was unaffected by this drug at 3.0 and 3.5 mA (Fig. 1E). Thus, within the range of continuous footshock parameters studied, briefer durations or lower intensities cause opioid analgesia as defined by naltrexone sensitivity (*46*), and longer durations or higher intensities cause analgesia insensitive to this drug and hence nonopioid in nature. It seems that the 2.5-mA, 3-minute continuous footshock conditions used in some of our earlier work (*30*) were at threshold for eliciting nonopioid stress analgesia, just between the briefer or weaker and longer or stronger values shown here to cause more purely opioid and nonopioid stress analgesia, respectively.

The results of this experiment suggest that for the continuous footshock parameters used there is a coulometric (intensity × duration) relation (*47*) such that, under our experimental conditions, naltrexone reduces stress analgesia only if the product of these variables remains below 7.5 mA·min (2.5 mA for 3 minutes) (*48*) (Fig. 2). However, these variables are not the sole determinants of the opioid or nonopioid nature of stress analgesia. For example, when the same total amount of footshock causing nonopioid analgesia (2.5 mA for 4 minutes) is applied intermittently (on for 1 of every 5 seconds) rather than continuously, it yields definite opioid analgesia (Fig. 1D). Thus, the temporal pattern of footshock or stress session length can also be made a critical factor.

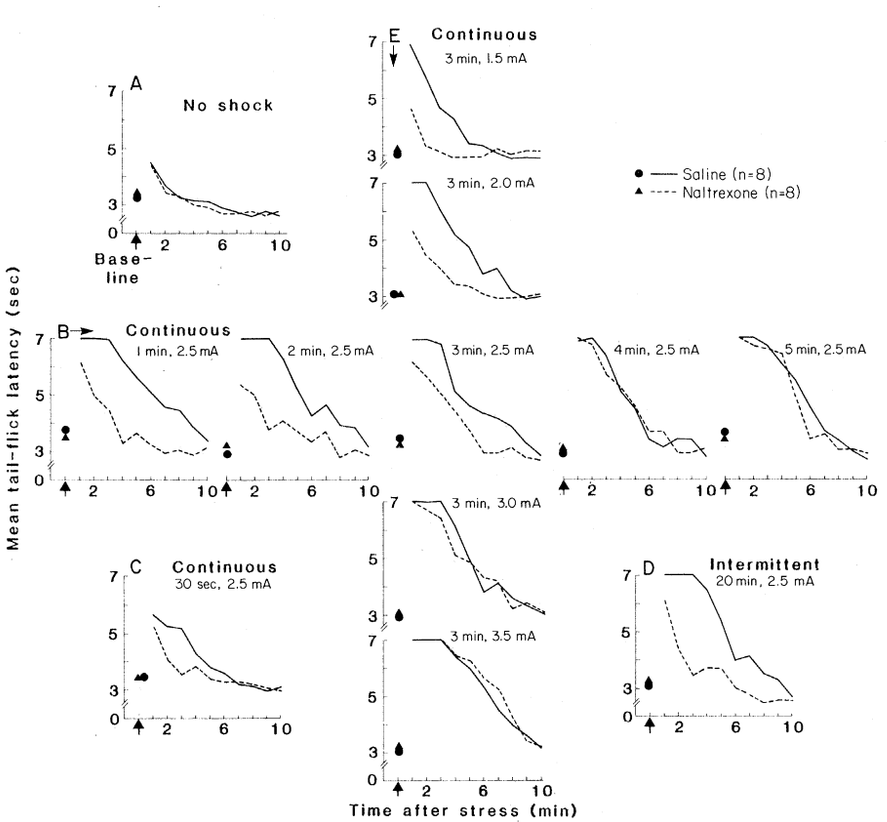


Fig. 1. The effects of naltrexone (5 mg/kg) on baseline and poststress tail-flick latencies with various paradigms of inescapable footshock. Whereas short duration (30 seconds or 1 or 2 minutes at 2.5 mA) or low intensity (1.5 or 2.0 mA for 3 minutes) parameters of continuous footshock produced analgesia significantly reduced by naltrexone, longer durations (4 or 5 minutes at 2.5 mA) or higher intensities (3.0 or 3.5 mA for 3 minutes) of footshock produced analgesia not significantly affected by this drug. Twenty minutes of intermittent footshock (1 out of every 5 seconds at 2.5 mA) also produced analgesia significantly attenuated by naltrexone.

