rington, D. C. Fenimore, R. W. Farmer, *Biochem. Biophys. Res. Commun.* **85**, 55 (1978).
10. R. K. Sharma, N. K. Ahmed, G. Shanker, *Eur. J. Biochem.* **70**, 427 (1976).
11. J.-P. Perchellet, G. Shanker, R. K. Sharma, *Science* **199**, 311 (1978).
12. H. Ahrens and R. K. Sharma, Abstract 3063, 62nd Annual Meeting of the American Society of Biological Chemists, Atlanta, Ga., June 1978.
13. G. N. Gill and L. D. Garren, *Biochem. Biophys. Res. Commun.* **39**, 335 (1970).
14. R. K. Sharma and R. S. Sawhney, *Biochemistry* **17**, 316 (1978).
15. R. J. Lefkowitz, J. Roth, W. Pricer, I. Pastan, *Proc. Natl. Acad. Sci. U.S.A.* **65**, 745 (1970).
16. W. W. Davis and L. D. Garren, *J. Biol. Chem.* **243**, 5153 (1968).
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Narcotic Analgesia: Fentanyl Reduces the Intensity but Not the Unpleasantness of Painful Tooth Pulp Sensations

Abstract. *Forty subjects rated the magnitude of painful electrical stimulation of tooth pulp before and after the intravenous administration of either fentanyl, a short-acting narcotic, or a saline placebo. The responses were choices of verbal descriptors from randomized lists of either sensory intensity (that is, weak, mild, intense) or unpleasantness (annoying, unpleasant, distressing) descriptors. The fentanyl significantly reduced the sensory intensity without reducing the unpleasantness of the tooth pulp stimuli, indicating that the mechanisms of narcotic analgesia may include a significant attenuation in pain sensation in addition to effects on pain reaction. These results stress the importance of using multiple measures of pain.*

Present beliefs (*1*) about the mechanisms of pain and narcotic analgesia remain virtually unchanged since the influential reports by Beecher (*2*). Beecher distinguished between relatively invariant "pain sensations" that relate to the intensity of noxious stimuli and varied "pain reactions" that reflect complex emotional and cognitive responses elicited by such stimuli. The latter are influenced by personality, past experience, and experiential context. He proposed that narcotics produce clinical analgesia primarily by altering the unpleasantness of pain reactions rather than by altering the intensity of pain sensations. This view, prevalent for the past 20 years, has de-emphasized the role of sensory processes in narcotic analgesia.

We now report evidence from human subjects that fentanyl, a short-acting narcotic, can reduce the intensity of electrically induced tooth pulp pain sensations independent of the reaction, or unpleasantness, that accompanies these sensations. We asked subjects to rate the magnitude of sensory intensity and unpleasantness by direct procedures, this having been done with other sensory modalities, such as taste, olfaction, and temperature (*3*). The subjects quantified painful electrical stimulation of tooth pulp by choosing words from randomized lists of 12 words that described either the sensory intensity or the unpleasantness associated with stimuli of varying magnitude (see Table 1). This method facilitates discrimination of a single dimension because it forces judgments based on word meaning rather than other cues in rating scales such as rank order or position in a rank-ordered list of verbal or nonverbal categories.

The relative magnitudes of the words within a dimension are quantified reliably by ratio scaling procedures (*4*). Standard testing criteria reveal a high degree of objectivity for both the sensory intensity and the unpleasantness scales, which indicates that an individual scale is predicted equally well by another scale from that individual or by a mean scale from another similar group (*5*). The validity of using quantified verbal descriptors to discriminate between sensory intensity and unpleasantness has been shown in an additional study. Subjects rated either the sensory intensity or unpleasantness of electrocutaneous stimuli before and after the administration of diazepam, a minor tranquilizer. Diazepam altered only the unpleasantness scale, consistent with evidence showing that diazepam attenuates the aversive aspect of stimuli but does not alter sensory magnitude (*6*).

