

Analgesic Action and Pharmacokinetics of Morphine and Diazepam in Man:

An Evaluation by Sensory Decision Theory

J. C. Yang, M.D.,* W. Crawford Clark, Ph.D.,† S. H. Ngai, M.D.,‡ Barry A. Berkowitz, Ph.D.,§
Sydney Spector, Ph.D.¶

The analgesic actions of intravenously administered morphine, 0.14 mg/kg, diazepam, 0.14 mg/kg, and saline solution, 10 ml, were studied in three groups of volunteers by observing their responses to thermal stimulation for approximately four hours. Serum concentrations of morphine, determined by radioimmunoassay, decreased with time from 30 min to three hours, with a half life of about 120 min. Treatment of the data by traditional pain threshold techniques revealed a marked increase in the pain threshold in the group treated with morphine. Treatment of the data by nonparametric sensory decision theory revealed that morphine, and to a lesser extent diazepam, decreased discriminability, $P(A)$, among the thermal stimuli. This suggests that less sensory information arrived centrally. Both drugs increased the subject's response bias, B , fewer pain reports. The decrease in $P(A)$ and the increase in B suggest that morphine and, to a lesser extent, diazepam, possess analgesic action. Subjects treated with saline injections showed no significant change in traditional pain threshold, discriminability or response bias over time. The changes in traditional pain threshold and sensory decision indices induced by morphine lasted at least three hours after injection and did not correlate with the rapidly declining serum concentrations of morphine. The duration of analgesia was greater than that found clinically, presumably because the anxiety component was missing in experimental pain. Based on these observations, the sensory, $P(A)$, and psychological, B , components of sensory decision theory could prove useful in distinguishing between the analgesic and the mood-altering properties of analgesics used for the treatment of clinical pain. (Key words: Analgesia; measurement. Analgesics, narcotic: morphine. Hypnotics: benzo-

diazepines, diazepam. Pain: experimental; sensory decision theory. Pharmacokinetics: morphine.)

IT HAS LONG BEEN BELIEVED that analgesics are ineffective in man in modifying experimental pain, presumably because emotional factors often associated with clinical pain are absent.¹ However, another possibility exists: the traditional psychophysical procedures used to determine threshold may be defective. By means of a new psychophysical procedure called signal-detection or sensory decision theory,² Clark³ demonstrated that the traditional pain threshold is influenced by non-sensory (psychological) variables, and hence is a poor index of sensory sensitivity.

The psychophysical and computational procedures have been described in detail by Clark.⁴ Lloyd and Appel⁵ and Clark⁶ have recently reviewed the rapidly increasing number of pain studies using sensory decision theory. A critique by Rollman⁷ and a reply by Chapman⁸ have also appeared.

Sensory decision theory is a psychophysical procedure that separates the sensory or discriminative component of a threshold from the psychological aspect. The sensory component, d' , or its nonparametric equivalent, $P(A)$, provides a relatively pure measure of discriminability between stimuli of various intensities. The psychological component, the likelihood ratio criterion, L_x , or its nonparametric equivalent, response bias, B , identifies the subject's reluctance or readiness to report a particular sensory experience as painful.

The results of recent studies⁹⁻¹¹ suggest that experimental pain responds to analgesics when sensory decision theory is employed. Such results are encouraging, since laboratory studies offer a convenient and swift means for the screening of drugs. In the present study, morphine and diazepam were used to investigate the effect of a recognized analgesic and psychotropic drug on sensory theory parameters as well as the traditional pain threshold. Diazepam was chosen because of the controversy surrounding its possible analgesic effects.

Chapman and Feather¹² found that orally administered diazepam failed to alter either d' or the pain criterion to noxious thermal stimulation, suggesting

* Assistant Professor of Anesthesiology, Columbia University.

† Research Scientist, New York State Psychiatric Institute.

‡ Professor of Anesthesiology and Pharmacology, Columbia University.

§ Associate Member, Roche Institute of Molecular Biology. Current address: Department of Pharmacology, Smith, Kline and French Laboratories, Philadelphia, Pennsylvania 19101.

¶ Member and Head, Department of Physiological Chemistry, Roche Institute of Molecular Biology; Adjunct Professor of Anesthesiology and Pharmacology, Columbia University.

