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PAIN SENSITIVITY, MOOD, AND PLASMA ENDOCRINE LEVELS IN MAN FOLLOWING LONG-DISTANCE RUNNING: EFFECTS OF NALOXONE

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by

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ABSTRACT

Pain sensitivity, mood, and plasma endocrine levels in man following long-distance running: Effects of naloxone.

by Malvin N. Janal

Advisor: W. Crawford Clark, Ph.D.

Anecdotal observations and research reports have suggested an association between stressful envrionmental situations (e.g., war, auto accidents, or athletic competition) and reduced sensitivity to painful stimuli. Further, exercise stress in particular has been associated with mood elevation, popularly known as runner's high. These two phenomena, analgesia and euphoria, are major effects of opiate drugs. Recent demonstrations of endogenous opiate-like peptides and receptor sites in the central nervous system of all vertebrates suggest that stress may have its effect on pain sensitivity and mood through alterations of activity at the opiate receptor. To examine these relationships, the effects of intense exercise on pain perception, mood, and plasma endocrine levels in man were studied under naloxone and saline conditions.

Twelve long-distance runners (mean weekly mileage= 41.5) were evaluated on thermal, ischemic and cold pressor pain tests and on mood visual analogue scales (VAS). Blood was drawn for determination of plasma levels of beta-endorphin immunoreactivity (BEir), growth hormone (GH), adrenocorticotrophic hormone (ACTH), and prolactin (PRL). These procedures were undertaken before and after a 6.3 mile run at 85% of

maximal aerobic capacity. Subjects participated on two occasions in a double-blind procedure counterbalanced for drug order: on one day they received two IV injections of naloxone (0.8 mg in 2 ml vehicle each) at 20 min intervals following the run; on the other day, two equal volume injections of normal saline (2 ml).

Sensory decision theory analysis of the responses to thermal stimuluation showed that discriminability, P(A), was significantly reduced post-run under the saline condition, a hypoalgesic effect; response bias, B, was unaffected. Ischemic pain reports were significantly reduced post-run on the saline day, also a hypoalgesic effect. Both effects were maximal prior to 25 min post-run. Naloxone reversed the post-run ischemic but not thermal hypoalgesic effects. Cold pressor pain reports were not altered by the run. Joy, euphoria, cooperation, and conscientiousness visual analogue scale ratings were elevated post-run; naloxone attenuated the elevation in joy and euphoria ratings only. In summary, the results show that long-distance running produces hypoalgesia and mood elevation in man.

Plasma levels of BEir, ACTH, GH, and PRL were significantly increased post-run. Correlational analysis of changes in pain sensitivity and plasma hormone levels indicate an association of analgesia and hyposecretion of ACTH and hypersecretion of PRL, effects consistent with a common underlying opioid mechanism. These effects were evident only at test periods within 30 min of completion of the run, consistent with the half-life of beta-endorphin, suggesting that activity of this peptide may underlie the covariation of analgesia and changes in ACTH and PRL levels. Analysis of correlations between hormone levels and mood reports did not consistently suggest opioid mediation of

effects.

The effects of naloxone and correlations between behavioral changes and pituitary hormone levels implicate endogenous opioid neural systems as mechanisms of some but not all of the run-induced alterations in mood and pain perception.

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I. INTRODUCTION

Many anecdotal observations suggest that pain perception is decreased during periods of stress or great emotional excitement: e.g., individuals injured in a fight, accident, or athletic event may be unaware of pain until some time after the event. Anecdotal observations also suggest mood alterations occur following stress; e.g., the "runner's high" when the stressor is exercise. Opiates are well-known for their dual pharmacological actions of analgesia and euphoria. Thus, it is not surprising that the endorphins (we use the term generically to refer to any member of the class of endogenous morphine-like peptides), whose activity is perhaps increased under stress, may exert a similar dual action on pain perception and mood by acting on the opiate receptor. Observations such as these have stimulated interest in controlled studies of the effects of stressful manipulations on pain perception.

In animals, a variety of stressors, such as inescapable foot shock, forced cold-water swims, and restraint have been associated with decreased sensitivity to pain for as long as two hours following the stress (Akil, Madden, Patrick and Barchas, 1976; Bodnar, Kelly and Glusman, 1978). This phenomenon, stress-induced analgesia (SIA), has recently been divided into five subtypes on the basis of differences in putative mechanisms activated by the different stressors (Watkins and Mayer, 1982). The demonstration of intrinsic pain regulatory systems (Hayes, Bennett, Newlon and Mayer, 1978; Lewis, Cannon and Liebeskind,

1980; Watkins and Mayer, 1982), raises the question of the role played by these systems in the modulation of pain perception following stress in man. Unlike pain, however, mood may only be studied in man. Studies will be reviewed below which support the existence of pain, mood, and pituitary function alterations following stress, particularly stress operationalized as intense exercise. The present study is designed to correct previous methodological flaws and to test whether this single common mechanism, increased central opioid activity, underlies stress-induced analgesia, mood elevation, and pituitary hormone level changes. The following hypotheses will be tested:

(1) That the stress induced by a long, hard run will reduce the perception of pain.

(2) That this stress will also elevate mood.

(3) That this stress will alter plasma levels of Beta-endorphin immunoreactivity (BEir), ACTH, PRL and GH.

(4) That alterations of pain and mood are attributable to alterations in central opioid systems as demonstrated by reversal of effects with the specific opioid antagonist naloxone.

(5) That pain, mood, and hormone levels are all related to a common, stress-induced mechanism and run-induced changes in the variables should therefore be correlated.

Previous literature related to hypotheses 1, 2, 3, and 4 are critically reviewed below. There is very little literature related to the inter-relationship of these variables. Thus, hypothesis 5 represents a unique contribution of this study to the literature.

Effects of exercise on pain perception.

Several clinical reports of SIA in man have appeared. Colt (1980) reviewing 26 cases of myocardial infarction in runners, 18 of which were fatal, found that the runners continued to run despite symptoms of myocardial ischemia. A case study (Colt and Spyropoulos, 1979) reported on a woman who continued her run despite numerous stress fractures of both tibiae. While exercise was inferred to be a causal factor, it is not clear from these reports whether running reduces the sensation of pain or whether people who run tend to be either pain insensitive or stoical.

Experimental studies of pain perception following exercise have also appeared. Black, Chesher, Starmer and Egger (1979) tested pain sensitivity to a tourniquet-ischemic stimulus. Briefly, this procedure involves expressing venous blood, inflating a cuff on the upper arm above systolic blood pressure, and exercising the hand; the cuff is left in place until the subjects tolerance is reached. In a single subject, pain tolerance was increased following 5 km runs at a slow pace (approximately 8 min/km). Each of 15 such runs was followed by a double-blind IV injection of saline or naloxone (0.4 or 1.2 mg); there was no difference between these conditions, suggesting that the run-induced analgesia was either insensitive to naloxone or an insufficient dose was used. Haier, Quaid and Mills (1981) tested the effect of a 1 mile self-paced run in 15 subjects who trained, on average, 15 mi/wk. Running increased the time to report as painful the pressure produced by a three pound weight on the index finger; this

effect was reversed by 10 by not by 2 mg of naloxone. Interestingly, the naloxone effect was greatest in subjects who trained at greater distances ($r = .55$), suggesting an interaction of long-term conditioning and the acute effects of a run. Because run intensity was not measured, however, this effect could be attributed to the better trained subjects running harder and thus stressing themselves more than the less trained subjects, or to long-term conditioning alterations in endorphin activity, or to other causes.

Pain, surgery and electrical non-painful stimulation stressors have also been studied. Jungkunz, Engel, King and Kuss (1983) tested four groups of eight subjects each in a 2 by 2 factorial design with two types of stress (ice-water foot immersion for 1-2 min or mental arithmetic) and two types of drug (naloxone, 0.8 mg or saline, IV). Pain threshold to a 100 ms constant-current stimulus delivered to the fingers was increased following the cold-water stress only; this hypoalgesic effect reached a maximum at 30 min post-stress and was naloxone reversible. Chen, Bromm and Treede (1983) stressed 10 subjects with the submaximal effort tourniquet procedure. During this stress, subject's rating of the intensity of electrical stimuli delivered to the fingers of the other hand, as well as the amplitude of the vertex evoked reponse, were reduced relative to both pre- and post-stress test periods, which did not differ from one another. Thus, reduced pain report did not outlast the stressor. The effects of naloxone were not tested. Other data suggest that stimulation need not be painful to reduce sensation. Clark, Hall and Yang (1974) have shown that electrical stimulation of the median nerve at the wrist (18 mA, .1 ms pulses

delivered at 100 Hz) for 20 min reduces discriminability of both high and low intensity thermal stimuli. That this effect was specific to the stimulated extremity suggests a peripheral neural fatigue rather than central effects.

Willer and colleagues have been unique in studying in man a polysynaptic nociceptive spinal reflex, that of the biceps femoris muscle following noxious stimulation of the sural nerve. They have shown this reflex to have two components, a short latency one associated with the application of light touch stimuli and a longer latency component (pain reflex), present only with the application of noxious stimuli (Willer, 1977), and occuring at the same intensity as the threshold of pain report. The pain reflex has been shown to be depressed by morphine chlorhydrate (0.3 mg/kg, IV) in a naloxone-reversible manner (0.03 mg/kg, IV), while the monosynaptic H-reflex was unaffected (Willer and Bussel, 1980). Further, these two effects have been demonstrated in spinal patients, indicating the sufficiency of a direct spinal mechanism in mediation of opioid effects on nociceptive reflex activity. Stress, successive 2-min periods during which the subject anticipated the delivery of a 70 mA stimulus to the sural nerve, increases the threshold of the pain reflex (Willer, 1977; Willer, Dehen and Cambier, 1981). Endogenous opioids have been implicated in the stress-induced elevation of the pain reflex (Willer et. al, 1981). Naloxone (5 mg, IV) administered double-blind not only reverses this stress-induced elevation of pain threshold, but results in a transient hyperalgesia (sub-normal pain threshold). Naloxone without pain stress had no effect on the reflex.

Critique. Psychophysical scaling in the above studies has generally relied on traditional threshold methodology, a procedure whose usefulness in pain assessment has been questioned. Clark (1969) has compared thresholds with indices provided by sensory decision theory (SDT): d', a measure of discriminability and an index of sensory functioning, and Lx, a measure of report criterion and an index of the observer's attitude toward the report of pain. Under instructions strongly suggesting the analgesic properties of a placebo, subjects showed increased thresholds and Lx values indicative of increased stoicism while discriminability remained unchanged. These results argue that threshold may change under conditions of constant discriminability and it is therefore unclear whether the hypoalgesia noted above reflects alterations in response criterion, discriminability, or both. In a later study, Yang, Clark, Ngai, Berkowitz, and Spector (1979) showed morphine, a potent analgesic, to reduce discriminability and raise report criterion to painful heat stimuli, while diazepam, an anxiolytic, raised report criterion with little effect on discriminability. Pain treshold was raised by both drugs, more so for morphine. These data indicate that SDT measures allow more precise definition of drug effects than threshold measures alone.

None of the studies cited above control for the distracting effects of the stressor, making it unclear whether pain sensitivity is specifically altered, or whether a general reduction in attention has occurred. Some studies (eg, Chen et al., 1983), measure pain concurrently with presentation of the stressor. We would not label this

paradigm as as one that illustrates SIA, saving this designation for paradigms that show effects following stressor termination. In these latter types of study, assessment of other sensory modalities or somatosensory non-pain sensation would be required to rule out non-specific attentional deficits. If the Willer studies, e.g., had found unchanged post-stress H-reflexes, pain specific effects could be argued.

Studies reviewed above suggest a number of experimental issues:

(1) The time course of hypoalgesic effects has been little studied. Jungkunz et al. (1983) provide the most systematic effort to date, studying pain sensitivity before and at 5, 10, 15, 30, and 60 min after stress. They found maximal effects at 30 min. Chen et al. (1983) found effects during stress but not after. Other studies have only taken single measurements, some during stress, others after. The paradigm used by Willer and colleagues is not amenable to multiple measurements, and would be unsuited to a time course analysis as the paradigm demands study of cumulative stress periods. Clearly, when hypoalgesia develops and how long it lasts are important questions that have only been partially explored.

(2) Various stressors have been used. While many have been shown to produce naloxone-reversible hypoalgesic effects it is not clear that all operate via the same mechanism. Animal studies have shown that varying the parameters of foot-shock stress can lead to selective activation of opioid-sensitive or -insensitive antinociceptive systems (Lewis et al., 1980; Watkins and Mayer, 1982), suggesting the importance of stressor

quality in the development of analgesia in man.