Forty dental patients scheduled for an oral surgical procedure (third molar extractions) participated individually in two 1-hour sessions approximately 1 week apart. Each subject was randomly assigned to either a sensory intensity or an unpleasantness descriptor group. Relative magnitudes of the descriptors were determined in the first session by asking each subject to match the force of handgrip strength and the duration of a button press to their perceptions of (i) the lengths of seven lines and (ii) the magnitude of the sensory intensity or unpleasantness implied by 12 descriptors presented twice in randomized order for each response measure. With this method, common responses (handgrip force or time duration) are made to both test (words) and standard (line lengths) stimuli, and ultimately the test stimuli are expressed in terms of the standard stimuli. Patient estimates of line lengths produced mathematical power functions that were used to transform the mean response to each word from units of handgrip force or time duration to common units of line length, referred to as units of relative magnitude. This procedure [for details see (*7*)] reduces bias that occurs in direct scaling experiments and permits the comparison of different response measures within individuals and the comparison of responses across individuals (*8*). After the descriptor scaling in

Table 1. The words used to describe the relative magnitudes of sensory intensity and unpleasantness. Each magnitude was determined by cross-modality matching of perceived handgrip force or duration of a button press to the magnitude of the sensory intensity or unpleasantness implied by each descriptor. Additional cross-modality matches to physically measurable line-length stimuli produced calibration functions used to transform mean handgrip or time-duration responses to each descriptor from units of force or time to common units of line length, referred to as units of relative magnitude.

Sensory intensity		Unpleasantness	
Descriptor	Relative magnitude	Descriptor	Relative magnitude
Extremely intense	59.5	Very intolerable	44.8
Very intense	43.5	Intolerable	32.3
Intense	34.6	Very distressing	18.3
Strong	22.9	Slightly intolerable	13.6
Slightly intense	21.3	Very annoying	12.1
Barely strong	12.6	Distressing	11.4
Moderate	12.4	Very unpleasant	10.7
Mild	5.5	Slightly distressing	6.2
Very mild	3.9	Annoying	5.7
Weak	2.8	Unpleasant	5.6
Very weak	2.3	Slightly annoying	3.5
Faint	1.1	Slightly unpleasant	2.8

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the first session, each subject received an ascending series of constant-current stimuli applied to the tooth pulp (1-second train of 1 msec, monopolar, monophasic, cathodal pulses delivered at 100 Hz) to determine current values for sensory threshold, pain threshold, and maximum pain tolerance (*9*).

The second session began 1 hour before the patient underwent oral surgery. Seven current intensities, varying in equal log steps from pain threshold to pain tolerance, were presented six times in randomized order at 20-second intervals. Impedance was monitored with every trial and maintained at constant levels by a 5-second air-jet stream which preceded each trial. Each subject rated the sensory intensity or the unpleasantness produced by each stimulus by choosing either a sensory or unpleasantness descriptor from a randomized list. After presentation of the stimuli, each subject was injected intravenously with either fentanyl (1.1 μg/kg) or saline placebo. The patients were informed that they would receive either a placebo or a small amount of one of the drugs used for sedation during their surgery. The instructions further specified that the clinical purpose of these drugs was not related to pain control since each patient would receive a local anesthetic. The oral surgeon, the experimenter, and the patient were not informed of the identity of the medications that were prepared by the surgical nurse who used a random sequence. Approximately 5 minutes after the intravenous injection, each subject repeated the descriptor scaling of another random series of 42 electrical stimuli applied to the tooth pulp.

A two-way analysis of variance with repeated measures (condition × stimulus) showed that in comparison to the responses after placebo administration, sensory responses were significantly reduced after the administration of fentanyl [$P < .05, F(1, 18) = 6.48$] (Fig. 1). The mean reduction in sensory intensity was 51 percent. A stimulus originally perceived as barely strong was rated as mild, and a stimulus originally perceived as mild was called weak, after fentanyl administration.