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Address reprint requests to Dr. Yang.

TABLE 1. Response Scale* and Its

Values of <i>B</i>	14	13	12	11	10	9
Response categories	Nothing	Maybe something	Faint warmth	Warm	Hot	Very hot

* The scale presented to the subject contained only the verbal report categories from Nothing to Very painful.

that analgesia had not been produced. Hall *et al.*¹³ reported that diazepam increased the thermal pain and pressure pain thresholds in some subjects. This conclusion, however, has been questioned by Chapman,¹⁴ who argues that the statistical treatment of the data was inadequate.

The purpose of the present study was to compare the effects of morphine, diazepam, and saline solution on traditional pain threshold, as well as on the sensory decision theory variables, discriminability, $P(A)$, and response bias, B , and to relate these measures to serum levels of morphine at half-hour intervals for three hours.

Materials and Methods

Twenty healthy young male volunteers (body weights 64–78 kg) were randomly assigned to three treatment groups: six subjects received morphine, 0.14 mg/kg; seven received diazepam, 0.14 mg/kg; seven received saline solution, 10 ml. All substances were injected intravenously. The volunteer was informed that he would receive an intravenous injection of morphine, diazepam, or saline solution, and that blood samples would be taken. Possible physiologic and psychological effects were described, and the subjects signed an informed consent form. The subject and the experimenter who administered the thermal stimuli were blind with respect to which of the three substances was injected.

Venous blood samples (3 ml) were obtained from an indwelling catheter from the arm opposite the injection site before and 5, 30, 60, 90, 120, 150, and 180 min after the injection. The samples were stored in cold until centrifuged, and then frozen until analyzed by radioimmunoassay according to the method of Spector.¹⁵ This assay is specific for morphine and is sensitive to picograms (10^{-12} g) amounts of the drug. Half-lives were estimated using the slope of linear regression lines calculated after logarithmic conversion of data according to the technique of Greenblatt *et al.*¹⁶

The radiant-heat stimuli were presented by a hand-held Hardy-Wolff-Goodell Dolorimeter** gunlike

projector, which housed a 100-watt projector bulb. The stimulus duration was 3 sec, unless the subject withdrew his arm. Withdrawal latencies were determined to ± 0.01 sec by means of a microswitch mounted on the tip of the projector. The output of the lamp was calibrated at each of the stimulus intensities used by means of a standard thermopile†† and a potentiometer-type galvanometer. The 2-cm-diameter heat stimuli were presented sequentially to seven patches of India ink applied to the volar surface of each forearm. The stimuli were presented every 15 sec; this allowed ample time (3 min) for the skin to return to its initial temperature. Temperatures of skin were determined by a thermistor‡‡; no change over time or among groups was observed.

The session was divided into eight periods, one preinjection period and seven postinjection periods, which began 15, 45, 75, 105, 135, 165, and 195 min after the injection. During each period, 98 stimuli, 14 at each of seven intensities, 0, 90, 180, 270, 320, 370, and 400 $\text{mcal}\cdot\text{sec}^{-1}\cdot\text{cm}^{-2}$, were presented randomly with respect to intensity. Each period involved 20 min of testing and 10 min of rest. The volunteer was instructed to assign each sensory experience to one of the categories on a scale ranging from Nothing to Very painful placed before him (table 1).

The stimulus–response data were analyzed in two ways: by the traditional method of constant-stimuli technique and by nonparametric sensory decision theory. The traditional pain threshold was obtained by dichotomizing the response continuum mentioned above in table 1 into “painful” and “not painful” report regions. The percentages of “painful” reports at the seven stimulus intensities were then treated by probit analysis¹⁷ to yield the best-fitting psychophysical ogive and the interpolated stimulus intensity at which the subject reported pain 50 per cent of the time.

A nonparametric sensory decision theory approach described by McNicol¹⁸ was used to generate measures of discriminability, $P(A)$, and response bias, B . $P(A)$

** Williamson Development Co., West Concord, Mass.

†† Williamson Development Co., Model RT2, West Concord, Mass.

‡‡ Yellow Springs Instrument Co., Yellow Springs, Ohio.