Similarities Between the Two Opioid Systems

Additional evidence for the opioid and nonopioid bases of these stress analgesias comes from studies of the development of tolerance and cross-tolerance (*49*). Morphine-tolerant rats (*50*) exhibited significantly less stress analgesia than saline-treated controls (cross-tolerance) when footshock parameters were used that caused naltrexone-sensitive, but not naltrexone-insensitive, analgesia (*51*). Also, rats showed a significant reduction in analgesia (tolerance) after 14 daily exposures to these same opioid, but not nonopioid, procedures. Comparing various footshock parameters eliciting naltrexone-sensitive and -insensitive stress analgesia, we found that repeated exposure to one set of parameters caused a reduction in analgesia (cross-tolerance) on initial exposure to another set only if

both sets separately caused analgesia blocked by naltrexone. Thus, for example, rats exposed to 14 daily sessions of continuous footshock for 1 minute at 2.5 mA showed the same analgesia as naïve rats if given a nonopioid type of stress on day 15 (continuous for 4 minutes at 2.5 mA) but showed diminished analgesia if given another opioid type of stress (continuous for 3 minutes at 2.0 mA, or intermittently for 20 minutes at 2.5 mA). On the other hand, rats repeatedly given footshock for 4 minutes continuously at 2.5 mA manifested no cross-tolerance when exposed for the first time to any other set of footshock parameters (*52*).

This demonstration of cross-tolerance between the opioid forms of stress analgesia caused by continuous and intermittent footshock suggests that they share not only a common neurochemistry but also a common receptor, although the locus of this receptor is unknown. Further support for this hypothesis comes from studies of cross-tolerance between stress analgesia and SPA. As described earlier, opioid (naloxone-sensitive) and nonopioid (naloxone-insensitive) forms of SPA appear to coexist in close proximity in ventral and dorsal areas within the periaqueductal gray matter (*20*). Repeated exposure to either the 1-minute or 20-minute opioid stress analgesia causes a significant elevation in SPA thresholds (cross-tolerance) for the opioid but not nonopioid SPA sites (*53*). No such effect is seen after repeated exposure to the nonopioid (4-minute) stress (*53*).

Differences Between the Opioid Systems

Our previous findings that opioid stress analgesia from 20-minute intermittent footshock was reduced by hypophysectomy (*30*) and especially by adrenalectomy or adrenal demedullation (*32*) prompted an investigation into the role of these organs in opioid stress analgesia from continuous footshock (*51*). For conciseness of presentation, tail-flick latencies for each animal after stress were plotted as in Fig. 1 and an "analgesia score" was derived by measuring the area under the resultant curve, with the use of that animal's baseline latency as the ordinate's zero point. Although analgesia from the 20-minute paradigm was again significantly reduced by hypophysectomy (Fig. 3A) and even more so by adrenalectomy (Fig. 3B), neither surgical procedure had this effect on opioid or nonopioid stress analgesia from continuous footshock (Fig. 3, A and B) (*54*). It seems that stress analgesia from continuous footshock, at least within the range of values used in these studies, is independent of pituitary and adrenal mechanisms. The apparent reliance of the 20-minute intermittent form of opioid stress analgesia on adrenal medullary enkephalins (*32*) points to a first major difference between the two opioid mechanisms of stress analgesia.

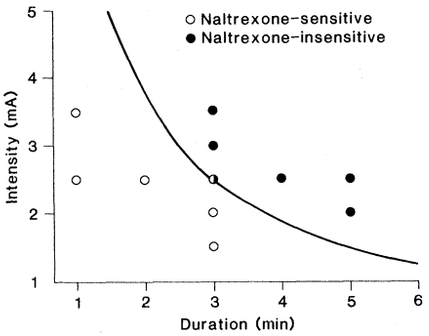


Fig. 2. Diagrammatic representation of the relation between footshock intensity and duration determining the opioid (naltrexone-sensitive) and nonopioid (naltrexone-insensitive) basis of analgesia from continuous footshock. Naltrexone-sensitive stress analgesia is seen only if the product of footshock intensity × duration is less than 7.5 mA·min. Apparently, this coulometric value of shock severity is at threshold between the briefer or weaker and longer or stronger values causing more purely opioid and nonopioid stress analgesia, respectively.