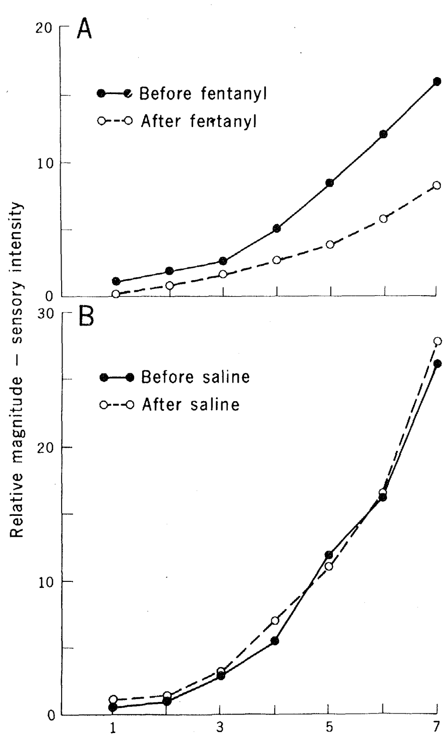

Fig. 1. The relative magnitude of sensory intensity. Relative values of patients' verbal responses to electrical stimulation of tooth pulp before and after the intravenous administration of (A) fentanyl (1.1 μg/kg) and (B) saline. Seven stimuli that increase in equal log steps from pain threshold (17.8 ± 8.9 μA; mean ± standard deviation) to pain tolerance (32.9 ± 23.8 μA) are shown on the abscissas; the relative magnitude of the sensory intensity is shown on the ordinates. Each point is the geometric mean of 60 observations from ten subjects. Symbols: ●, responses before, and ○, responses after the intravenous administration of fentanyl or saline.

The demonstration of a narcotic-induced reduction in the sensory intensity of the noxious stimulation of tooth pulp is consistent with physiological evidence of narcotic modification of sensory aspects of nociceptive input in the spinal cord dorsal horn and in trigeminal nucleus caudalis (*10, 11*). The narcotic-induced reduction in sensory intensity in human subjects also correlates with the behavioral evidence of decreased sensory discrimination by monkeys of noxious thermal stimuli after the administration of morphine but not diazepam (*12*). This behavioral evidence and the present psychophysical evidence in man contribute to a growing physiological literature on opiate effects on neurons involved in sensory-discriminative aspects of pain (*10, 13*). It appears that narcotic analgesics have a greater influence on pain sensation than previously suspected from Beecher's findings and from earlier largely anecdotal and clinical reports (*2*).

As shown in Fig. 2, the results with the unpleasantness descriptors differ from those found with the sensory intensity descriptors, the reduction in unpleasantness responses after fentanyl administration not being significantly greater than the reduction after placebo [$F(1, 18) = 2.53$]. However, a comparison of Fig. 2, A and B shows a trend in which unpleasantness judgments are reduced further by placebo than by fentanyl. This trend is consistent with previous observations that suggest that the amount of pleasantness or unpleasantness associated with narcotic analgesics depends on the situational context in which they are administered. Thus, when fentanyl is administered, the placebo factors that reduce unpleasantness may be partially offset by the dysphoric side effects of anxiety, fear, and nausea known to accompany the administration of narcotics to human subjects free of pain (*14*). In contrast, patients suffering from pathological pain often report experiences of heaviness, warmth, and euphoria (*14*). Therefore, it is important to repeat these experiments in patients with chronic pain.

Although we used strict double-blind procedures, fentanyl produced immediate and profound behavioral effects rarely observed after placebo administration. We repeated this study to ensure that the observed results reflected the action of fentanyl and not the influence of expectancies related to the presence or absence of a subjective drug effect. All subjects in the second study received an active placebo (diazepam; 0.11 mg/kg) immediately before either fentanyl or saline. All other conditions were identical to the first study. Diazepam was administered so that both groups of subjects

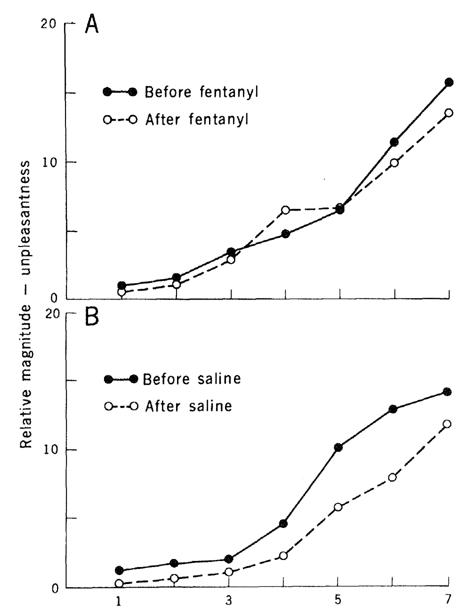

Fig. 2. The relative magnitude of unpleasantness. Relative values of patients' verbal responses to electrical stimulation of tooth pulp before and after the intravenous administration of (A) fentanyl (1.1 μg/kg) and (B) saline. Seven stimuli that increase in equal log steps from pain threshold (17.0 ± 9.4 μA) to pain tolerance (32.3 ± 24.3 μA) are shown on the abscissas; the relative magnitude of the unpleasantness is shown on the ordinates. Each point is the geometric mean of 60 observations from ten subjects. Symbols: ●, responses before, and ○, responses after the administration of fentanyl or saline.