Relationship to Values of B , Response Bias

8	7	6	5	Withdrawal Times (Sec)			
				4	3	2	1
Very faint pain	Faint pain	Pain	Very painful	2.66	2.32	2.00	≤1.99
				3.00	2.65	2.31	

is a nonparametric measure similar to d' . It indexes the subject's ability to distinguish between two stimuli of different intensities; the higher the value of $P(A)$, the fewer are the errors made by the volunteer. B is a nonparametric measure akin to the likelihood ratio criterion, L_x . It locates the subject's criterion for reporting pain; a high value indicates few pain reports. Since $P(A)$ is not normally distributed, it must be transformed to $2 \arcsin \sqrt{P(A)}$ [$2ARS - P(A)$] for statistical analysis. McNicol¹⁸ has elucidated the advantages of the nonparametric approach, a brief description of which appears in the Appendix.

Values of discriminability, $2ARS - P(A)$, and response bias, B , were computed for each subject, during each of eight periods at each of six pairs of stimulus intensities from 0–90 to 370–400 $\text{mc} \cdot \text{sec}^{-1} \cdot \text{cm}^{-2}$. Dunnett's test, which is more conservative than the t -test, was used to compare at each time period 1) each of the drug treatment means with the saline group mean, and 2) each of the within-treatment groups with its preinjection control period. This test sets an α level of significance, which is appropriate when a number of comparisons are to be made among several drug treatments and a single control condition. Winer¹⁹ recommends this test since the comparisons are not independent of each other. He notes that Dunnett's test may be undertaken regardless of the outcome of the overall analysis of variance F -tests. However, individual, two-factor (three treatments by eight periods) analyses of variance at each of the six pairs of stimulus intensities were also undertaken separately for discriminability and report criterion. These statistical analyses and associated tables are too voluminous to present here, but are available. §§ All values of $p < .05$ were considered significant. The data were then averaged over all stimulus intensity pairs to provide a convenient summary of the results, and to permit comparisons with traditional pain threshold measures and plasma morphine levels.

Results

The serum concentration of morphine was highest 5 min after intravenous injection (0.17 $\mu\text{g}/\text{ml}$) (fig. 1). There was a rapid decline of morphine concentra-

tion 30 min after injection. The mean half-life of morphine in the serum during the elimination phase was 120 ± 8 min.

The 50 per cent pain thresholds increased over time from the preinjection value of approximately 295 to 390 and 335 $\text{mc} \cdot \text{sec}^{-1} \cdot \text{cm}^{-2}$ for morphine and diazepam, respectively. The saline control group showed little change (fig. 2). A two-factor analysis of variance for drug treatment by period yielded a significant period effect, $F(7,119) = 3.61$, which was due to the morphine group only.

Changes in thermal discriminability, $2ARS - P(A)$, averaged over all stimulus intensities (fig. 3), show that the mean discriminability for the saline control group did not change over time. Discriminability for the morphine group declined rapidly relative to both the saline control group and its own preinjection period, and remained low for the duration of observation. Discriminability for the diazepam group began below that of the saline control group and remained low; however, relative to its own preinjection control, discriminability first declined and then recovered after 45 min.

Although it serves to give an overall impression, averaging over a number of stimulus intensities obscures the effect of drug treatment on sensory decision indices. Since discrimination and response bias must be measured between stimuli of two adjacent intensities, separate analyses of variance were undertaken at each of the six stimulus intensity pairs. These results are available from NAPS. §§

During the preinjection period, the discriminability, $2ARS - P(A)$, for morphine and diazepam groups did not differ from that of the saline control group at any of the intensity pairs. The saline control group did not vary in discriminability over time at any intensity

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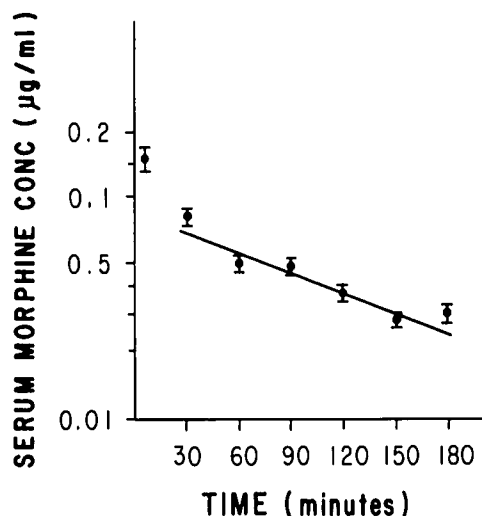