(3) Related closely to (2), previous studies have assessed only one type of pain. Given the dual systems of rostrad pain transmission in man (neo- and paleospinothalamic; Barr, 1979) and the fact that different animal tests reveal SIA of varying strengths and durations (Kelly, 1982), suggests the importance of studying multiple pain measures.

Summary. There have been both clinical and experimental reports of hypoalgesic effects in man associated with diverse stressors including running, ice-water immersion, tourniquet ischemia, and anticipation of intolerable shock. Where tested, naloxone has been shown to block hypoalgesia in most instances, suggesting an opioid sensitive mechanism mediating these effects. These studies are, however, subject to significant criticism, both with regard to algesiometry (types of pain) and statistical design issues.

Effects of exercise on mood.

Exercise has been associated with mood elevation. Following exercise, acute measures of anxiety are reduced (Bahrke and Morgan, 1978; Berger and Owen, 1983; Markoff, Ryan, and Young, 1982; Morgan, 1979; Wilson, Berger, and Bird, 1981), anger is reduced (Markoff et al., 1982), and depression is reduced in both clinically depressed populations (Greist, Klein, Eischens, Faris, Gurman, and Morgan, 1979) and among normal volunteers (Berger and Owen, 1983; Wilson et al., 1980). Jorgenson and Jorgenson (1979) have reported salutary effects of habitual running; of some nearly 500 runners questionned, more than 90%

reported increased emotional and physical well-being, and 73% reported more friendships since starting running. Similar findings are presented by Callen (1973) on 424 runners who reported reduced anxiety and increased contentedness, happiness, altertness and mood. Runner's high was reported to occur 44% of the time by 69% of the sample and 63% believed the high to be a distance related phenomenon.

Some attempts have been made to assess quantitative effects of stressors. Wilson et al. (1980) found 10 marathoners (6- 20 mi, 6-7X/wk) to be significantly less anxious, depressed and angry than a group of 10 joggers (1- 2 mi, 3-5X/wk), who in turn had less of these qualities on the Profile of Mood States (POMS; McNair, Lorr, and Droppleman, 1970) than a group of 10 sedentary controls, suggesting that chronic exercise improves mood in a dose-dependent manner. Chronic mood-elevating effects of exercise, reduced anxiety and depression, have also been reported in a group of 20 subjects at risk for coronary heart disease (Folkins, 1976). Morgan (1979) found reduced anxiety on the IPAT questionnaire in groups exercising vigorously for both 15 and 45 min, but not in groups that either rested or walked 1 mi, suggesting also an effect of acute exercise stress.

Other studies indicate, however, that the effects noted can be attributed to distraction. Bahrke and Morgan (1978) found significant and equal anxiety reduction in each of 3 groups of 25 subjects, one exercising at 70% of aerobic capacity on a treadmill, one practicing the relaxation response, and one that simply sat quietly. Similar mood elevation was found in 3 groups of approximately 10 subjects each which either ran 1 mi (in less than 8 min), did a 40 min aerobics class, or

ate (Wilson et al., 1981). These latter, negative, findings were both found using the State form of the State-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, and Lushene, 1970), while the more positive findings were found with the POMS and IPAT, suggesting greater sensitivity of the POMS.

One study has tested the opioid relation to run-induced anxiety reduction. Markoff et al. (1982) injecting naloxone (0.8 mg, subcutaneous) or saline after a 10 mi training-pace run in 11 subjects, failed to reverse post-run reductions in anxiety and anger, suggesting these mood alterations were not opioid mediated.

One study of the post-run time course of mood alterations found reduced anxiety at 25 but not 5 min after a run of 45 min duration, while a 15 min run gave reduced anxiety at both 5 and 30 min test times (Morgan, 1979), a result which suggests a relationship more complex than a simple linear one.

In terms of parametric relations, three types of studies are needed; (1) the effects of different intensities of exercise stress; (2) the time course of mood elevation and return to baseline; and, (3) the interaction of stressor intensity and time course of mood-elevation. Further, the admittedly circumstantial but seemingly powerful association of exercise and runners high demands further investigation of opioid effects in spite of the negative Markoff et al. (1982) finding. Recently, naloxone infusions have been shown to dose-dependently increase anxiety in normal volunteers (Cohen, Cohen, Pickar, Weingartner and Murphy, 1983), suggesting opioid-mediated regulation of mood. It is conceivable that Markoff et al. (1982) failed

to reverse run-induced mood alterations because they used too low a dose of naloxone.

Two other methodological issues are suggested by the data. First, adequate controls for distraction, when applied, have sometimes shown exercise to be no more anxiety-reducing than either eating (Wilson et al., 1981) or relaxation (Bahrke and Morgan, 1978) and at other times to be superior (Wilson et al., 1980). As in the pain studies above, controls for the non-specific distraction effects of stress are needed. For example, mood states unrelated to anxiety shoud be examined, e.g., pleasure, cooperativeness, fear, conscientiousness and attention. Second, anxiety effects have been found using the IPAT and POMS inventories but not the STAI. There is some question, therefore, as to validity and/or sensitivity of the STAI.

Critique and summary. Present studies suggest a relationship of mood-elevation and exercise, but do not go far enough in delineating either parametric influences on mood elevation or physiological mechanisms underlying mood elevation.

Effects of exercise on plasma levels of pituitary hormones.

The levels of a number of pituitary and adrenal hormones (including what are also known as neurotransmitters, neurohumors and neuromodulators) have been measured in the plasma and cerebrospinal fluid (CSF) of man under a variety of stressful conditions. Studies reviewed here will concentrate on exercise as the stressor, since there are indications of different hormonal responses to different stressors (Aubock and Konzett, 1983; Frankenhaeuser, Lundberg and Forsman, 1980; Ward, Mefford, Parker, Chessney, Taylor, Keegan and Barchas, 1984).

Beta-endorphin. Levels of plasma beta-endorphin immunoreactivity (BEir; includes varying amount of cross-reactivity with beta-lipotropic hormone, B-LPH) have consistently been shown to increase with acute exercise stress (Bortz, Angwin, Mefford, Boarder, Noyce and Barchas, 1981; Carr, Bullen, Skrinar, Arnold, Rosenblatt, Beitens, Martin and McArthur, 1981; Colt, Wardlaw and Franz, 1981; Farrell, Gates, Maksud and Morgan, 1982; Fraioli, Moretti, Paolucci, Alicicco, Crescenzi and Fortunio, 1980; Gambert, Garthwaite, Pontzer, Cook, Tristani, Duthie, Martinson, Hagen and McCarty, 1981). Stressors have generally been quite intense. Bortz et al. (1981) measured BEir in 34 subjects at the 60 and 100 mi points of the 1980 Western States 100 Race. Carr et al. (1981) exercised 7 women on a bicycle ergometer for 1 hr at up to 85% of aerobic capacity. Fraioli et al. (1980) stressed 8 athletes on a treadmill at a speed of 15 km/hr. Gambert et al. (1981) stressed 9 untrained subjects on a treadmill at 80% of maximal heart rate for 20 min. One study that failed to find a significant BEir increase used a

less intense stressor, a bicycle ergometer at 15-20 mi/hr for 10 min (Naber, Bullinger, Zahn, Johnson, Huhtaniemi, Pickar, Cohen and Bunney, 1981). Two studies have systematically varied stressor intensity. Colt et al. (1981) found that 20 subjects who had run approximately 9 km at a training pace (50-70% aerobic capacity) had smaller increases in BEir than 15 subjects running the same distance at 80-90% of aerobic capacity (149 vs. 341% increases). Farrell et al. (1982), however, found no difference in BEir levels in 6 runners tested at 60 and 80% of aerobic capacity. Thus, while increased plasma BEir levels have been consistently related to exercise, it is not clear whether a monotonic or step function intensity-response relationship exists.

One study has addressed the important issue of the time course of changes in BEir levels following stress. Fraioli et al. (1980) found a 5-fold increase in BEir immediately post-run, a 350% increase at 15 min, and less than 200% at 30 min, indicating the importance of sampling times in assessing BEir changes following stress. This is supported by Gambert et al. (1981) who found BEir levels to increase continuously during exercise on a treadmill at 80% of maximal heart rate, and to return to baseline within 45 min of cessation of activity.

Two studies suggest that chronic exercise modifies the acute post-exercise BEir response. Colt et al. (1981) showed an inverse relation of BEir increase and training level, suggesting some form of response adaptation. Carr et al. (1981), however, found a positive training/BEir increase relation over a 2-month training period. These contradictory findings are not presently resolvable. We might point out, however, that: (1) the Colt et al. (1981) subjects had been training for

much longer than two months and might therefore have achieved a further change in endocrine response; and, (2) Carr et al. (1981) studied the same subjects over time while Colt et al. (1981) employed separate groups. Since subjects self-selected into higher or lower intensity training regimens, selection bias is a possible alternative explanation in the latter study. These data suggest that during initial phases of training, chronic exercise facilitates the BE response to acute stress, and that at later stages of training, this response is blunted.

Few workers have studied post-exercise indices of perceived stress or their relation to BEir levels. Farrell et al. (1982) found an inverse relation between BEir increases and perceived activity, a relationship quite opposite to that suggested by physiologically-defined activity levels. Naber et al. (1981) administered the MMPI and found state anxiety to be positively related to both baseline and post-stress levels of BEir; they do not, however, report on the critical relation between post-run changes in BEir and any psychological scales. While these studies suggest that BE release may be responsive to factors other than the physical stressor, the issue of the covariation of stressor, perceived stress, and BEir levels is still quite unexplored.

Some studies have shown a correlation between behavior and BEir levels following surgical stress. Cohen, Pickar, and Dubois (1983) and Cohen, Pickar, Dubois, Nurnberger, Roth, Cohen, Gerson, and Bunney (1982) have shown post-surgical morphine requirements to be lower in patients with higher post-surgery plasma BEir levels. Similar results were obtained using CSF BEir levels (Tamsen, Hartvig, Dahlstrom, Wahlstrom, and Terenius, 1980). Thus, some patients may require less

post-surgery exogenous opiates because they produce more of their own.

These data raise the issue of what significance may be attributed to levels of BEir in either the plasma or CSF. While the comments below may be applicable to determining the functional significance of plasma levels of any pituitary hormone, they are directed specifically at BE because of the extensive speculation on and study of the activity of this peptide. There are three major, although often unstated, interpretations of increased plasma BEir levels: (1) Plasma BE makes its way back into the CNS to produce behavioral effects. (2) Plasma BE reflects the activity of brain systems upstream of the pituitary which have behavioral consequences. (3) Plasma BE is proportional to CNS BEir, and thus reflects alterations at behaviorally meaningful locations. These points will each be discussed in turn.

BE injected into the CNS, either spinally or introcerebroventricularly, reduces pain sensitivity in primate (Yaksh, Gross and Li, 1982; Yaksh and Rudy, 1978). Since the major source of plasma BE is the anterior pituitary and there is no known target organ outside the CNS sensitive to the pain-attenuating effects of BE, plasma BE must presumably reenter the CNS to be directly analgesic. BE, however, crosses the blood-brain barrier with great difficulty (Rapaport, Klee, Pettigrew and Ohno, 1980). Foley, Kourides, Inturissi, Kaiko, Zaroullis, Posner, Houde and Li (1979) have shown massive IV injection BE (1-10 mg) to have no effect on pain, mood, vital signs or pupil diameter, but to increase levels of PRL and decrease levels of GH in man. Thus, an IV dose of BE 1000-fold greater than that found in plasma following stress was sufficient to induce pituitary hormone

responses but was behaviorally inactive. Gerner, Sharp and Catlin (1982), however, report that slow IV infusion of 7 - 15 mg of BE over 30 min led to a 5-fold increase in CSF BEir in 3 subjects at both 2 and 4 hr and 2-fold increases as long as 17 hr after infusion, suggesting that Foley et al. (1979) failed to find penetrance due to use of a bolus injection. Gerner et al. (1982) did not, however, assess either behavioral (e.g., pain) or physiological (e.g., PRL release) indices of opioid activity, so it is unknown whether these CSF increases affected functionally meaningful sites.

There have also been suggestions of cephalad flow in the pituitary portal vessels, which would carry pituitary hormones directly back to the hypothalamus or into the CSF and thus to other brain areas (Bergland and Page, 1980). While this transport has been demonstrated to be anatomically feasible and would deliver BE to the arcuate nucleus where BE cell bodies are located (Zimmerman, Liotta and Krieger, 1978), evidence of physiologically meaningful operation of such a system has not been demonstrated.