(receiving placebo or fentanyl) experienced a profound subjective drug effect. There is evidence that diazepam produces no sensory effects (*15*). The results of the second study were similar to the results of the first (*16*), in that the sensory intensity responses were reduced significantly in comparison to the responses with placebo. Unpleasantness responses were not significantly reduced, although a clear trend of greater reduction after placebo was noted. These results show that although subjective effects of fentanyl could be detected, they did not influence the results.

Our experiments demonstrate that the words chosen for a pain scale can influence significantly the outcome of experimental and clinical studies of the efficacy of pain control agents. They also indicate the need for independent measures of the multiple dimensions of the pain experience (*17*). In studies in which singular indices of pain are used, critical pain dimensions may not be assessed adequately.

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References and Notes

1. A. Goth, *Medical Pharmacology* (Mosby, St. Louis, 1972), p. 278; J. H. Jaffe, in *The Pharmacological Basis of Therapeutics*, L. S. Goodman and A. Gilman, Eds. (Macmillan, New York 1975), p. 248.
2. H. K. Beecher, *J. Chron. Dis.* **4**, 11 (1956); *Science* **130**, 267 (1959); *Measurement of Subjective Responses* (Oxford Univ. Press, New York, 1959); *Science* **151**, 840 (1966).
3. H. R. Moskowitz, R. A. Kluter, J. Westerling, H. L. Jacobs, *Science* **184**, 583 (1974); G. Mower, R. Mair, T. Engen, in *The Chemical Senses and Nutrition*, M. Kare and O. Maller, Eds. (Academic Press, New York, 1977), p. 104; D. A. Thompson, H. R. Moskowitz, R. G. Campbell; *J. Appl. Physiol.* **41**, 77 (1976); G. Mower, *J. Comp. Physiol. Psychol.* **90**, 1152 (1976); R. L. Doty, *Percept. Psychophys.* **17**, 492 (1975).
4. R. H. Gracely, P. McGrath, R. Dubner, *Pain* **5**, 5 (1978).
5. The ratio-scale values for these descriptors have been reliable within subjects from session to session (mean $r = .93$) and reliable between individual subjects and mean scales from groups of 15 subjects similar in age and education (mean $r = .93$). These equivalent correlations show that an individual scale is predicted equally well by another scale from either that individual or a similar group. This equivalence shows that the scales are highly objective and supports the use of group normative descriptor scales for the analysis of individual scaling data [J. P. Guilford, *Psychometric Methods* (McGraw-Hill, New York, 1974)].
6. R. H. Gracely, P. A. McGrath, R. Dubner, *Pain* **5**, 19 (1978); C. R. Chapman and B. W. Feather, *Psychosom. Med.* **35**, 330 (1973); K. Blum, *Psychopharmacology* **17**, 391 (1970); H. E. Shannon, *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **33**, 474 (1974).
7. B. Tursky, in *Pain: New Perspectives in Therapy and Research*, M. Weisenberg and B. Tursky, Eds. (Plenum, New York, 1976), p. 171.
8. S. S. Stevens and H. B. Greenbaum, *Percept. Psychophys.* **1**, 439 (1966); S. S. Stevens, *Psychophysics: Introduction to Its Perceptual, Neural and Social Prospects* (Wiley, New York, 1975).
9. Stimuli from 6 to 100 μA were delivered by means of a hand-held nylon probe to the labial surface and incisal edge of intact healthy upper central incisors. The electrode was incorporated into the notched end of the probe, and contact was made with conductive paste. The metal handle of the probe served as an indifferent electrode. In a related study (M. W. Heft, R. H. Gracely, P. A. McGrath, R. Dubner, unpublished observations) we have shown that the sensations produced by these stimuli arise from pulpal nerve fibers rather than as a consequence of current spread to nonpulpal fibers in adjacent periodontal and gingival tissue. Dental patients undergoing endodontic treatment did not perceive stimuli up to 100 μA applied to saline-filled pulp chambers after the pulpal nerves were removed.
10. See D. J. Mayer and D. D. Price [*Pain* **2**, 379 (1976)] and Liebeskind and Paul (*11*) for reviews.
11. J. C. Liebeskind and L. A. Paul, *Annu. Rev. Psychol.* **28**, 41 (1977).
12. R. L. Hayes, R. D. Harris, P. J. Wolskee, R. Dubner, *Neurosci. Abstr.* **3**, 483 (1977).
13. D. D. Price and R. Dubner, *Pain* **3**, 307 (1977).
14. L. Lasagna, J. M. von Felsinger, H. K. Beecher, *J. Am. Med. Assoc.* **157**, 1006 (1955); G. M. Smith and H. K. Beecher, *J. Pharmacol. Exp. Ther.* **136**, 53 (1962).
15. C. R. Chapman and B. W. Feather, *Psychosom. Med.* **35**, 330 (1973).
16. R. H. Gracely, R. Dubner, P. A. McGrath, unpublished observations.
17. R. Melzack, *Pain* **1**, 277 (1975); ____ and K. L. Casey, in *The Skin Senses*, D. R. Kenshalo, Ed. (Thomas, Springfield, Ill., 1968), p. 423; R. Melzack and W. S. Torgerson, *Anesthesiology* **34**, 50 (1971).
18. We thank D. P. Butler, M. W. Heft, A. A. Macynski, and J. B. Sweet for assistance, and G. J. Bennett, R. L. Hayes, and D. D. Price for critical comments of the manuscript.