Another distinction between the two types of opioid stress analgesia is the different effect exerted on them by deep pentobarbital anesthesia (55 mg/kg). This effect is seen by considering the data from all 48 groups described earlier (including the 24 groups in Fig. 1). For conciseness, we have also converted these data to analgesia scores as above (Fig. 4). Whereas anesthesia virtually eliminated stress analgesia from the 20-minute intermittent footshock (Fig. 4A), it was completely without effect on opioid analgesia from continuous footshock of either short duration (Fig. 4A) or low intensity (Fig. 4B) (*54, 55*). In fact, anesthesia had no effect on analgesia from any of the continuous footshock paradigms, opioid or nonopioid, with or without naltrexone (Fig. 4, A and B) (*56*).

The mechanism by which pentobarbital anesthesia blocks stress analgesia from 20 minutes of intermittent footshock is not known. The depressant action of barbiturates on sympathetic ganglia (*57*) seems an obvious choice considering the importance of the sympathoadrenal system in this stress analgesia (*32*). The depressant action of this drug on forebrain function may also play a role in that disconnecting the forebrain from the lower brain stem by midcollicular decerebration blocks only that form of stress analgesia sensitive to pentobarbital (*58*). Moreover, only this paradigm of stress analgesia leads to an escape learning deficit termed "learned helplessness" (*59, 60*), produced by inescapable but not escapable shock (*61*). Thus, the pentobarbital-sensitive form of opioid stress analgesia appears to require the animal's perceiving the shock as inescapable (*62, 63*).

The fact that different stress parameters evoke opioid forms of analgesia that differ from one another in their reliance on hormonal systems, may help to explain some apparently discrepant findings. In some studies (*47, 64*), among them those of Watkins and Mayer and co-workers (*65*), opioid stress analgesia was not attenuated by hypophysectomy or adrenalectomy; in other studies—Maier's group (*66, 67*), ours (*32*), and others (*68, 69*)—opioid stress analgesia was blocked by such interventions. The fact that the opioid analgesia studied by Watkins and Mayer derived from short duration continuous shock and the one studied by Maier's group and ours from long duration intermittent shock is an encouraging "interlaboratory" parallel (*70*).

The differences between the two opioid forms of stress analgesia might reflect the existence of completely independent analgesia substrates or only different paths of access to a common neural core. That cross-tolerance develops between the brief continuous and prolonged intermittent opioid forms suggests they share a common synapse. Given this fact and the fact that spinal lesions disrupt both forms of stress analgesia (*34, 35, 58*) but bulbar raphe lesions disrupt only the continuous type (*36, 37*), we conclude that the two opioid systems follow separate pathways through the brain stem to the cord where they converge on and activate the receptor mechanism (possibly opioid) that they share.

The demonstration that footshock intensity can play a role in differentially producing opioid and nonopioid stress analgesia may prove integrative. For example, Watkins and Mayer have activated opioid and nonopioid analgesia in rats by selectively shocking the front paws and hind paws, respectively (*27*). They conclude that the body region shocked is critical for determining the opioid or nonopioid nature of footshock-induced analgesia (*27, 71*). We have also found that front paw shock can cause opioid analgesia and hind paw shock can cause nonopioid analgesia (*72*). However, in agreement with our findings from experi-

ments in which we shocked all four paws, we now find that lower shock intensities cause opioid analgesia and higher shock intensities cause nonopioid analgesia regardless of whether front paws or hind paws are shocked. Thus, we believe that the parameters of stress are more important than the body region shocked in determining the neurochemical bases of these forms of stress analgesia.

As is evident from the foregoing discussion, several groups have attempted a systematic analysis of electrical shock-induced analgesia in rats (*27, 73*). Yet even among these groups and despite collaborative efforts between them (*34, 59, 74*), some differences in results are apparent and some differences of opinion persist.

Immunosuppressive and Tumor-Enhancing Effects of Stress

These studies of stress analgesia make it clear that Selye's conception of stress (*75*) is no longer tenable. We have seen that different parameters of even a single stressor have different psychological, neurochemical, and endocrinological consequences. This view prompted us to investigate the relation of stress to alterations in immune function and tumor development, an area of research characterized by conflicting results (*76*). On the basis of our dissection of stress into parameters causing opioid and nonopioid forms of analgesia, we have sought to account for some of that variability.