FIG. 1. Serum morphine concentrations in volunteers after intravenous injection of a single dose of morphine (0.14 mg/kg). Results (mean \pm SE) are from four subjects.

pair. Both morphine and diazepam groups showed decreased discriminability, $2ARS - P(A)$, among the thermal stimuli, but morphine yielded a much larger number of significant differences than did diazepam. All subjects reported some pain at $270 \text{ mcal} \cdot \text{sec}^{-1} \cdot \text{cm}^{-2}$. During each of the seven postinjection periods, morphine decreased the subject's ability to discriminate on 14 occasions among the nonpainful (below $270 \text{ mcal} \cdot \text{sec}^{-1} \cdot \text{cm}^{-2}$) and on eight occasions among the painful stimulus intensity pairs ($270 \text{ mcal} \cdot \text{sec}^{-1} \cdot \text{cm}^{-2}$ or more) compared with controls, whereas diazepam decreased discriminability on six occasions with nonpainful intensities and on five occasions among the painful intensity pairs. Values of discriminability, $2ARS - P(A)$, obtained from thermal intensities $320\text{--}370 \text{ mcal} \cdot \text{sec}^{-1} \cdot \text{cm}^{-2}$ and $370\text{--}400 \text{ mcal} \cdot \text{sec}^{-1} \cdot \text{cm}^{-2}$ were not significantly changed by either morphine or diazepam.

The mean thermal response bias, B , averaged over all stimulus intensities for the saline control group did not change with time (fig. 4). However, immediately following the injection of diazepam or morphine, response bias increased (fewer pain reports). When data were computed separately for each subject at each of the six intensity pairs (NAPS) during the preinjection period, the response bias, B , for morphine and diazepam did not differ from that for the saline control group at any of the intensity pairs. The saline control group did not vary in response bias at any of the intensity pairs. Both the morphine and diazepam groups showed increase in response bias, B , among the thermal stimuli. During each of the seven postinjection periods, morphine increased response bias, fewer pain reports, on 19 occasions among the painful intensity pairs. Yet it did not alter response bias to the nonpainful stimulus

intensity pairs, whereas diazepam increased response bias to the painful stimulus intensity pairs on 15 occasions and to the nonpainful intensity pairs on five occasions.

Discussion

Morphine produced a significant increase in the traditional pain threshold, demonstrating that experimentally induced pain does respond to analgesics. Diazepam had a positive but not significant effect on the pain threshold. The threshold is influenced by both sensory and psychological components, measured by sensory decision theory as discriminability and report criterion. The sensory decision theory data suggest that the increase in the pain threshold of the morphine-treated group is due to the combination of a decrease in discriminability and an increase in the pain response bias. In contrast, the smaller increase in the pain threshold in subjects treated with diazepam is caused mainly by the increase in the response bias. It may be concluded that the increase in threshold from diazepam is caused more by drug-induced distraction or emotional and attitudinal variables than by a specific sensory loss, while the morphine-produced threshold increase reflects a sensory loss in addition. This fine-grain analysis cannot be accomplished with the single measure of pain provided by the traditional threshold measure.

The poorer discriminability between stimulus intensities induced by morphine suggests that less sensory

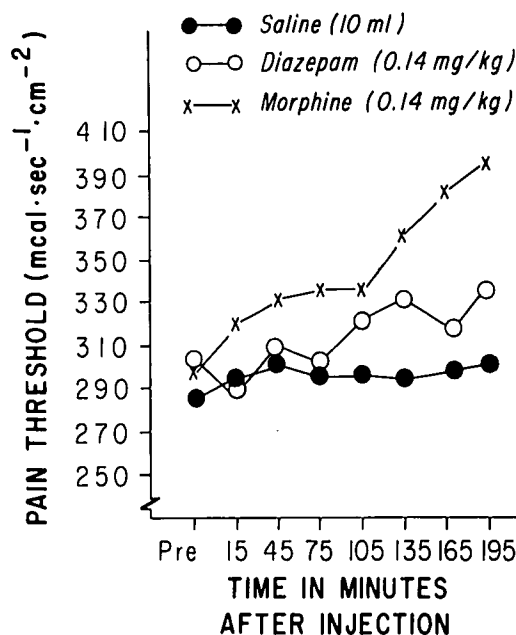


FIG. 2. Traditional threshold for very faint pain. Changes in mean pain thresholds over a period of three hours after a single intravenous injection of saline solution, morphine, or diazepam.