These data make it fairly clear that BE measured in the plasma has no direct effect on behaviorally meaningful sites in the CNS, leaving only the two following indirect interpretations of its significance to function:

(1) Release of hormones from the pituitary is under the control of specific neurons and neurotransmitters in the hypothalamus, which are in turn responsive to other inputs. Thus, the presence of particular hormones in the plasma allows inferences about systems further upstream. This logic, while theoretically sound, is in reality difficult to apply

due to the multiplicity of controls on the release of individual pituitary hormones. Still, use of this logic to understand the biochemical nature of major depressive disorders has achieved some success (Sachar, Asnis, Halbreich, Nathan, and Halpern, 1980). In the present context, alterations in the CNS which lead to analgesia or mood elevation could also lead to pituitary secretion of BE; the hormone is then a marker of central activity of systems mediating these behavioral effects, although not necessarily causal of their presence. There are data indicating opioid regulation of pituitary BE release. In rats, naloxone increases levels of hypothalamic and pituitary BE, suggesting a tonic opioid inhibitory effect on pituitary BE release (Lee, Panerai, Bellabarba and Friesen, 1980). This might explain why opioid anesthetics reduce the BEir increase to surgical stress noted by Cohen et al. (1982, 1983). The physiological function of this particular circuit may be related to negative feedback responsive to BE released from the adrenal in man (Evan, Erdelyi, Wever and Barchas, 1983). Available data suggest, therefore, that if stress increases central opioid activity, decreased plasma levels of BE should result.

(2) If plasma BE levels are proportional to central levels, they could be used as a marker of activity in the CNS, where mood and pain effects are mediated. However, in the one study relating these levels in man, Sclachter, Wardlaw, Tindall and Frantz (1983) failed to find a correlation in 13 cancer patients; it is not clear whether this is a a result of the disease, but nevertheless does not support this hypothesis. Studies of foot-shock stress in rats show increases in plasma but not central levels of BEir or enkephalin (Rossier, French,

Rivier, Ling, Guillemin and Bloom, 1977), and studies of caffeine infusion show a similar dissociation of effects (Arnold, Carr, Togasaki, Pian and Martin, 1982). Thus, available data do not indicate covariation of plasma and CNS opioids.

To summarize, plasma BE is uncorrelated with central BE and, furthermore, does not gain entry to the CNS. Plasma levels are, however, indicative of changes in central levels of other neurotransmitters, although the multitude of possible mediators of BE release at present precludes specifying effects due to a single transmitter. This specificity may be achieved in future studies by employing specific transmitter antagonists (e.g., naloxone for opioids, propranolol for beta-adrenegic receptors).

ACTH. Plasma ACTH increases in man have been reported following exercise stress (Fraioli et al., 1980; Gambert et al., 1981; Risch et al., 1980). Cortisol increases have also been reported following exercise (Carr et al., 1981; Dessypris, Kuoppasalmi and Adlerkreutz, 1976) and surgical stress (Cohen et al., 1983). One study of the time course (Carr et al., 1981) found the cortisol increase to peak at 30 min after exercise. That this is a reflection of the lag in adrenal response to ACTH rather than a delay in the ACTH response itself is suggested by Fraioli et al. (1980) who found a 10-fold ACTH increase immediately following exercise which decreased to 4-fold at 15 min and returned to baseline by 30 min.

There is some evidence that the cortisol response to exercise stress has a high threshold. Hartley, Mason, Hogan, Jones, Kotchen, Morigey, Wherry, Penington and Rickets (1972) have shown that 5 min ergometer

work by 7 untrained subjects at 98% but not 40 or 70% of aerobic capacity increases plasma cortisol; this result was unaffected by a 7 wk training program. Similarly, Spiler and Molitch (1980) failed to find a cortisol increase after 30 min of low intensity bicycle work. Work at 75% of aerobic capacity to exhaustion (40 min) does, however, yield cortisol increases (Hartley et al., 1972), suggesting that intensity and duration of exercise interact. There are also suggestions that long duration, low effort work is a better elicitor of ACTH release than short duration, high intensity work. Kuoppasalmi, Naveri, Hehunen, Harkoknen and Adlerkreutz (1976) found, in 5 subjects, that 3 300 m maximal effort runs, with 3 min rests between efforts, failed to alter plasma cortisol levels. Other data indicate that anxiety in a physically nondemanding circumstance is associated with a cortisol response. Vaernes, Ursin, Darragh and Lambe (1982) studied 62 nonswimming Navy recruits who were required to jump into deep water and float for 5 min. Plasma cortisol increased after the stress. Psychometric testing showed the highest cortisol responders to report the greatest anxiety. These data suggest that measures of perceived stress as well as specification of the physical stressor are required to separate what may be independent contributions to cortisol level increases. The hormonal response to stress is further influenced by behavior: if coping responses are available, the ACTH response to stress is attenuated relative to uncontrollable stress (Weiss, 1968), and this effect is related to hypothalamic levels of NE (Weiss, Goodman, Losito, Corrigan, Charry and Bailey, 1981).

Immunocytochemical data indicate that ACTH cell bodies are located

in the brain stem and mediobasal hypothalamus, while fibers are found in the periventricular and amygdaloid nuclei, as well as the PAG (Watson, Richard and Barchas, 1978), suggesting a neurotransmitter or neuromodulatory role for ACTH in the CNS. Central and plasma levels of ACTH appear independent. Allen, Kendall, McGilvra and Vancura (1974) found lumbar CSF and plasma levels correlated 0.2, and infused ACTH failed to cross over into CSF in significant amounts.

Neuroendocrine control of pituitary ACTH secretion is complex, involving multiple regulators of the hypothalamus (which secretes corticotropin releasing factor, CRF, from the suprachiasmatic nucleus) as well as the possibility of direct releasing mechanisms in the anterior pituitary. There is also evidence of opioid mediation of ACTH release. Naloxone, 8 mg IV, (Naber, Pickar, Davis, Cohen, Jimerson, Elchisak, Defraites, Kalin, Risch and Buchsbaum, 1981) but not 0.4 mg (Spiler and Molitch, 1980) increased plasma cortisol levels and potentiated stress-induced ACTH increases (Morley, Baranetsky, Wingert, Carlson, Hershman, Melmed, Levin, Jamison, Weitzman, Chang and Varner, 1980). Administration of opioids depresses ACTH and cortisol levels (Morley, 1983). Like BE, then, stress-induced increases in central opioid activity should decrease plasma ACTH levels. Thus, changes in plasma ACTH can be used to infer the activity of many different neurotransmitter systems. It would be hoped that future studies could disentangle the meaning of post-stress endocrine changes through use of specific transmitter antagonists.

While ACTH and BE are produced in equal molar quantities by cleavage of the proopiocortin molecule (Guillemin et al., 1977), their release

from pituitary stores may be independent under some circumstances. Measurement of plasma levels attributable to the pituitary are further confounded by release of these substances by the adrenal in man (Evans et al., 1983). At rest, both plasma (Guillemin et al., 1977) and CSF (Nakao, Oki, Tanaka, Horii, Nakai, Furui, Fukushima, Kuwayama and Imura, 1980) levels of BEir and ACTH are correlated approximatley 0.75. Surgical stress (Cohen et al., 1983) or physostigmine infusion (Risch, Kalin, Janowsky, Cohen, Pickar and Murphy, 1983), produce increased levels of both peptides, but the increases are uncorrelated (Cohen et al., 1982). By contrast, amphetamine infusion yields correlated increases in BE and ACTH immunoreactivity (Cohen et al., 1982). Pilot data fail to show a correlation of ACTH and BE after exercise stress (Gambert et al., 1981).

Prolactin (PRL). PRL is another anterior pituitary hormone implicated in the response to stress. Plasma PRL levels in man have been shown to increase under surgical stress conditions (Adashi, Rebar, Ehora, Naftolin and Yen, 1980; Corenblum and Taylor, 1981) as well as the anticipation of surgery (Corenblum and Taylor, 1981). Vaernes et al. (1982) report increased PRL levels in non-swimmers after treading deep water for 5 min which were directly correlated with reports of fear and anxiety. PRL does not, however, seem involved only in negative emotional states. Jevning, Wilson and Vanderlaan (1978) report increased serum PRL in 24 subjects practicing Transcendental Meditation but not 12 subjects who simply relaxed with eyes closed for 40 min. The effects of intense exercise on PRL levels suggest an intensity dependent phenomenon. Spiler and Molitch (1980) failed to find any change in PRL levels after low

intensity bicycle ergometer work, but Mayer, Wessel and Kobberling (1980) found elevated plasma PRL levels in 10 untrained males exercising on an ergometer for 20 min at 80% of aerobic capacity. The latter study is supported by Moretti, Fabbri, Gnessi, Cappa, Calzocari, Fraioli, Grossman and Besser (1983), who report large naloxone-reversible PRL increases in trained athletes exercising at 80% of maximal HR.

An extensive literature indicates reliable release of PRL by either endogenous or exogenous opiates and naloxone-induced reductions of basal PRL levels in the rat (Bruni, van Vugt, Marshall and Meites, 1977; Dupont, Cusan, Ferland, Lemay and Labrie, 1979; Grandison, Fratta and Guidotti, 1980; Meites, Bruni and Van Vugt, 1979). Intraventricular BE releases PRL. This response is blocked by systemic naltrexone or section of hypothalamic afferents. BE does not induce PRL release in in vitro pituitary preparations (Grandison et al., 1980), indicating a neural, hypothalamic role for opioids in PRL control. One way of activating these hypothalamic afferents is through stress. Ether and suckling (Dupont et al., 1979) as well as shock (Rossier, French, Rivier, Shibasaki, Guillemin and Bloom, 1980), heat, restraint or blood-sampling stress (Meites et al., 1979) increase PRL levels in a naloxone-reversible manner (Morley, 1983), suggesting that PRL release is a marker of increased opioid neural activity in the hypothalamus.

It is believed that the common final path of this opioid circuit is through disinhibition of tonic DA inhibition. Morphine and haloperidol (a DA antagonist) administered together result in a PRL release no greater than that seen with haloperidol alone, suggesting that DA blockade and morphine act on the same system. This is supported by

findings of PRL increases following administration of sub-effective doses of morphine and haloperidol which summate to yield a PRL release (Meites et al., 1979).

Dopamine and opiate challenges in man suggest similar mechanisms to those seen in the rat. Haloperidol, morphine (Gold, Redmond, Donabedian, Goodwin and Extein, 1978), and methadone (Judd, Risch, Parker, Janowsky, Segal and Huey, 1982) all induce PRL release from the pituitary. Naloxone by itself fails to induce any change in PRL levels (Cohen et al., 1983; Morley, 1983; Naber et al., 1981), suggesting the absence of tonic opioid control of PRL levels. Corenblum and Taylor (1981) show that both during-surgery and pre-surgery (apprehension) PRL increases are reversed by naloxone, suggesting that stress-induced increases in opioid activity will increase plasma PRL levels. Exercise may, however, operate via a non-opioid mechanism. Mayer et al. (1980) pretreated their 10 subjects with 4 mg of naloxone double-blind and failed to block exercise-induced PRL increases.

Growth Hormone (GH). The effects of stress on GH levels are less studied than those above. Exercise induces a serum GH increase (Kuoppasalmi et al., 1976; Moretti et al., 1983) that is independent of changes in blood glucose level (Hunter and Greenwood, 1964), a potent GH stimulus. Surgical stress also induces GH increases (Adashi et al., 1980) while meditation (Jevning et al., 1978) has no effect. Subjects in Vaernes et al. (1982) study of non-swimmers showed reduced post-swim GH levels, although these were elevated before the swim. Reduced levels are also found in restrained monkeys (Brown, Seggie and Chambers, 1978). Primates and rodents have different GH responses to stress (Makara et

al., 1980), making sub-primate data unusable.

Three excitatory neurotransmitters are traditionally associated with GH regulation-- DA, NE, and 5-HT. Recently, in the rat, opiates have been shown to reliably increase serum GH and naloxone to reduce basal levels (Bruni et al., 1977; Dupont et al., 1979; Grandison et al., 1980; Meites et al., 1979), indicating opioid regulation of tonic levels of GH. This issue is confused in man. Morley et al. (1980) report that 10 mg naloxone does not affect serum GH, while higher doses (6 mg/kg, Cohen et al., 1983) reduce GH levels. GH increases were reversed by low-dose naloxone administration in the Spiler and Molitch (1980) study, but Mayer et al. (1980) failed to reverse GH increases with a high dose of naloxone. These data indicate the need for further study of the mechanism of GH response to different stressors in man.