Comparing so far only intermittent and continuous patterns of footshock (yielding opioid and nonopioid analgesia, respectively), we have found that only the parameters causing opioid analgesia are immunosuppressive and tumor-enhancing. These effects are blocked by naltrexone. We first showed that exposure of rats to intermittent, but not continuous, footshock decreased the mitogen-stimulated proliferation of T lymphocytes (*77*). We also found that the cytotoxic activity of rat splenic natural killer (NK) cells is reduced by only the intermittent footshock (*78*). In both cases, naltrexone given before stress prevented the immunosuppression (*77, 78*), and high doses of morphine mimicked the effect of opioid stress on NK cells (*78*). The findings with NK cells are noteworthy in that this subpopulation of lymphocytes is thought to have a special role in selectively recognizing and killing certain tumor cells (*79*). In this regard we have made parallel observations showing that intermittent footshock decreases percent survival and median survival time in rats injected with an immunogenic mammary ascites tumor (*77, 80*). This effect too is prevented by naltrexone (*80*) and mimicked by high doses of morphine (*81*). Suggestive as these findings are of a causal relation between NK suppression and enhanced tumor development, much more evidence is required before these effects can be considered more than correlated.

The foregoing studies reveal that seemingly minor differences in stress parameters (the same total amount of footshock applied intermittently compared with continuously) determine whether or not stress will be immunosuppressive and tumor enhancing, just as such parametric variations were seen to determine the neurochemical basis of stress analgesia. It also seems that these temporally different footshocks mean different things to the animals. As mentioned above, stressing rats with the intermittent, but not the continuous, footshock causes certain learning deficits, or "learned helplessness" (*59*), normally associated with inescapable shock. Inescapable, but not escapable, shock suppresses T-cell responsiveness to mitogens (*82*) and enhances tumor development in rats (*83*). In a collaborative study with Maier's group, we found that inescapable, but not escapable, tail shock suppresses NK activity in rats (*84*), and our initial data suggest that this effect is blocked by naltrexone. It seems reasonable to conclude that the experience of "helplessness" is important for the immunosuppressive and tumor-enhancing effects of stress we have seen, and that opioid peptides causing analgesia associated with "helplessness" (*59, 85*) are also involved in mediating these immunologic and oncologic effects.

Conditioned Activation of Intrinsic Analgesia Systems

Until now we have considered only the relatively short-term effects of stress, but stress can also have enduring effects. One enduring and adaptive response to stress is learning to associate neutral environmental cues regularly accompanying or preceding stress with its aversive properties. Thus, when rats are merely placed in a chamber where footshock has occurred many responses resembling those caused by the footshock can be observed. One such response is pain suppression, and this conditioned analgesia has been widely investigated. Results of the earliest studies differed as to whether or not naloxone blocked conditioned analgesia (*23, 86*). More recently, agreement seems to have been reached that this analgesia is opioid-mediated in that it can be blocked by opiate antagonists and shows cross-tolerance with morphine (*85, 87, 88*). This form of opioid stress analgesia appears not to depend on the pituitary-adrenal axis (*65*).

We have recently addressed the question of whether conditioned analgesia represents direct conditioning of the analgesic response to stress or rather conditioning of some mediating response such as fear. We found (*88*) that even when the analgesic response to stress was blocked on conditioning trials by administration of naltrexone, on the test day, when animals were exposed to the nonelectrified footshock apparatus and room cues, unmistakable conditioned analgesia occurred. Because conditioning took place in the absence of a normal analgesic response, we conclude that conditioned analgesia is actually an unconditioned response to a conditioned mediator. This hypothesis is further supported by the findings of Watkins and Mayer (*27*) that the opioid nature of conditioned analgesia is independent of the neurochemical (opioid or nonopioid) sequelae of the specific stressor used as the unconditioned stimulus during the acquisition phase. Moreover, it ties in well with a series of studies by Fanselow and his colleagues demonstrating the analgesic effects of conditioned fear (*89*). In view of these findings, investigators need be cautious in designing studies that involve repeated exposure to pain or stress to be assured that conditioned and unconditioned effects are not confused.