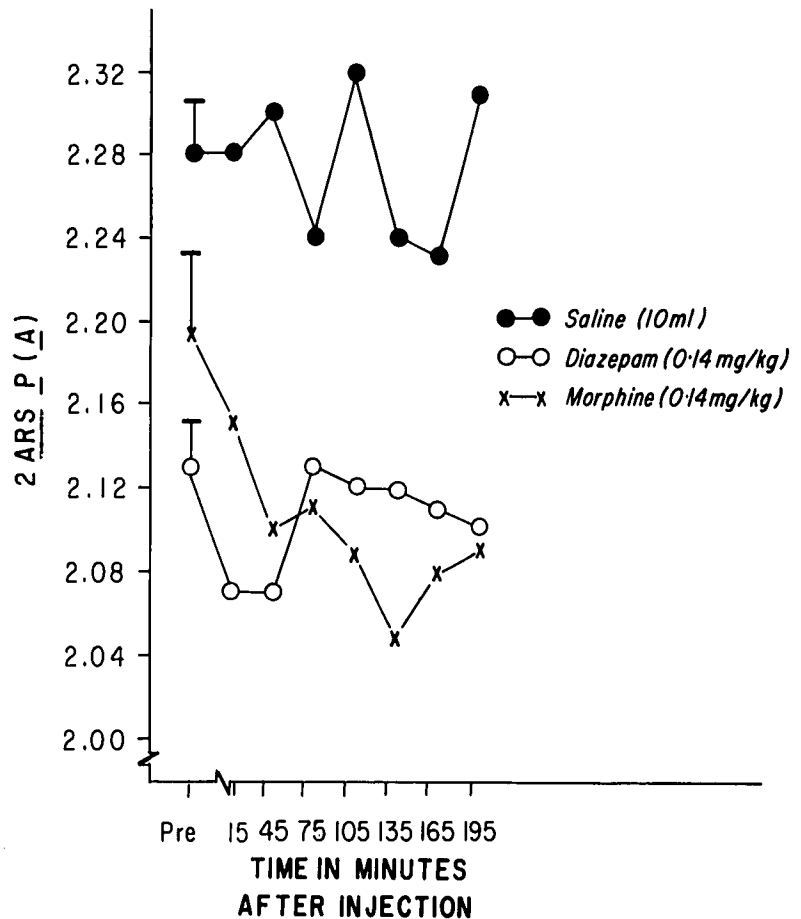


FIG. 3. Changes in discriminability to thermal stimuli, expressed as $2ARS - P(A)$, average of all stimulus intensities, over a period of three hours after a single intravenous injection of saline solution, morphine, or diazepam. Vertical bars are SE. Zero time indicates preinjection control value.

information arrived centrally. The increased pain response bias relative to the saline placebo control directly reflects the analgesic properties of morphine. Accordingly, both the discriminability and the pain response bias measures suggest that morphine had attenuated afferent neural input. Of the two sensory decision theory measures, the decrease in discriminability is of greater importance, for it is determined by hit and false-alarm rates, which are independent of the verbal labels used by the subject to describe his sensory experiences. Response bias, on the other hand, has been shown to be influenced by nonsensory attitudinal variables such as placebo and instructions.³

The finding that morphine altered threshold as well as discriminability and response bias is in marked contrast to the widely held belief that experimental pain does not respond to strong analgesics, and hence is an inadequate method for studying the effect of drugs. Denton and Beecher,²⁰ using the method of limits and also a very small number of observations, reported that morphine did not increase the thermal pain threshold. But the traditional techniques are subject to very high variability, which masks experimental effects. Even under carefully controlled conditions,

individual pain thresholds range from 170 to 472 $\text{mcal} \cdot \text{sec}^{-1} \cdot \text{cm}^{-2}$.²¹ This high variability does not appear with sensory decision theory measures because the traditional threshold is separated into discriminability and response bias.