In summary, opioid activity has been shown to influence levels of all the pituitary hormones presented above. These data suggest that opioid release PRL and GH and inhibit release of BE and ACTH from the pituitary. If exercise stress increases central opioid activity to reduce pain sensitivity and elevate mood, this activity should also be reflected in reduced ACTH and BEir, and increased PRL and GH levels.

While the data reviewed above indicate post-exercise stress reductions in pain report, elevations of mood, and altered hormone levels, no study to date has studied all three variables concurrently. The concurrent data are important to obtain because: (1) stress levels in hormone studies have generally been higher than those employed in either the pain or mood studies, making comparisons among these studies

difficult; and (2) only by collecting all three types of measures are correlations between variables possible.

The pain studies reviewed above may be faulted both for the lack of breadth in their use of test stimuli and their failure to use sophisticated psychophysical techniques. The present study incorporates three measures of pain sensitivity: thermal, tourniquet ischemic, and that produced by ice water (cold pressor). The first assesses superficial, while the latter two assess deep pain. While tourniquet pain may be attributed to ischemia, the pain associated with ice-water immersion may be variously attributed to the effects of cold fiber stimulation, ischemia consequent to reduced blood flow, and release of 5-HT from platelets. Superficial and deep pain systems were tested separately because it has been suggested that they are differentially responsive to opiates (Procacci, Zoppi and Maresca, 1977; Watkins and Mayer, 1982).

Attempts to relate stress-induced hormonal and behavioral changes are hindered by statistical naievete. Correlations have been inferred from concurrent changes in mean measures of pituitary function and behavior (eg., pain thresholds) obtained before and after stress. This is, of course, a fallacy; each of these changes, while temporally contiguous, are not necessarily produced by the same subjects. If peptide levels are functionally related to behavior, then larger stress-induced changes in these levels will be found in those subjects who evidence larger changes in behavior. These are the type of analyses done in the present study.

Sensory decision theory (SDT) 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, Lx, or its nonparametric equivalent, B, identifies the subject's reluctance or readiness to report a particular sensory experience as painful. Several studies (Clark, 1969; Clark, Janal, Zeidenberg and Nahas, 1981) have supported the interpretation of P(A) as reflecting the amount of neurosensory information arriving centrally, and of B and Lx as indices of the subject's attitude toward reporting pain, i.e., his stoicism or lack of it. The use of SDT in the present study allows the important ability to separate neurosensory from attitudinal variations in pain report.

II. METHODS

Subjects were 12 males, mean age 38.8 yr (SD 12.1) who trained an average of 41.5 mi/wk (SD 14.0). They gave informed consent and were paid $20.00 for each of 2 sessions conducted between 9 and 12 AM.

Procedure. Before the run, a 35 ml blood sample was drawn for plasma endocrine determinations, and the 3 pain tests and mood scales were administered. Subjects then ran a 6.3 mi city-street course at a pace they would use when racing. Effort was quantified as the % VO2 MAX (per cent of maximum oxygen uptake) according to the method described by Colt, Wang and Pierson (1981). The run was completed in an average of 43.9 min (SD 5.3) each day at a mean of 85.3 % VO2 MAX (SD 5.5), which approaches the maximal effort for this distance. Immediately upon their return, another 35 ml blood sample was drawn, followed by 2 ml IV injections of either saline or naloxone (0.8 mg) to which the subject and the pain tester were blind. Pain and mood testing followed, but was interrupted after 20 min to administer a second injection of the same substance (naloxone, 0.8 mg, or saline).

In session 2, the same procedure was followed but the other agent (saline or naloxone) was given; drug order was randomly determined and balanced over subjects.

Thermal Pain Test. Radiant heat stimuli of 390, 340, 50 and 0 mcal/sec/sq cm were presented by a subject-held Hardy-Wolff-Goodell

dolorimeter (Williamson Development Co., Model RT2, West Concord, MA). The stimulus duration was 3 sec unless the subject withdrew his arm. Withdrawal latencies were determined within 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, 12 at each intensity, were presented randomly with respect to intensity to 3 patches of India ink applied to the volar surface of each forearm. Subjects were instructed to give their verbal responses as quickly as possible and to withdraw the projector if the stimulus became too painful. The intensity of each stimulus was rated verbally on the following scale: Nothing; Maybe Something; Warm; Hot; Very Faint Pain; Faint Pain; Pain; Very Painful; and behaviorally, by the latency of Withdrawal.

Data were treated to yield the nonparametric SDT indices of discriminability, P(A) and response criterion, B, and the parametric index, Lx, as described by McNicol (1972). This method computes P(A) by the trapezoidal rule as the area below the ROC curve generated by cumulating probabilities of hits and false alarms at each response category. P(A) values of 0.5 indicate chance discrimination, values of 1.0, perfect discrimination. B is computed as the median response category. High B values indicate a high criterion, few pain reports; the measure ranges from 0 to the total number of response categories, in this case, 12, including the 3 different withdrawal latencies. Lx was computed as the ratio of the ordinates of overlapping noise and signal + noise distributions at the criterion for Faint Pain. High Lx values

indicate few reports of pain. Lx was used because this measure provides an index of response criterion at each level of response, while B provides the equivalent of an average over these various levels. The P(A), B, and log transform of Lx values generated for the noxious (390-340) and innocuous (50-0) pairs of intensities were used in data analysis. Further details concerning this test and the application of SDT to the analysis of response data may be found in Clark (1974) and Yang, Clark, Ngai, Berkowitz and Spector (1979).

Ischemic Pain Test. Details concerning the procedure and the treatment of sensory reports are presented in full in Yang, Clark, and Ngai (1980). In a sitting position, the subject raised his arm and an Esmarch bandage was wrapped around the hand and arm to the elbow to express venous blood. An automatic tourniquet cuff (Walter Kidde and Co., Bloomfield, NJ) placed above the elbow was then inflated to 250 torr. The Esmarch bandage was removed, and the subject squeezed a hand dynamometer to half of maximum strength for 20 2-sec periods. He the reported his sensory experience every 10 sec using the scale: Nothing; Slight Sensation, Non-painful; Strong Sensation, Non-painful; Faint Pain; Definite Pain; Severe Pain. In addition, the subject was instructed to use the numbers 1 through 10 to differentiate finer gradations of sensations within each of the categories above the first (higher numbers indicated stronger sensation). Subjects were asked to tolerate the tourniquet for as long as possible up to a maximum of 15 min. The verbal reports were converted to a numerical scale by assigning "0" to Nothing, "1" to Slight Sensation, and continuing until "5" for

Severe Pain. The ten numbers within each verbal rating category were divided by 10 and summed with the category value. Thus, a rating of "Strong Sensation, 5" would be scored as 2.5. The response at the 30 sec point within each min was used in data analysis.

Cold Pressor Test. Determinations of the temperature of the distal phalanx of the thumb were made with a precision thermometer (Bailey Instruments, Saddle Brook, NJ, 07662, Model BAT 8). The subject immersed his hand up to the wrist in an ice water bath and gently moved it. He was instructed to tolerate the stimulus as long as possible with the maximum time specifiec to be 3 min. During this immersion, the subject gave sensory reports of his sensation using the scale: Warm; Nothing; Cool; Cold; Very Cold; Faint Pain; Definite Pain; Severe Pain. Within the last category, the numbers 1 through 10 were used to express additional increments. Immediately upon withdrawal from the water bath, a second determination of thumb temperature was made. Verbal reports were converted to a numerical scale in a manner similar to that for ischemia data above. The verbal reports elicited at 10 sec intervals and thumb temperatures before and after immersion were used in data analysis.

Mood Tests. Mood was assessed using visual analogue scales (VAS). Each 85-mm, horizontal line with descriptor words at each pole was presented on a separate card. Scales of this type have been found reliable and sensitive to variation in mood (Folstein and Luria, 1973). The three Happiness scales had stems of "Emotionally, I feel...", followed, respectively, by these poles on the VAS:

Depressed--Euphoric.

Regretful--Joyful.

Pleasant--Miserable.

The other 7 scales were statements to which the subject made a mark to indicate his agreement on scales with poles of "Not at all" and "Very Much So". One of these was designed to assess the subject's arousal or energy level:

I (feel, felt) I (will, did) have a good run today.

Two were designed to assess anxiety:

I am apprehensive about these procedures.

I am worried about being hurt.

Two were designed to measure opiate-like and/or fatigue effects:

I feel alert and attentive.

I feel "out of it", as though I'm not really here.

Finally, two scales were designed to assess cooperation and conscientiousness, the subjects desire to perform at his best:

I am pleased that I volunteered for this study.

I am concerned about doing well.

The per cent of full scale distance was used for data analysis.

Plasma Endocrine Determinations. Blood samples were collected in heparinized tubes and cooled in ice water until centrifuged (within 10 min) at 5 deg C for 20 min at 1500 g. Plasma was stored at -70 deg C until analyzed. BEir was determined by a radioimmunoassay (RIA) procedure involving the extraction of BE and LPH using ODS (C18) silica columns. After elution, the BEir was measured using a double antibody

RIA procedure (Immunonuclear Corp., Stillwater, MN). Plasma ACTH was determined by a direct double antibody RIA equilibrium procedure (Immunonuclear Corp., Stillwater, MN). PRL was determined by the RIA method of Frantz (1976). GH was measured by the RIA method of Frantz and Rabkin (1964).

Test times. It took 15 min to administer the thermal test, 20 min for the ischemic, 5 min each for the cold pressor and mood scales, 10 min to collect blood samples, and 2 min to administer each IV injection. Combined with the 5-10 min to return to the lab following the run, the entire procedure took between 65 and 70 min.

Test lag groups. Each subject was randomly assigned to one of the 24 possible orders of pain and mood test administration; this same order was kept pre- and post-run and on each of the two test days. Although each had a different order, groups of three could be formed post hoc which received one particular test in each of the 4 possible orders. Thus, 3 subects received the thermal test test first, 3 received the ischemic first, etc. In the text that follows, test lag will be used to identify the time (20, 30, 40, and 50 min) that each of these groups started each of these tests; this time was determined by the order and number of antecedent test completed by the subject.

Data Analysis. Two sets of hypotheses were analyzed: the effect of running + saline on pain and mood and the effect of running + naloxone on these variables. First, to evaluate any absolute difference in pain perception or mood as a result of running, each of the pain tests and

mood scales was analyzed for the saline day alone using pre- and post-run scores as a repeated factor and test lag as a grouping factor in a split-plot 2-way ANOVA (Dixon and Brown, 1979). For the thermal data, ANOVAs using this design were run for each of P(A), B, and log Lx as dependent variables. Analysis of the ischemic and cold pressor verbal report data used the above design with ischemic duration and immersion duration as repeated factors, 3-way ANOVAs. Mood scale data used the same basic design with 2-way ANOVAs done separately for each scale. CD refers to the critical difference between means necessary for significance ($P < .05$) in a priori (planned) t-tests; df follow CD in parentheses. Second, to compare the effects of naloxone with those of saline, post- minus pre-run difference scores were obtained and analyzed by a split-plot ANOVA using drug as a repeated factor and including other factors as specified above.

Hormone data were analyzed using 1-way ANOVA for repeated measures on pre- and post-run levels for each hormone.

III. RESULTS

Thermal Pain Test.

Discriminability. P(A) means by stimulus intensity, pre- vs post-run period, and test lag (time after the run) for the saline condition are presented in Table 1. Results show reduced discriminability post-run at both noxious and innocuous intensities. ANOVA at the 390-340 (noxious) intensity pair showed a period X test lag interaction indicative of significantly reduced discriminability ($F(3,8)= 9.5$, $P < .01$) for those subjects tested at the 20 min lag ($CD(8)= 0.09$; pre-run $M= .85$, post-run $M= .69$); values at longer lag times were not significant. ANOVA at the 50-0 (innocuous) intensities showed an overall period effect ($F(1,8)= 10.9$, $P < .02$) of reduced post-run discriminability. The period X test lag interaction at the innocuous intensity failed to reach significance ($F(3,8)= 1.3$, ns). Post-hoc tests based on the error term from this interaction ($CD(.05, 8)= .15$) did, however, show a significant post-run reduction in the 40 and 50 min lag groups (at 40 min, pre-run $M= .71$, post-run $M= .54$; at 50 min, pre-run $M= .80$, post-run $M= .64$). Reductions in discriminability for the lower intensity pairs appear, therefore, to follow a different time course of activity, suggesting they are not mediated by the same mechanism.