Conclusions

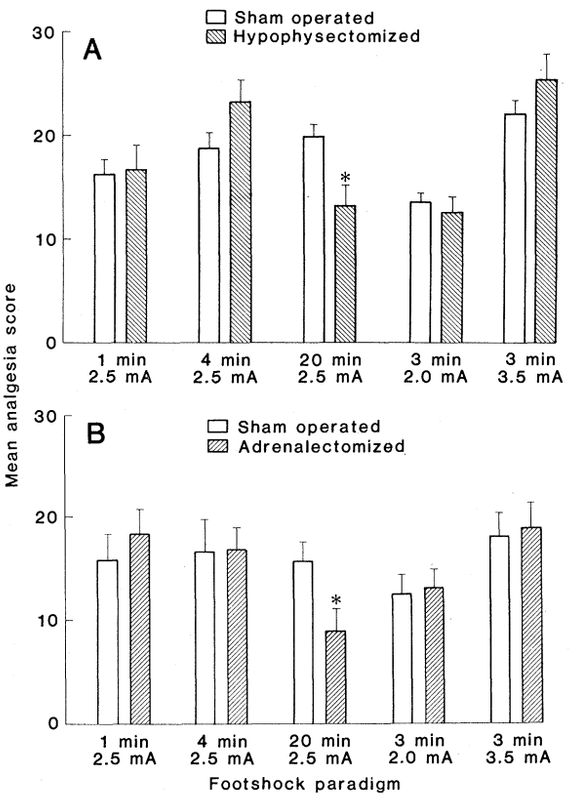
Studies of stress analgesia do not require sophisticated technology, and perhaps partly for this reason, many are now being conducted. In much of this work, in order for stress to cause significant pain inhibition (or immunosuppression) it must be relatively intense, inescapable, and perceived by the conscious animal. Therefore scientists engaged in or planning such studies should feel constrained not only to fulfill such obvious ethical requirements as minimizing stress parameters and number of subjects used but also to consider with special care the anticipated benefits of their research. Some relevant issues that we have considered and some areas in which we anticipate making useful gains are the following.

1) By studying the role of stress as a natural stimulus activating intrinsic pain-suppressive mechanisms of the brain, we expect to learn more about how these

mechanisms operate. Footshock, however, is obviously not itself a natural stimulus. But we have found it to be a useful tool with which to model stress. It is a quantifiable and reliable stimulus. It can be repeated without causing tissue damage and its aversive effects dissipate rapidly with stimulus termination. The fact that more natural stressors such as fighting (*90*), sexual arousal (*91*), food deprivation (*92*), and thermal stress (*93*) have also been reported to provoke analgesia supports the view that footshock is a valid stress model.

2) An interesting observation made in these studies is that both the opioid and nonopioid forms of stress analgesia from brief, continuous footshock can be observed in rats anesthetized with pentobarbital at doses usual for surgery. A series of electrophysiological studies in anesthetized rats provides an intriguing parallel at the cellular level to our behavioral findings. LeBars and his colleagues (*94*) found that noxious peripheral stimuli activate descending circuits that inhibit spinal nociceptive neurons, an effect that occurs across remote receptive fields and is apparently opioid mediated. Such findings make it evident that useful information about intrinsic pain-suppressive systems can be obtained from studies of the anesthetized preparation. However, despite the many advantages of using anesthetized animals, all new results obtained in this way need to be verified in the unanesthetized preparation. The observation that morphine activates neuronal firing in the medial brain stem of awake but not anesthetized rats (*12*) exemplifies the need for caution in interpreting data obtained from anesthetized animals. In any case, even if some forms of stress analgesia can be studied under anesthesia to clear ethical advantage, other forms unfortunately cannot.

3) Whether studies of stress analgesia will provide results that will lead to applications in humans remains to be seen. There are demonstrations of opioid and nonopioid analgesia evoked in man by one or another procedure that might be stressful, including acupuncture (*95*) and transcutaneous electrical nerve stimulation (*96*). In fact, in parallel with our stress analgesia findings, transcutaneous stimulation provides both opioid and nonopioid analgesia as a function of the precise parameters of stimulation (*97*). But comparisons between such studies and ours are difficult, and it seems unlikely that stressors such as we have studied can themselves ever be clinically useful anodynes. Nonetheless, elucidating the neuroanatomical and neurochemical bases of stress analgesia can reasonably be expected to lead ultimately to the development of new techniques for pain management, just as identifying the substrate of stimulation-produced analgesia in the rat resulted in neurosurgical applications (*14*). Perhaps the greatest promise for such development lies in explorations of nonopioid analgesia. Activating this system should cause pain inhibition lacking such unwanted opiate sequelae as tolerance and dependence. Determining its neurochemistry is an essential