Diazepam also decreased discriminability and increased the pain response bias, suggesting that it, too, possesses analgesic properties. However, diazepam at the dose level used was clearly less effective than morphine, since fewer significant changes in discriminability and pain response bias were found and the duration of the effects was shorter.

Our finding that diazepam behaves as an analgesic differs in part from the results obtained by Chapman and Feather.¹² They found no change in either thermal discriminability or pain response bias following the oral administration of diazepam, 10 mg, in spite of the fact that they did find a change in the report of tourniquet pain. The routes of administration represent an important difference between the two studies. According to Pesker and Spector,²² following intravenous injection of diazepam, 10 mg, serum diazepam concentration was 300 ng/ml at 5 min. It then decreased exponentially to 180 ng/ml one hour and 70

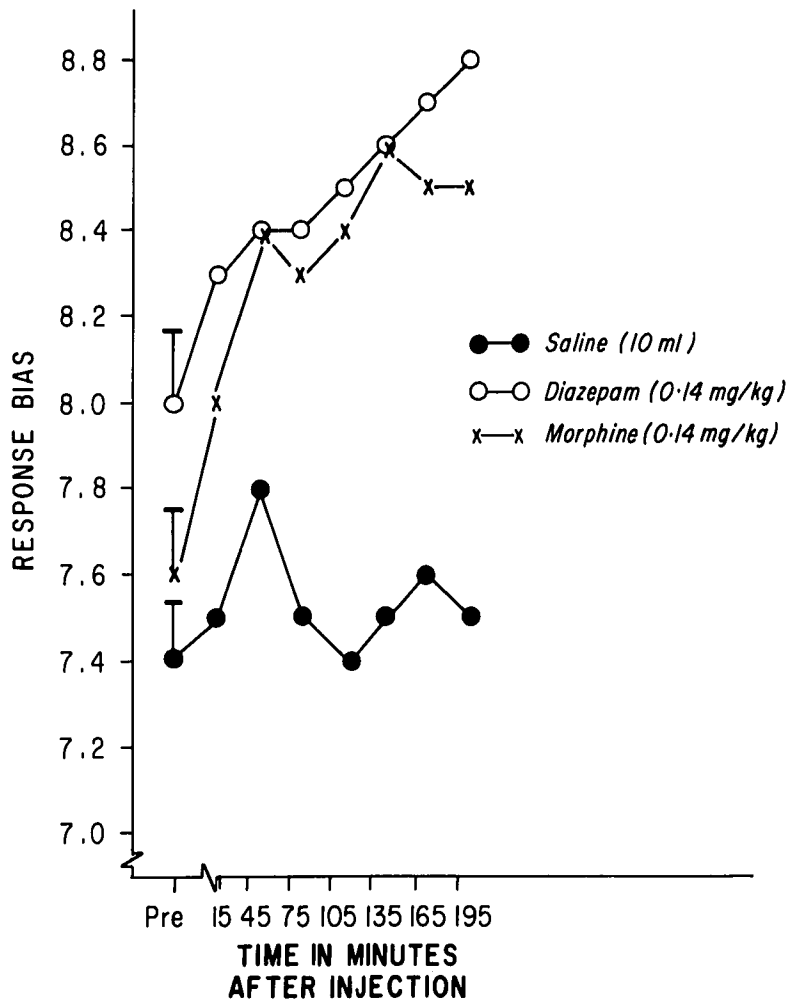


FIG. 4. Changes in response bias to thermal stimuli, average of all intensities, over a period of three hours after a single intravenous injection of saline solution, morphine, or diazepam. Vertical bars are SE. Zero time indicates preinjection control value.

ng/ml three hours after injection, whereas after oral administration of diazepam, 10 mg, serum concentration peaked at one hour (150 ng/ml) and decreased to 70 ng/ml at three hrs. It is likely that a higher initial serum diazepam concentration following intravenous injection would result in a higher brain drug level and act more effectively as an analgesic. Furthermore, Chapman and Feather¹² did not use the less variable nonparametric sensory decision theory approach, and they also probably decreased d' by pooling data obtained during different sessions.