Table 2 displays the mean P(A) scores by test lag, test period, and stimulus intensity on the naloxone day. ANOVA failed to show significant variation in discriminability as a function of any of the experimental

Table 1. Mean (SD) thermal P(A) scores by intensity (mcal/sec/sq cm), period and test lag (min) for the saline day.

Test Lag	Period	Intensity 390-340	Intensity 50-0
20	pre	.85 (.04)	.71 (.08)
	post	.69 (.07)	.62 (.20)
30	pre	.83 (.01)	.62 (.11)
	post	.77 (.04)	.61 (.06)
40	pre	.74 (.04)	.71 (.13)
	post	.82 (.09)	.54 (.04)
50	pre	.81 (.07)	.80 (.12)
	post	.79 (.02)	.64 (.22)
Mean	pre	.81	.71
	post	.77	.60

Table 2. Mean (SD) thermal P(A) scores by intensity (mcal/sec/sq cm), period and test lag (min) for the naloxone day.

Test Lag	Period	Intensity 390-340	Intensity 50-0
20	pre	.73 (.07)	.60 (.11)
	post	.71 (.15)	.54 (.04)
30	pre	.83 (.05)	.58 (.04)
	post	.77 (.10)	.61 (.12)
40	pre	.76 (.02)	.61 (.04)
	post	.75 (.05)	.60 (.05)
50	pre	.85 (.10)	.62 (.23)
	post	.80 (.09)	.69 (.14)
Mean	pre	.79	.60
	post	.75	.61

conditions (save intensity ($F(1,8)= 26.6$, $P < .001$), suggesting a naloxone-mediated reversal of post-run reductions in discriminability.

Direct comparisons of saline and naloxone difference scores, however, fail to support the hypothesis of opioid-mediated reductions in discriminability. ANOVA on the mean post- minus pre-run difference scores for the noxious stimulus intensities as a function of test lag, intensity, and drug conditions (Table 3) shows that saline and naloxone conditions yielded differences in the same direction. The test lag X intensity X drug interaction, the appropriate ANOVA effect for determining naloxone reversal, failed to reach significance ($F(3,8)= 2.0$, $P < .19$). The CD based on the error term from this interaction (.20, $P < .05$) shows that no comparisons between drugs at equivalent levels of lag and intensity differed significantly, failing to support the hypothesis of opioid mediation of post-run reductions in discriminability seen at the 20 min lag on the saline day. Averaging over test lag did yield a trend in the direction of naloxone reversibility (drug X intensity interaction, $F(1,8)= 2.2$, $P < .18$, $CD(.05,8)= .10$) for the innocuous stimuli (saline= -.09, naloxone= .01). Comparison of means shows significantly lower discriminability under saline conditions (-.09) compared to naloxone (.01) for the low intensity stimulus pair. Thus, there is some indication that reductions in the discriminability of the low intensity pair was opioid mediated, although this effect was not tied to specific test lag periods.

Individual subject difference scores (Table 3) support the basic conclusions reached from analysis of the mean data (Table 1). These individual subject differences show: (1) for the 390-340 intensity pair

Table 3. Thermal P(A) difference scores (POST- minus PRE-RUN) by subject, test lag (min), intensity (mcal/sec/sq cm) and drug condition.

Test	ID	Saline		Naloxone	
Lag		390-340	50-0	390-340	50-0
20	3	-.12	-.21	.24	-.08
	7	-.11	-.15	-.15	-.03
	12	-.24	.10	-.13	-.14
	Mean	-.16	-.09	-.01	-.08
30	4	-.02	-.02	0	.01
	5	-.06	-.07	-.06	.19
	11	-.10	.06	-.14	-.07
	Mean	-.06	-.01	-.07	.04
40	1	.03	-.21	.02	.05
	6	.14	-.07	-.01	-.04
	10	.06	-.23	-.04	-.01
	Mean	.08	-.17	.01	0
50	2	-.11	.04	-.13	-.03
	8	-.07	-.08	-.06	.07
	9	.03	-.28	.01	.17
	Mean	.05	-.11	-.06	.07
Column	Mean	-.05	-.09	-.04	.01

under saline conditions at the 20 min lag, all 3 subjects showed reduced post-run discriminability, indicating that the mean data reported above are representative; (2) similar conclusions are supported by the 50-0 mcal intensity pair on the saline day at 40 min— but not for the 50 min lag, where the extreme score of subject 9 biases the group data to produce a mean effect; (3) under naloxone conditions at the high intensity and 20 min lag, 2 of the 3 subjects showed post-run reductions in discriminability, while one evidenced a large increase. The latter effect thus accounts entirely for the indication of naloxone-reversibility suggested in the mean data.

Day Effects. ANOVAs comparing day 1 pre-run vs. day 2 pre-run P(A) and B scores by test lag, period and intensity failed to show any differences between these control values. The absence of a day effect suggests that the observed run effects are not a result of learning, fatigue, or adaptation to the test procedure.

Report Criterion. ANOVAs on the report criterion, B, failed to reveal any significant post-run effects for the saline condition alone or relative to naloxone. These data may be found in Tables 4 and 5. Analysis of Lx data also failed to show a post-run shift in reponse bias (saline, pre vs post, $\underline{t}(11)= -.08$, ns; naloxone, $\underline{t}(11)= -.17$, ns) averagd over test lag. Incomplete data precluded doing ANOVAs evaluating lag and intensity effects parallel to those presented for P(A) and B above.

Ischemic Pain Test.

Table 4. Mean (SD) B values for saline and naloxone days by test lag (min) and intensity (mcal/sec/sq cm) (N= 12).

Test		Saline		Naloxone	
Lag		390-340	50-0	390-340	50-0
20	pre	5.54 (1.56)	10.05 (0.31)	4.39 (2.32)	10.15 (0.40)
	post	4.66 (2.83)	10.22 (0.19)	4.70 (2.56)	10.22 (0.41)
30	pre	6.86 (1.45)	9.97 (0.42)	6.71 (1.58)	10.12 (0.27)
	post	7.10 (0.80)	10.06 (0.39)	6.22 (1.43)	10.23 (0.22)
40	pre	6.69 (1.91)	10.18 (0.03)	6.70 (1.76)	10.16 (0.36)
	post	6.38 (1.91)	10.24 (0.19)	6.25 (1.77)	10.29 (0.08)
50	pre	4.60 (2.16)	9.44 (0.50)	5.19 (2.28)	9.81 (0.40)
	post	5.10 (2.15)	9.57 (0.09)	5.25 (2.54)	9.79 (0.52)
Mean	pre	5.92	9.91	5.75	10.16
	post	5.81	10.02	5.60	10.13

Table 5. Mean B difference scores (POST- minus PRE-RUN) for saline and naloxone days by test lag (min) and intensity (mcal/sec/sq cm) (N= 12). Positive scores indicate increased post-run stoicism.

Test		Saline		Naloxone	
Lag	ID	390-340	50-0	390-340	50-0
20	3	.19	.43	1.09	.04
	7	-.50	.29	.22	.05
	12	-2.33	-.21	.11	.11
	Mean	-.88	.17	.47	.07
30	4	-.71	.10	0	0
	5	.48	.16	-1.57	.33
	11	.95	0	.11	0
	Mean	.24	.09	-.50	.11
40	1	-.94	-.06	-.97	.04
	6	.15	.26	-.15	-.20
	10	-.14	0	-.23	.54
	Mean	-.31	.07	-.45	.13
50	2	-1.00	.76	-.58	-.15
	8	2.20	0	.70	.09
	9	.30	-.37	.05	-.01
	Mean	.50	.13	.06	-.02

Verbal report means partitioned by duration of ischemia, period, and test lag for the saline condition are shown in Figure 1. Results showed reduced pain reports when subjects were tested at 20 min post-run, increased reports when tested at 30 min and no effects thereafter. ANOVA failed to show a period X duration X test lag interaction ($F(42,112)= 1.2$, $P < .28$). However, because a priori hypotheses predicted an effect at 20 min, post hoc tests (CD (.05, 112)= 0.42, within test lags and between periods) were done which showed that pain report was reduced significantly in subjects tested 20 min after the run. Subjects tested at 30 min showed significantly increased pain report between 5 and 9 min. Subjects tested after 40 min showed no pre-post differences.

Figure 2 (Panel A) shows ischemic verbal report means by drug condition, test period, and ischemic duration averaged over test lag. ANOVA on the saline data showed a significant period X ischemic duration trend ($F(14, 112)= 1.5$, $P < .12$; $CD(.05, 112)= .21$), such that verbal report was reduced post-run at all ischemic durations past 9 min and significantly so at 11, 14 and 15 min. These data, presented above as a function of test lag, showed the reduced post-run verbal report to be most prominent in the 20 min lag group. Thus, these mean data represent a "washed out" hypoalgesic effect that is mainly representative of the performance of the 20 min lag group. They are presented again in order to contrast the naloxone findings, presented in Panel B of Figure 2. ANOVA revealed a significant period X ischemic duration interaction ($F(14,112)= 2.1$, $P < .02$; $CD(.05,112)= .27$). Comparison of means shows increased reports of sensation post-run at all times after 6 min, significantly so at min 7, 8, 9, 11, and 15. Thus, reduced post-run pain

Figure 1. Mean verbal report of stimulus intensity (2= Slight Sensation, 4= Faint Pain, 6= Severe Pain) on the ischemic pain test as function of period (pre-run= closed circle, post-run= open circle), ischemic duration (min) and test lag (min) for the saline day.