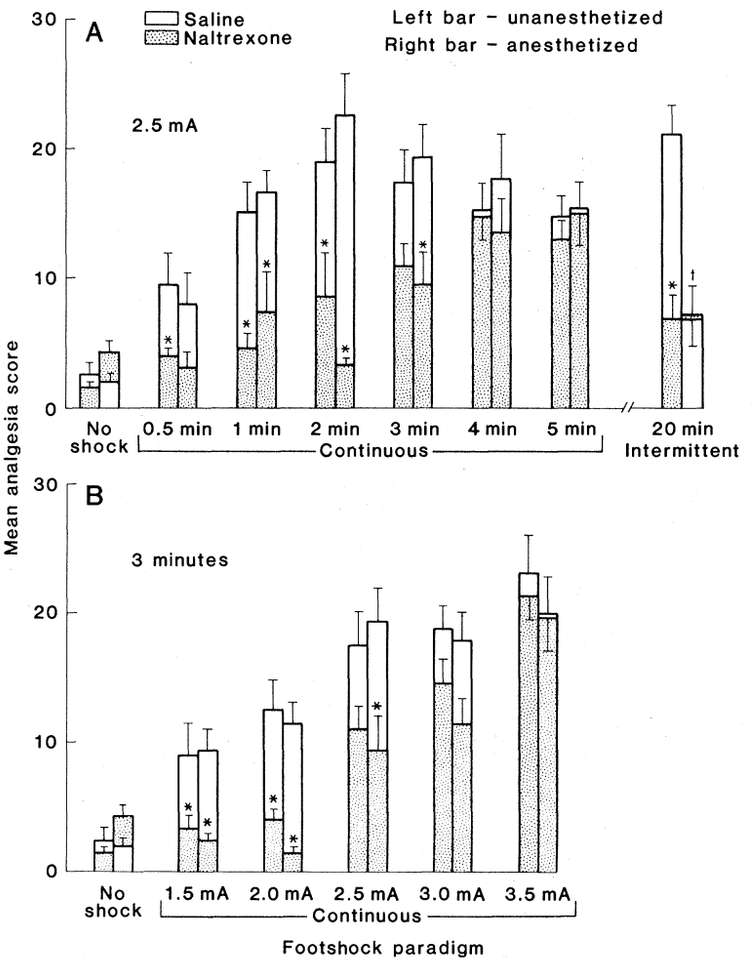


Fig. 3 (left). The effects of hypophysectomy (A) and adrenalectomy (B) on opioid and nonopioid stress analgesia produced by several paradigms of footshock (n = 8) 3 weeks after surgery. Whereas both hypophysectomy and adrenalectomy attenuated the opioid analgesia produced by 20 minutes of intermittent footshock at 2.5 mA, neither procedure had any effect on stress analgesia elicited by continuous footshock, irrespective of its opioid or nonopioid mediation. *Statistically significant differences from sham-operated control animals. Fig. 4 (right). The effects of pentobarbital anesthesia (55 mg/kg) on stress analgesia. Whereas anesthesia virtually eliminated stress analgesia from the 20-minute intermittent footshock (A), it had no effect on analgesia from any of the continuous footshock paradigms, opioid or nonopioid, with or without naltrexone (A and B). *Statistically significant difference between naltrexone-injected and saline-injected groups. †Statistically significant difference between anesthetized and unanesthetized groups.

first step to devising nonnarcotic analgesic drugs. Our results showing that opioid and nonopioid stress analgesia have comparable magnitude and duration suggest that such centrally acting nonnarcotics will be as potent as opiates.

4) Finally, by defining and bringing under control the precise parameters of footshock stress activating anatomically, neurochemically, and hormonally different analgesia substrates, we have begun to explain apparent discrepancies in stress analgesia investigations and account for some of the variance that has obscured the relation between stress and immune function and tumor growth.