The changes in both the traditional pain threshold and sensory decision indices were not correlated with the serum morphine concentration, nor did they correlate with the serum diazepam concentration reported by Peskar and Spector.²² This suggests that the sensory decision theory measures of analgesia were related to the levels of these drugs in the central nervous system, not to serum levels.

The detailed analysis at each pair of stimulus intensities served two important functions: it demon-

strated that the apparent difference during the preinjection control period between the saline control and diazepam groups (fig. 3) was an artifact caused by averaging, and that the analgesics did not affect discriminability at the highest stimulus intensities studied. That morphine or diazepam had no significant effect on discriminability at 320–370 and 370–400 $\text{mcal} \cdot \text{sec}^{-1} \cdot \text{cm}^{-2}$ agrees with the results of Chapman, Murphy and Butler,¹⁰ who found that the effects of analgesics on discriminability are more apparent at the lower intensity levels. From a sensory decision theory point of view, this result is not unexpected. Discriminability is a function of the difference between the noise (N) and signal-plus-noise (S + N) distributions, or in the instance of high intensity stimuli, between the $S_L + N$ and the $S_H + N$ distributions, where S_L and S_H refer to hypothetical distributions of neural activity induced by lower and higher stimulus intensities, respectively. Thus, if an analgesic decreased neural activity produced by each member of the pair of stimulus intensities (e.g., 370–400 $\text{mcal} \cdot \text{sec}^{-1} \cdot \text{cm}^{-2}$)

by, say, 100 impulses/sec, then the difference between $S_L + N$ and $S_H + N$ would remain constant and so would discriminability. However, at lower intensities, particularly at the "border" between detection, heat, and pain systems, it is possible that the analgesic is more effective against neural response to the higher (noxious) stimulus than against that to the lower, *i.e.*, $S_H + N$ is decreased more than $S_L + N$. When the difference between the neural activities induced by the two intensities becomes less, they are more confusable at the perceptual level, and discriminability decreases.

One of the striking findings was that morphine lost none of its analgesic effect, whether measured by traditional pain threshold or sensory decision indices, for at least three hours after injection. This duration of analgesia is contrary to the observation based on studies of morphine demand by patients with cancer pain,²³ namely, that the analgesic effect apparently has markedly declined three hours after injection. The prolonged analgesic effect of morphine in the present study indicates an important difference between clinical and experimental pain. It is well known that clinically acute pain has a prominent anxiety component, while chronic pain is frequently coupled with depression. It seems quite likely that a patient's demand for morphine is not because its analgesic properties have declined, but because the patients have a psychological need for its euphoric or sedative properties. In contrast, experimental pain in healthy volunteers possesses only a minimal emotional overlay and the prolonged analgesic effect of morphine becomes apparent. Thus, studies of effects of analgesics on laboratory pain permit the study of a drug's analgesic properties in relative isolation from its possible sedative and mood-altering effects.

It is possible that certain drugs that are believed to potentiate the analgesic effects of morphine on clinical pain actually affect only mood. This view is supported by Beecher,²⁴ who found that a dose of barbiturate too small to produce an analgesic effect relieved symptoms of pain because it relieved anxiety and fear. Dextroamphetamine has been reported to potentiate the analgesic effect of morphine in acute postoperative pain.²⁵ This may be due to its mood-altering properties, which could change the response bias. On the other hand, in the case of chronic-pain patients treated with large doses of narcotics and diazepam, their discriminability may decrease to the extent that all unpleasant sensations will be reported as pain. Gradually withdrawing such drugs from these patients could decrease pain report, because after the withdrawal, discriminability will increase to the level that the patients can differentiate the sensations of discomfort from pain. These examples suggest that, pro-

vided sensory decision theory is used to identify the sensory and psychological components of the pain report, studies of laboratory pain can yield valuable supplemental information about clinical pain.

Recently, Lineberry and Kulics²⁶ have studied the effects of diazepam and morphine on signal detection theory pain measures in trained rhesus monkeys, reporting that the behavioral changes produced by the drugs could be exclusively attributed to changes in response bias. The discrepancy between their observation and ours in discriminability changes by the drugs is probably due to the difference in experimental species. The human volunteers should definitely perform better than monkeys in discrimination of stimuli, hence changes were more readily detected in our study.