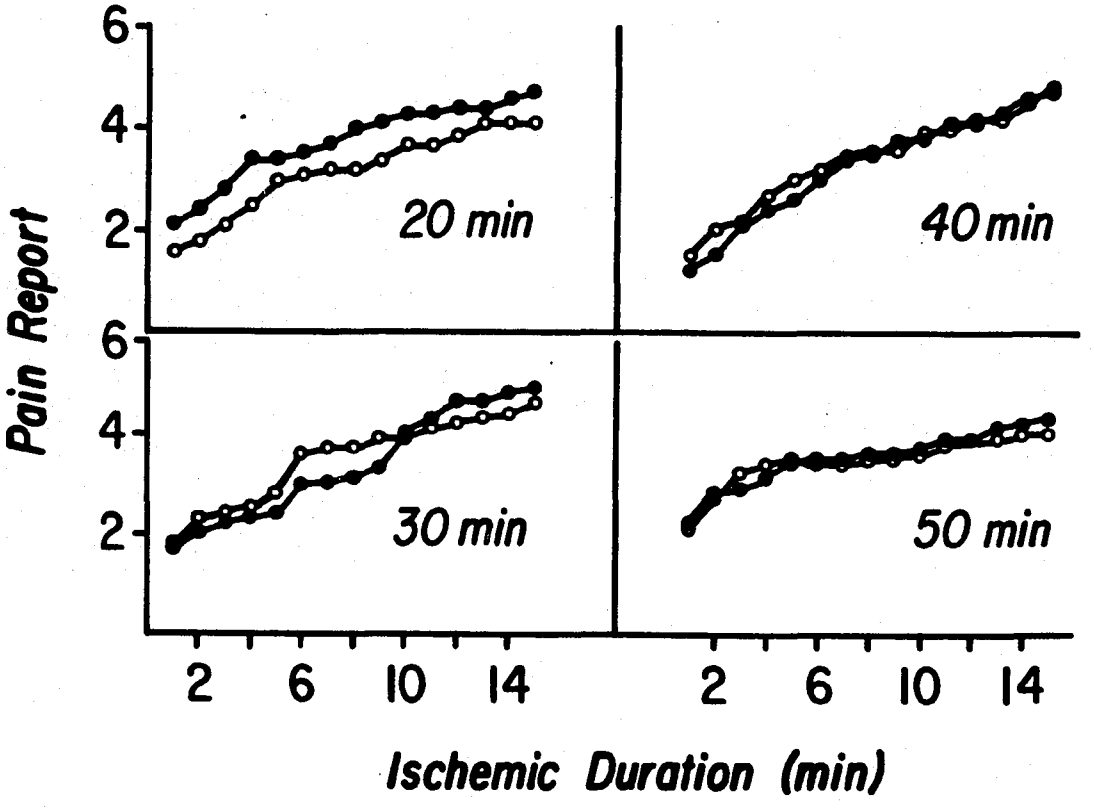
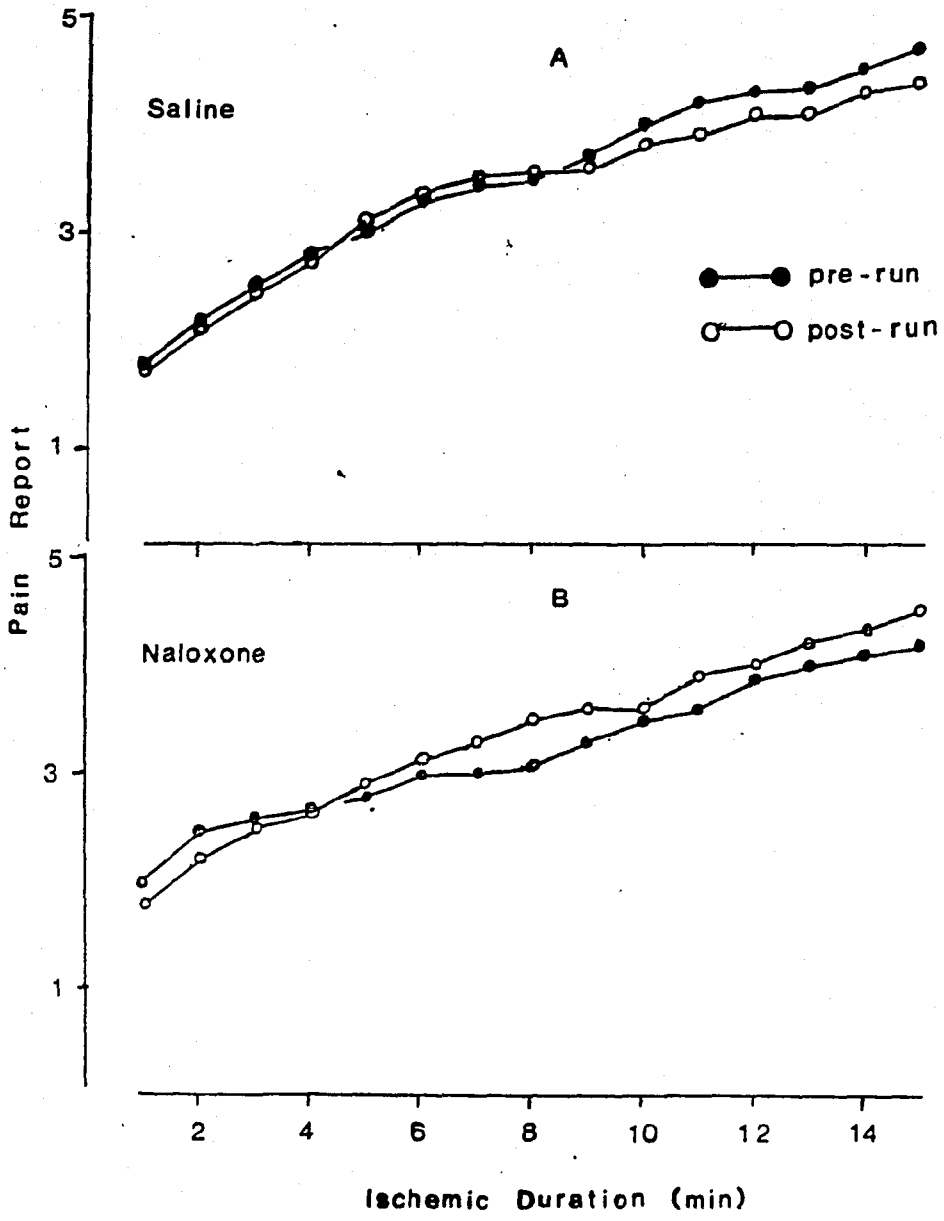

Pain Report
6
4
2
20 min
40 min
30 min
50 min
2
6
10
14
Ischemic Duration (min)

Figure 2. Ischemic verbal report (1= Slight Sensation, 3= Strong Sensation, 5= Definite Pain) means by drug condition (saline, naloxone), test period (pre-run, closed circle; post-run, open circle), and ischemic duration (min) averaged over test lag (min) (N= 12).


A
Saline
pre-run
post-run
B
Naloxone
Pain Report
5
3
1
2
4
6
8
10
12
14
Ischemic Duration (min)

report under saline and increased report under naloxone conditions were found, each relative to the same days' baseline and averaged over test lag, suggesting a naloxone reversal of analgesia. There was no interaction of test lag X period X ischemic duration on the naloxone day ($F(42,112)= 0.3$, ns).

Direct comparisons of the post- minus pre-run difference scores are presented in Figure 3. ANOVA of the ischemic duration X drug interaction ($F(14,112)= 2.3$, $P < .01$; CD $(.05, 112)= .36$), showed that significantly more pain was reported under naloxone than saline conditions at 7 to 15 min ischemic durations, i.e., at times when the stimulus was reported as between "Strong Sensation" and pain, confirming a reversal by naloxone of analgesia seen on the saline day. Note that verbal report decrements and their reversal occurred only at ischemic durations greater than 8 min, i.e., at times when the stimulus was reported to be painful, but not at innocuous intensities. The test lag X duration X drug interaction was insignificant ($F(42,112)= 0.7$, ns), although the naloxone-saline difference was largest at the 20 min lag (see Figure 4).

The proportion of post-run verbal reports to ischemic stimulation reduced relative to pre-run reports are shown in Table 6 by subject, drug condition, and duration of ischemia, which has been dichotomized into periods of less than 8 min duration (innocuous stimulation) and above 8 min (noxious stimulation). Proportions greater than .50 indicate a preponderance of post-run reductions in verbal report. Under saline conditions, 20 min subjects all reported less sensation post-run at both "stimulus intensities." These same subjects, under naloxone treatment, showed considerable individual variability; at the shorter ischemic

Figure 3. Mean change in ischemic verbal report (POST- minus PRE-RUN) averaged over test lag groups for the saline (closed circle) and naloxone (open circle) days as a function of ischemic duration (min). Negative scores indicate post-run hypoalgesia.

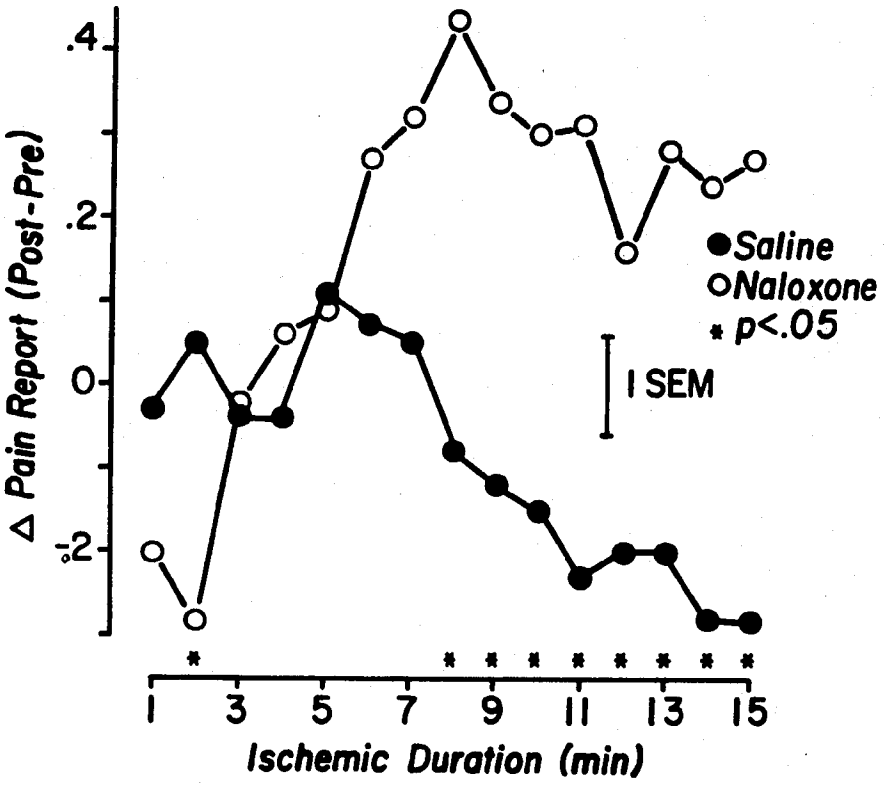

.4
.2
0
-.2
Δ Pain Report (Post-Pre)
Saline
Naloxone
* p<.05
1 SEM
1
3
5
7
9
11
13
15
Ischemic Duration (min)

Figure 4. Ischemic verbal report change scores (POST- minus PRE-RUN) as a function of ischemic duration (min), drug conditions, and test lag (min). Negative scores indicate post-run hypoalgesia (N= 12, 3 per test lag group).

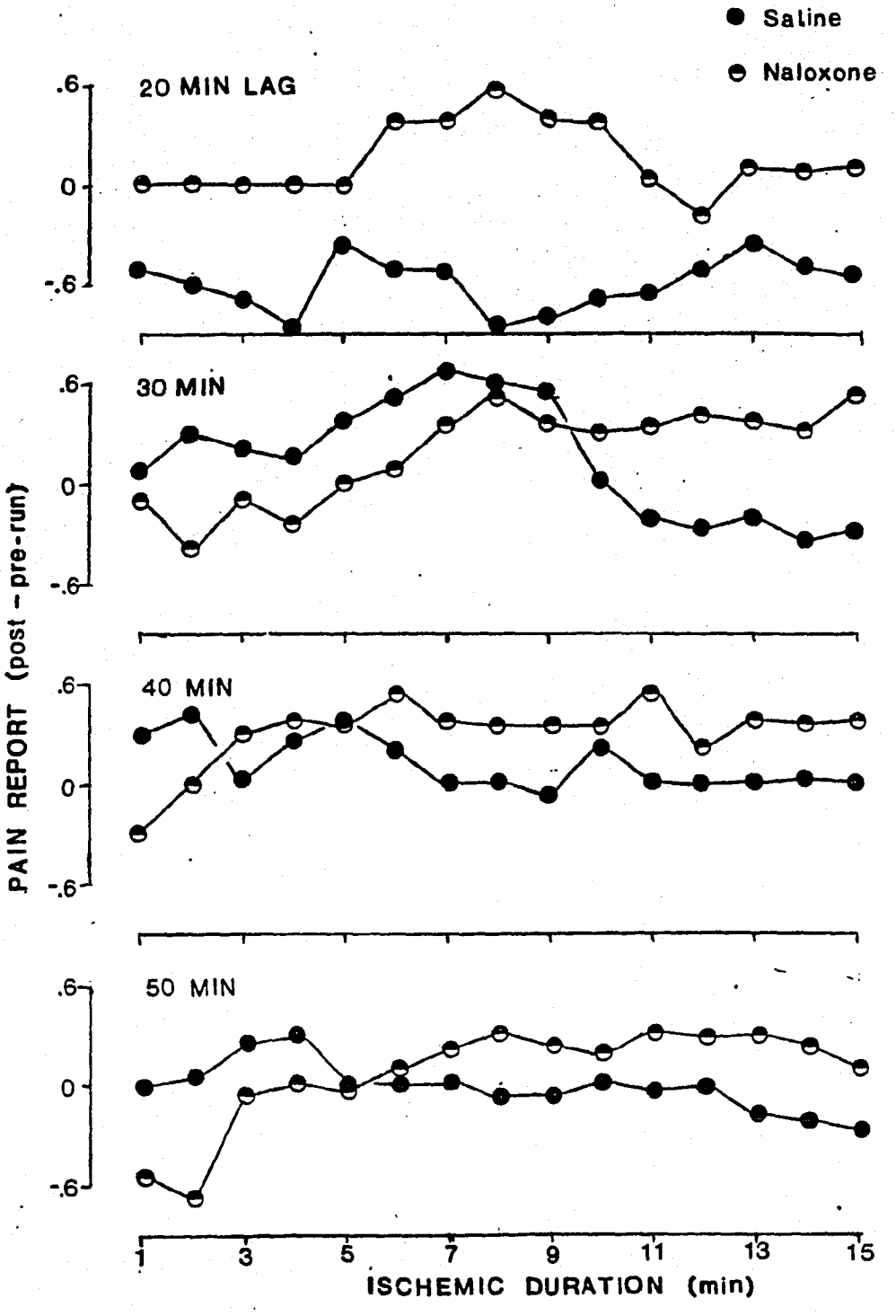

Saline
Naloxone
20 MIN LAG
30 MIN
40 MIN
50 MIN
.6
0
-.6
PAIN REPORT (post - pre-run)
1
3
5
7
9
11
13
15
ISCHEMIC DURATION (min)

Table 6. Proportion of reduced reports to ischemic stimulation by subject, test lag (min), drug condition and ischemic duration (min).