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Possible Mechanism for Pressurized-Liquid Tank Explosions or BLEVE's

Abstract. *The hypothesis is made that rapid depressurization of hot, saturated liquids may result in an explosion. The temperature of the hot liquid must, however, be above the superheat limit temperature at 1 atmosphere, and the drop in tank pressure must be very rapid. Two examples of large-scale pressure-letdown explosions are cited and possible preventative measures suggested.*

Reports of explosions of tank trucks or railroad cars carrying pressurized liquids are frequently in the news. Investigation of such accidents usually reveals a common scenario. The tank truck or railroad car has been involved in an accident with a resultant fire. Energy transfer from the fire to the tank has two effects. First, the liquid contents are heated, and there is a concomitant rise in tank pressure as determined by the vapor pressure of the liquid. The tank metal wetted by the liquid increases only slightly in temperature, although the pressure can change significantly since the vapor pressure is an exponential function of temperature. Second, for areas of the tank not in contact with liquid, there is no efficient heat absorption mechanism and the fire can lead to rapid and large increases in the temperature of the metal. In time, the pressure rise causes the safety valves to operate and more fuel is released to exacerbate the local fire. Eventually, through a combination of high internal tank pressure and high metal wall temperatures in regions not covered by liquid, localized metal failure is initiated.

To this point, the mechanism described is well accepted and is normally invoked in explaining BLEVE's (boiling liquid expanding vapor explosions). The new element suggested in this report concerns events that immediately follow the initial failure of the tank metal. Soon after metal failure there is usually an explosion accompanied by a shock wave that destroys and often fragments the tank. The very rapid release of fuel is manifested in an impressive fire—even a fireball—and portions of the tank can be scattered over a wide area. In some cases there may be a secondary fuel-air explosion not dissimilar to those used by the military to produce damaging shock waves over wide areas. The question of primary interest is: What is the source of the initial powerful explosion?

The explanation suggested here is related to the behavior of the hot liquid as the tank is very rapidly depressurized after failure of its metal wall. Just before failure, the liquid was saturated—that is, the temperature and pressure were as expected for a system where the liquid was in equilibrium with the vapor phase. With a rapid decay in tank pressure due to failure of the metal wall, the bulk liquid should boil and reduce the temperature to a value compatible with the lower pressure. But initiation of the boiling process requires efficient nucleating sites. There are no such nucleating sites in the bulk of the liquid, and for a brief period after depressurization, this bulk liquid is superheated—that is, at a temperature higher than the boiling temperature predicted at the existing pressure. If the bulk temperature is sufficiently above the expected boiling point, a superheated liquid-vapor explosion would be expected. Such explosions are known to occur in the microsecond time domain with concomitant shock waves.

Superheated liquid-vapor explosions occur frequently in some industrial operations. Usually, however, they occur when two liquids—one hot and nonvola-

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