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APPENDIX

Nonparametric Sensory Decision Theory Indices

The nonparametric sensory decision theory measure, $P(A)$, was used instead of d' in order to avoid assumptions about the shape of the underlying noise and signal-plus-noise distributions. The d' measure requires that the distribution be gaussian and of equal variance. Like d' , $P(A)$ is a measure of the subject's sensitivity, that is, his ability to distinguish observation intervals containing a higher intensity stimulus from those containing a lower intensity stimulus. $P(A)$ is the area under the receiver operating characteristic (ROC) curve, a plot of hit rate against false-affirmative rates at each of the various criteria locations.

When hit and false-affirmative rates are equal, the points fall along the negative diagonal; in this instance, the area under the ROC curve is 0.5, and discriminability is zero. As discriminability increases, hit rates increase and false-affirmative rates decrease, causing points on the ROC curve to move toward the upper left, and the area under the curve to approach 1.0. The advantage of $P(A)$ is that it indexes the degree of overlap of the signal-plus-noise and noise-alone distributions regardless of their shapes, and it incorporates all of the points on the ROC curve to yield a single measure of discriminability. This is in contrast to d' , which is based on a single point or set of single points, which are then averaged.

Because it is based on more observations, $P(A)$ provides a much more stable measure of discriminability, particularly when the number of observations is relatively low. McNichol,¹⁸ in an excellent introduction to signal-detection theory, describes a geometrical method for computing $P(A)$ which may be readily written as a computer program. $P(A)$ is based on probabilities and has an upper limit of 1.0. When some subjects in a sample have high sensitivity, the distribution of $P(A)$ will tend to be skewed toward the upper limit. In order that the assumption of normality required for most statistical tests be met, McNichol recommends use of the customary transformation for probabilities: 2 arcsin square root $P(A)$ [$2ARS - P(A)$]. The relationships between $P(A)$, $2ARS - P(A)$, rating d' , and hit and false-affirmative rates appear in Appendix table 1. As is apparent, the relationship between $2ARS - P(A)$ and d' is approximately linear up to $d' = 3.0$; thus, it may be used instead of $P(A)$ and d' up to this value.

In addition to measuring discrimination, sensory decision

APPENDIX TABLE 1. Relationship between Hit and False-affirmative Rates (at $L_x = 1$), d' , and Values of $P(A)$ and 2 Arcsin Square Root $P(A)$ [$2ARS - P(A)$]

$P(A)$	$2ARS - P(A)$	Rating d'	Hit Rate	False-affirmative Rate
0.50	1.57	0	0.500	0.500
0.55	1.67	0.13	0.536	0.464
0.60	1.77	0.25	0.572	0.428
0.65	1.87	0.38	0.608	0.392
0.70	1.98	0.52	0.644	0.356
0.75	2.09	0.67	0.682	0.318
0.80	2.21	0.84	0.723	0.277
0.85	2.35	1.04	0.769	0.231
0.90	2.50	1.28	0.819	0.181
0.95	2.69	1.64	0.877	0.123
0.99	2.94	2.32	0.949	0.051
0.9995	3.08	3.29	0.990	0.010

theory yields a measure of report bias: the likelihood ratio criterion, L_x . However, when a relatively small number of observations is obtained, it is obvious that small errors in the estimation of hit or false alarms will cause large errors in the estimation of L_x . In this situation, McNichol¹⁸ suggests that the nonparametric response bias measure, B , be used instead of L_x . Like $P(A)$, B has the advantage of being based on all of the points on the ROC curve, not merely those identified with a single criterion. B is defined as the rating scale criterion at which the cumulated hit-plus-false-alarm probabilities equal unity. Equivalently, B locates that rating scale criterion at which half of the responses (to both stimulus intensities) are to higher response categories and half are to lower. An example from the response scale used in the present experiment will serve to introduce B . The subjects were asked to select their responses from the categories from Nothing to Very painful (table 1). (The category numbers as well as the withdrawal times of less than 3.0 sec were not given to the subject.) The response category with the shortest withdrawal time (less 1.99 sec) is assigned the number 1, since it represents the most painful sensation, and the response category Nothing is designated C (in the present study $C = 14$). Thus, high B scores represent a conservative or stoical pain report criterion (equivalent to high L_x) and low B scores represent a tendency to report "pain" frequently.