Test Lag	ID	Innocuous		Noxious	
		Saline	Naloxone	Saline	Naloxone
20	2	1.0	1.0	1.0	.50
	5	1.0	0	1.0	.63
	11	1.0	.14	1.0	0
	Mean	1.0	.38	1.0	.38
30	3	1.0	.83	1.0	0
	6	0	.43	0	0
	10	0	.60	0	0
	Mean	.33	.62	.33	0
40	4	1.0	0	.75	1.0
	8	0	.71	.38	0
	9	0	.20	.17	0
	Mean	.33	.30	.43	.33
50	1	1.0	.43	0	0
	7	1.0	.50	1.0	1.0
	12	.20	*	*	*
	Mean	.73	.47	.50	.50
Column Mean		.60	.44	.57	.30

* more than 50% of reports were tied, data excluded

duration, subject 2 failed to show reversal, while at the longer duration, all 3 subjects showed some degree of reversal. These data support the hypothesis that naloxone reverses post-run reductions of pain, but not innocuous sensations. For the 30 min group, the consistent presence of increased pain report on the naloxone day at the longer, but not the shorter, ischemic durations supports the mean finding (Figure 1) of post-run hyperalgesia in this lag group. No consistent effects were seen in the 40 or 50 min lag groups. Averaged over lag, at the later ischemic durations there was a larger difference between saline and naloxone (57% vs 30% reduced pain reports) than at the shorter durations (60% vs 44%), suggesting that naloxone reversal was limited to reduced perception of the stronger sensations.

Day effects. Differences between day 1 and day 2 pre-run periods were evaluated by ANOVA as a function of ischemic duration, day, and test lag. Results showed less intense reports (Day 2 $\underline{M}$= 3.6 , Day 1 $\underline{M}$= 3.1; $\underline{F}(1,8)$= 9.1, $\underline{P}$ < .02). All interactions failed to reach significance, indicating an equivalent reduction at all ischemic durations and for all test lag groups. This finding supports the use above of only within day comparisons when the absolute values of verbal report are considered, and the comparison between days (drugs) of difference scores only.

In summary, reports of painful but not nonpainful ischemic stimulation were reduced post-run. This analgesic effect was reversed by naloxone, indicating the presence of stress-induced opioid mechanisms of analgesia.

Cold Pain Test.

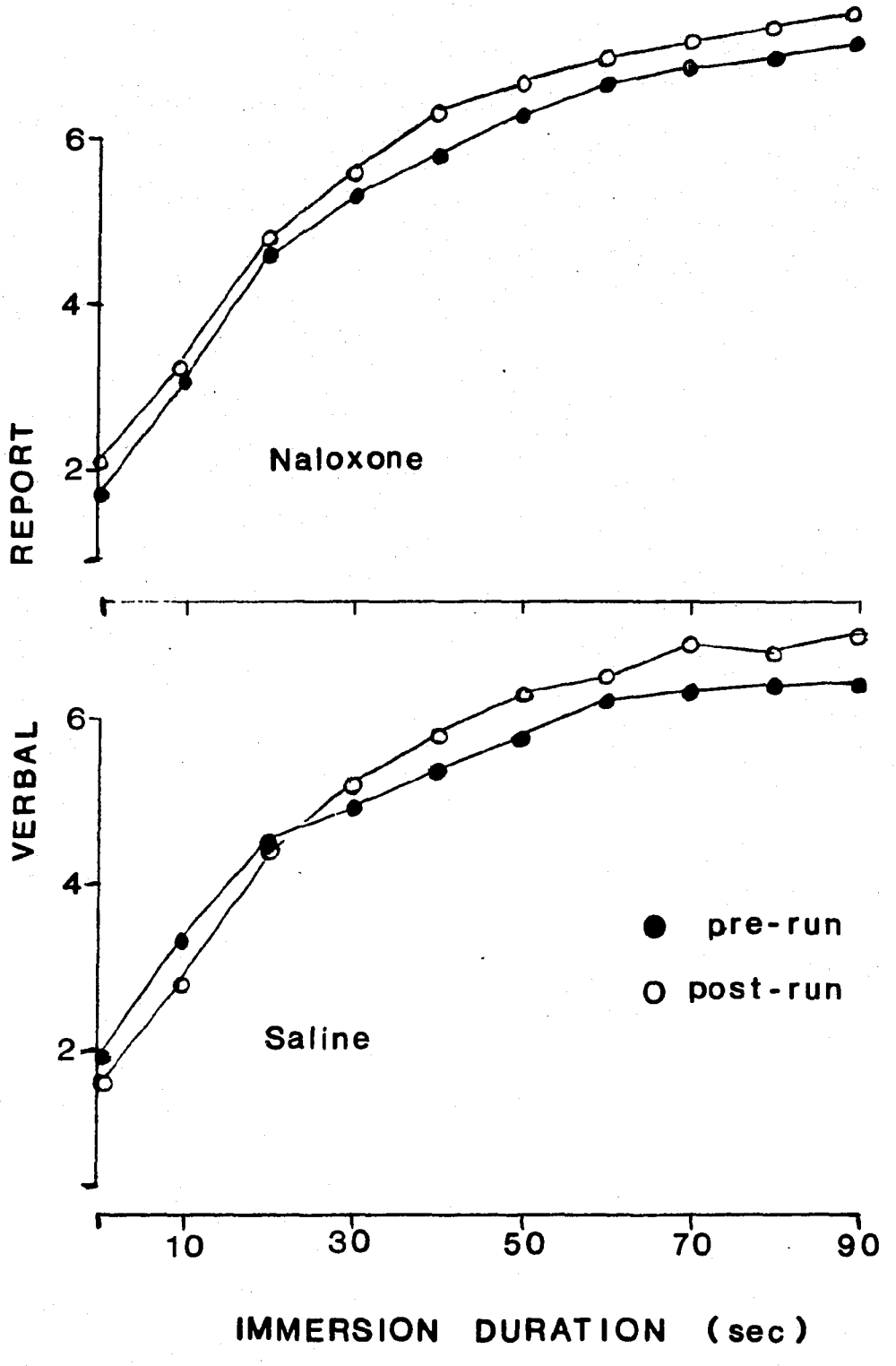
In brief, reports of sensation to the cold-water stimulus failed to show any post-run alteration in perception.

In the following analyses, verbal report data acquired during the first 90 sec of ice-water immersion are used. Data beyond this point were missing in 6 of the 12 subjects. Where withdrawals occurred before 90 sec, the last verbal report given by the subject while his hand was immersed was used to fill the remaining cells of the data matrix. (This was generally the maximal verbal report, "Severe Pain 10".)

Figure 5 depicts mean verbal report over the first 90 sec of immersion for the pre- and post-run periods and for the two drug conditions. In general, post-run reports of pain were greater than pre-run under both drug conditions. ANOVA of the saline data showed a period X duration interaction ($\underline{F}(9,72)= 2.7$, $\underline{P} < .02$; $\underline{CD}(.05,72)= 0.5$), such that reduced post-run verbal report was found at 0 and 10 sec durations and increased reports were found at 50, 70 and 90 sec durations. There was no evidence of an interaction of test lag with period and duration ($\underline{F}(27,72)= 0.4$, ns). On the naloxone day, the period X duration interaction failed to reach significance ($\underline{F}(9,72)= 0.2$, ns). Post-hoc comparisons ($\underline{CD}$ $(.05,72)= 0.5$) failed to show pre- vs post-run report changes. While the magnitude of changes on the naloxone day were similar to those found with saline, the absence of significant naloxone effects may be attributable to increased error variability on the naloxone day (Error Mean Square= .44 vs .33).

Direct comparisons of post- minus pre-run differences under the two drug conditions also failed to show effects due to test lag or immersion

Figure 5. Mean verbal report of cold pain (2= Cool, 4= Very Cold, 6= Definite Pain) as a function of immersion duration (sec), drug conditions, and test period (N= 12).


REPORT
6
4
2
Naloxone
VERBAL
6
4
2
Saline
pre-run
post-run
10
30
50
70
90
IMMERSION DURATION (sec)

duration (all P's > .25). It may be concluded that cold stimulus sensitivity was not reduced post-run. On the contrary, there is some indication of increased post-run reports of pain that were unaffected by either latency of post-run testing or the two drug conditions.

Verbal report data were also analyzed using the immersion time required to report the sensation as either "Faintly" or "Definitely Painful" as ANOVA criteria. Effects in this analysis comparable to those presented above showed numerically higher P levels, suggesting the verbal report measure used above is the more sensitive index. No significant effects were uncovered using the latter measure.

ANOVA of thumb temperature (deg C) as a function of test lag, period, drug, and immersion time (before immersion and after withdrawal) was also undertaken (see Table 7). Averaged over all conditions, the mean pre-immersion temperature was 28.9 (SD= 2.5) and the mean withdrawal temperature was 10.9 (SD= 5.5). There was a trend toward higher temperatures after the run (before immersion, +1.7, $F(1,11)= 2.9$, ns; after withdrawal, +.6, $F(1,11)= 1.3$, ns). Eight of the 12 subjects showed increased post-run temperatures before immersion (binomial test ns) and 7 of the 12 showed higher temperatures at withdrawal (binomial test ns). Clearly, then, the data fail to confirm a consistent post-run increase in skin temperature.

ANOVA of the temperature drop during immersion also failed to reveal significant run effects (Table 8), although there was a trend in the direction of larger post-run mean drops (18.6 vs 17.4; $F(1,11)= 0.8$, ns). Thus, the change in skin temperature associated with withdrawal was not affected by the run.

Table 7. Mean thumb temperature (deg C) as a function of drug condition, test lag (min), test period, and immersion duration (min) in ice-water bath (N= 12).

SALINE

Test	Pre-run		Post-run	
Lag	Pre-immersion	Withdrawal	Pre-immersion	Withdrawal
20	27.6	7.6	30.6	8.6
30	30.6	15.9	28.7	16.3
40	27.7	6.0	27.8	5.2
50	27.0	9.2	30.0	14.3
M	28.2	9.7	29.3	11.1

NALOXONE

20	30.2	10.2	32.1	10.8
30	32.2	16.7	30.0	17.7
40	23.3	7.3	27.9	7.5
50	25.9	11.5	31.0	9.6
M	27.9	11.4	30.2	11.4

Table 8. Mean temperature drop (deg C) in ice-water bath as a function of drug condition, test lag (min), and test period (N= 12).

Test Lag	Saline		Naloxone	
	Pre-run	Post-run	Pre-run	Post-run
20	20.0	22.0	20.0	21.3
30	14.7	12.3	15.5	12.3
40	20.7	22.6	16.1	20.4
50	17.8	15.7	14.4	21.4
M	18.3	18.2	16.5	18.9

Analysis of the day effect failed to show consistent changes for either verbal report or skin temperature variables.

Mood Tests.

Table 9 shows mean ratings of euphoria and joy by test period and test lag for the saline day. These VAS support the hypothesis that running produced an improved mood. ANOVA showed a period X test lag interaction on the Euphoria scale ($\underline{F}$ (3, 8)= 4.2, $\underline{P} < .05$; $\underline{CD}$ (8)= 10.7), indicating more euphoric ratings post-run at test lags of 30 and 40 min only. A period X test lag interaction was also found on the Joy scale ($\underline{F}$ (3, 8)= 6.2, $\underline{P} < .02$; $\underline{CD}$ (8)= 16.4), which indicated more joyful ratings post-run at the 30 min test lag only. Parallel data from the naloxone day are presented in Table 10. ANOVA failed to reveal any signficant effects under this condition.

ANOVA on the post- minus pre-run differences showed naloxone-induced reversals of Euphoria and Joy rating increases (see Table 11). ANOVA showed an overall drug trend (Saline $\underline{M}$= 10.7, Naloxone $\underline{M}$= 2.1; $\underline{F}(1,8)$= 5.0, $\underline{P} < .06$), indicative of attenuated increases of post-run Euphoria ratings under naloxone conditions. A test lag X drug trend ($\underline{F}(3,8)$= 2.7), $\underline{P}< .12$; $\underline{CD}$ (8) = 18.33) indicated that this naloxone effect was maximal and significant only at 40 min. A test lag X drug trend ($\underline{F}(3,8)$= 2.4, $\underline{P} < .15$; $\underline{CD}$ (8)= 13.71) indicative of reduced ratings of Joy under the naloxone condition at 30 min was also found. These data indicate naloxone-reversal of post-run mood elevation, supporting the hypothesis of opioid mediation of these effects.