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46. Like the opioid analgesia elicited by 20 minutes of intermittent footshock, we find that this form of analgesia can also be blocked by even very low doses of naltrexone (0.05 mg/kg, subcutaneously) or naloxone (0.1 mg/kg, subcutaneously) [G. W. Terman, J. W. Lewis, J. C. Liebeskind, *Proc. West. Pharmacol. Soc.* **26**, 49 (1983)].
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51. Conditions for testing opioid stress analgesia were 1 minute of continuous footshock at 2.5 mA, 3 minutes of continuous shock at 2.0 mA, and the usual 20 minutes intermittent footshock. Parameters for nonopioid stress analgesia were 4 minutes continuous at 2.5 mA and 3 minutes continuous at 3.5 mA.
52. Illustrating what seems to be a dynamic interaction between the mechanisms underlying opioid and nonopioid stress analgesia is the observation that no cross-tolerance occurs between the 4-minute and 1-minute treatments at 2.5 mA despite the obvious fact that the animal experiences daily the 1-minute footshock embedded within the 4-minute stress condition. It appears that the last 3 minutes of the 4-minute stress counteracts or eradicates whatever opioid influence the first minute generates.
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55. We acknowledge the problem in using the term "stress analgesia" to describe a reduction in the amplitude of a spinal nociceptive reflex caused by a footshock stimulus that, because of deep anesthesia, does not cause the usual psychological, physiological, and endocrinological reactions normally associated with or defining "stress." In spite of the semantic problem we point out the following. (i) If pain is a conscious perception and analgesia its absence, then another term without implication of consciousness, such as "antinociception," might be preferable. However, the same footshock conditions described here cause significant threshold elevations (unpublished data) in such responses as paw-lick, jump, and vocalization, which, unlike the tail-flick, are supraspinally mediated and suppressed by anesthesia; these findings indicate that nociceptive responses organized in the brain and requiring consciousness for their elicitation are also affected by footshock stress. Thus, "analgesia" may not be an inappropriate word in this context. (ii) Although stress, defined as pituitary-adrenal activation, is not a sufficient condition for eliciting analgesia (*23, 27*), a sufficient number of different kinds of stressors cause reductions in pain responsiveness to warrant use of some more generic descriptor such as "stress analgesia." Research into the adequate stimuli for stress analgesia and its physiological mechanisms may itself be expected to provide better definitions of the various terms used in these investigations, including the designation of the phenomenon (or phenomena) being studied.
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Trends in Industrial Use of Energy

Robert C. Marlay

Summary. Industry's use of energy, accounting for approximately 40 percent of U.S. consumption, changed significantly after 1973. In 1982 industry consumed one-third less energy than trends established before 1973 would have predicted. Part of this reduction resulted from improvements in the efficiency of industrial process technologies. Most is attributed, however, to slower growth in industrial economic activity and unprecedented changes in the composition of industrial output away from industries that consume large amounts of energy.

During the 10 years following the 1973 Arab oil embargo, significant changes took place in U.S. energy consumption (*1, 2*). After decades of steady growth, annual demand for energy leveled off and began to decline. Total energy consumption in 1983 was less than that in 1973, despite economic growth over this same period averaging 2.5 percent per year (*3–5*).

In response to higher prices, occasional fuel shortages, and other factors, individuals, businesses, and institutions reduced energy use to minimize rising energy costs. Consumers, for example, purchased more efficient vehicles and drove them less (*6*), and homeowners insulated their homes and turned down thermostats (*7, 8*). Some industries modernized their plants and equipment; others had to shut down because of obsolescence (*9–12*). Economic growth slowed, and the economy underwent a transformation, moving away from energy-intensive activities (*13*). By 1983, energy consumption had fallen more than 30 percent below what long-established historical trends would have otherwise predicted.

Development plans of a number of energy supply projects were disrupted. Particularly hard hit were those with long lead times for implementation. Large power plants are visible examples, but similar fates were dealt to liquefied natural gas import facilities, synthetic fuel plants, deep wells for natural gas, certain coal mines and petroleum refineries, expansion plans for uranium enrichment, and others.

In retrospect, such projects built on expectations of future energy requirements that failed to materialize within the time frames expected. Year after year, long-range forecasts were revised down (*14*). The extent of the revisions challenged the basic understanding of energy demand. Planning projections increasingly fell short. The resulting uncertainty about the need for future facilities, combined with high interest rates, had a chilling effect on new investment in energy production and supply.

This uncertainty raises a concern for energy planning. In an expanding economy with stabilized energy prices, might not energy demand again begin to rise and return to past patterns of growth? Then, because of the long lead times required for implementation, might not the energy facilities needed to meet the demand and nurture economic growth be years out of phase? A better understanding of energy demand would help to reduce this uncertainty and its associated risks, restore investor confidence in the legitimate need for certain energy supply facilities, and improve the infor-

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