Table 9. Mean (SD) Euphoria and Joy ratings (% of full scale distance) by period and test lag (min) for the saline day.

Scale	Test Lag	Pre	Post
Euphoria	20	54.1 (5.6)	52.9 (3.0)
	30	48.2 (9.9)	65.9 (15.4)
	40	33.3 (11.6)	52.6 (13.0)
	50	63.9 (9.1)	71.4 (8.2)
Joy	20	62.0 (0.4)	55.7 (9.3)
	30	46.7 (9.2)	74.9 (4.8)
	40	44.3 (3.7)	32.6 (7.7)
	50	71.0 (16.0)	76.5 (13.5)

Table 10. Mean (SD) Euphoria and Joy ratings (% of full scale distance) by period and test lag (min) for the naloxone day.

Scale	Test Lag	Pre	Post
Euphoria	20	47.5 (0.7)	55.3 (16.2)
	30	58.4 (15.9)	66.7 (8.3)
	40	45.5 (6.5)	44.3 (13.4)
	50	74.5 (27.6)	75.7 (23.4)
Joy	20	61.2 (10.1)	60.0 (29.1)
	30	66.3 (18.8)	64.7 (5.4)
	40	44.3 (6.0)	41.6 (8.5)
	50	72.6 (30.6)	74.5 (20.7)

Table 11. Mean (SD) Euphoria and Joy change scores (POST- minus PRE-RUN) by drug and test lag (min). Positive scores indicate improved mood.

Scale	Test Lag	Saline	Naloxone
Euphoria	20	-1.2 (6.2)	7.8 (16.7)
	30	17.6 (12.4)	8.3 (13.3)
	40	18.8 (6.6)	-1.2 (12.7)
	50	7.5 (4.5)	-6.7 (6.0)
Joy	20	-7.8 (9.5)	-1.2 (31.8)
	30	28.2 (15.4)	-1.6 (13.6)
	40	-11.8 (15.4)	-2.7 (3.0)
	50	5.5 (2.7)	2.0 (10.0)

This conclusion is supported by analyses of individual subject data. Table 12 shows, by subject, the post- minus pre-run difference scores for the Euphoria and Joy scales by drug and test lag. Positive scores indicate relatively improved post-run mood ratings. It may be seen that all 40 min lag subjects showed improved post-run Euphoria ratings under saline conditions and either reversed or attenuated improvement under naloxone conditions. A similar, though less robust, effect may be seen in the 30 and 50 min lag subjects on the Euphoria scale. The consistency of these data support the conclusions drawn above from the group means. Similar observations may be made about the Joy scale, where 30 min lag subjects showed a consistent mood elevation on the saline day that was reversed or attenuated under naloxone conditions.

Two other scales were affected by the run, equally under saline and naloxone conditions and at all test lags. ANOVA showed increased concern with "doing well" post-run (35.4 vs 25.8); and, increased pleasure post-run at having volunteered for the study (73.6 vs 70.4), both $\underline{P}$'s < .10. Thus, while the subjects were more conscientious and cooperative post-run, these effects were not reversed by naloxone, while shifts in euphoria and joy were. Ratings of energy, fatigue, and test anxiety were unaffected by the run.

Analysis of differences in pre-run baselines between days 1 and 2 failed to show significant changes in the report of mood.

In summary, ratings of euphoria and joy were increased post-run in a naloxone-reversible manner, indicating an opioid mechanism of post-run mood elevation. That other scales were also elevated, in a naloxone-resistant manner supports the specificity of these findings.

Table 12. Post- minus pre-run difference scores on Euphoria and Joy scales by subject, test lag (min), and drug condition. Positive scores indicate improved mood.

Test Lag	ID	Euphoria		Joy	
		Saline	Naloxone	Saline	Naloxone
20	1	-7	-6	-16	-28
	8	1	22	-2	26
	10	3	4	-2	-1
30	2	26	1	38	-12
	7	14	20	22	11
	9	5	0	12	-3
40	3	21	-4	4	-2
	5	10	-10	-12	-3
	12	17	11	-22	0
50	4	9	-10	6	10
	6	8	0	6	-7
	11	2	-7	2	2

Plasma Endocrine Levels.

Figure 6 shows mean plasma levels of PRL, GH, BEir, and ACTH by test period. All hormones increased significantly post-run: ANOVA showed a period effect for PRL ($F(1, 11)= 24.5$, $P < .001$>; for GH, $F(1, 11)= 5.5$, $P < .04$; for BEir, $F (1, 11)= 10.3)$, $P < .01$; and for ACTH, $F(1, 11)= 10.3$, $P < .01$). There was a trend toward reduced post-run increases of ACTH on day 2 ($F(1,11)= 4.3$, $P < .07$). There were no differences between days for the other hormones.

Relationship of pituitary hormone levels to each other and to post-run changes in level.

Tables 13 through 17 show the correlations of a) pre-run, b) post-run, and c) post- minus pre-run differences in levels of PRL, GH, BEir, and ACTH. Table 13 shows there were no significant correlations among the pre-run hormone levels. Table 14 shows but one post-run relation, BEir and GH covarying positively. Thus, the post-run increases of these hormones were predominantly independent of one another. The absence of a correlation between BEir and ACTH is particularly noteworthy.

Table 15 depicts correlations between pre- and post-run levels of the pituitary hormones. Pre-run PRL and ACTH were each associated with post-run levels of the same substance, i.e., subjects who started with high or low levels of these substances retained their rank after the run.

Figure 6. Mean levels of prolaction, growth hormone, beta-endophin immunoreactivity, and ACTH by test period (PRE- and POST-RUN) (Bars indicate +/- SEM, N= 12).

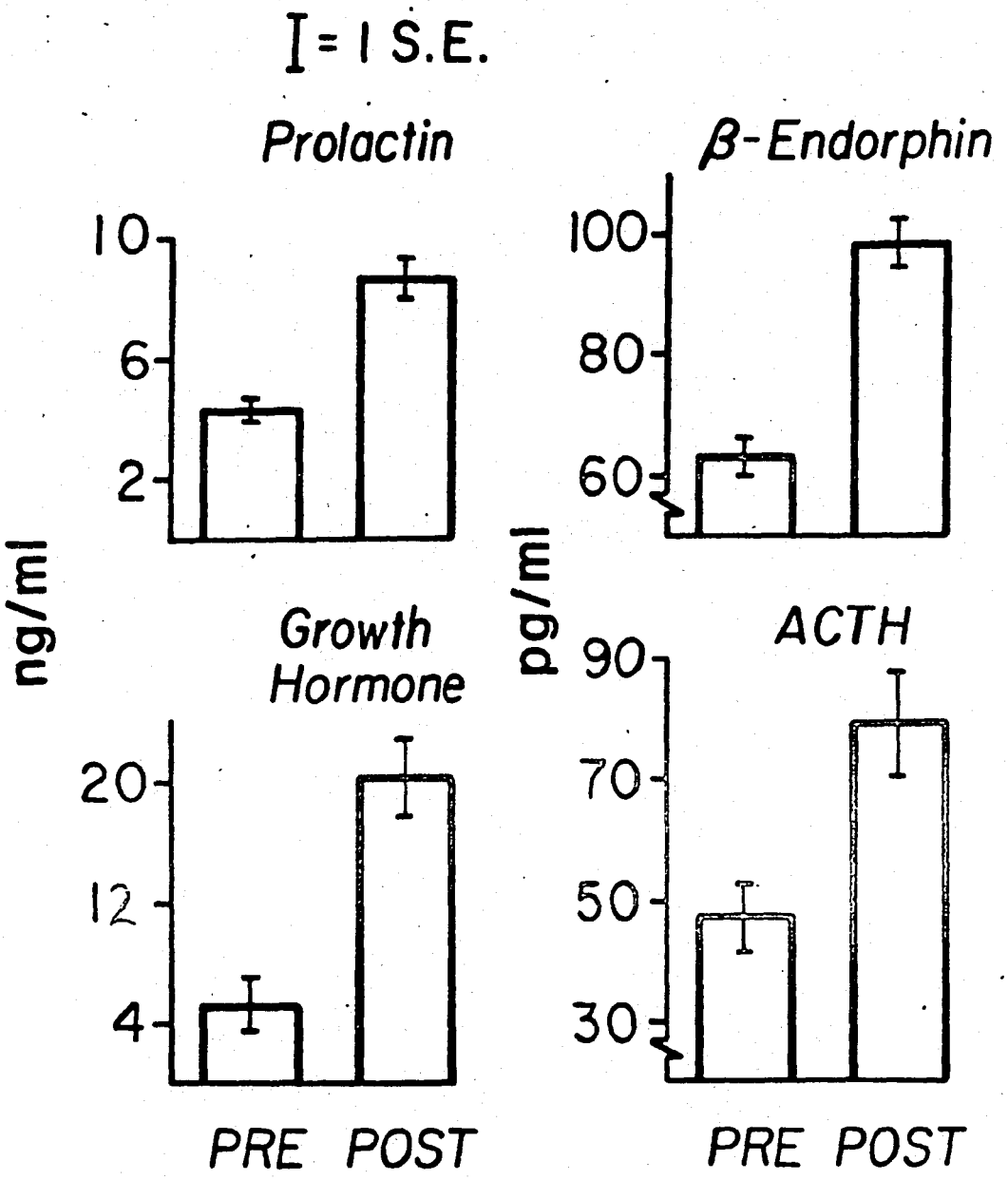

I = 1 S.E.
Prolactin
β-Endorphin
ng/ml
pg/ml
10
6
2
100
80
60
Growth Hormone
ACTH
20
12
4
90
70
50
30
PRE POST
PRE POST

Table 13. Correlations between pre-run levels of PRL, GH, BEir and ACTH (N= 12).

	PRL	GH	BEir	ACTH
PRL	-			
GH	-.35	-		
BEir	-.06	-.24	-	
ACTH	.41	-.09	.06	-

* $\underline{P} < .10$

** $\underline{P} < .05$

Table 14. Correlations between post-run levels of PRL, GH, BEir and ACTH (N= 12).

	PRL	GH	BEir	ACTH
PRL	-			
GH	.26	-		
BEir	.21	.80**	-	
ACTH	.07	.29	.39	-

* $\underline{P} < .10$

** $\underline{P} < .05$

Table 15. Correlation between pre- and post-run plasma levels of PRL, GH, BEir and ACTH (N= 12).

	Post-run			
Pre-run	PRL	GH	BEir	ACTH
PRL	.70**			
GH	-.30	-.38		
BEir	.10	.47	.28	
ACTH	.49	.47	.38	.66**

* $\underline{P} < .10$

** $\underline{P} < .05$

Table 16. Correlations between pre-run levels and the (post- minus pre-run) change in levels of PRL, GH, BEir and ACTH (N= 12).

	Pre-run			
	PRL	GH	BEir	ACTH
Post - Pre				
PRL	.25			
GH	.34	-.60**		
BEir	.31	.15	-.42	
ACTH	.18	0	-.44	-.04

* $\underline{P} < .10$

** $\underline{P} < .05$

Table 17. Correlations between post-run levels and (post- minus pre-run) change in levels of PRL, GH, BEir and ACTH (N= 12).

	Post-run			
	PRL	GH	BEir	ACTH
Post - Pre				
PRL	.86**			
GH	.31	.97**		
BEir	.13	.43	.76**	
ACTH	-.35	-.05	.17	.72**

* $\underline{P} < .10$

** $\underline{P} < .05$

While covariation in PRL and ACTH pre- and post-run was found, there were no significant between-hormone relations. Data concerning the contribution of pre- and post-run hormone levels to the post-run change scores are presented in Tables 16 and 17. Table 16 shows an association of post-run changes to pre-run levels only for GH, larger increases being found in subjects with lower baseline levels. Table 17 shows that increments of each hormone were positively related to post-run levels. Except for GH, then, higher post-run levels of all substances can be attributed specifically to the effects of the run. Changes in any one hormone were not related to either the pre- or post-run levels of any other hormone.

Relationship of hormone levels to pain and mood reports.

To evaluate the interrelation of hormone levels and verbal reports of pain and mood, while limiting the number of correlation coefficients calculated, summary measures of ischemic and cold stimulus responses were derived by averaging over stimulus duration. Since there were only three observations per cell in the 3 X 4 matrix of stimulus type by test lag, it was also necessary to collapse (average) over stimulus types and test lags to allow a sufficient sample size for determination of correlations. When data were collapsed over test lag, 12 pairs of hormone and verbal report values became available for each stimulus type (4 lag times multiplied by 3 subjects per lag). Similarly, when stimulus type was collapsed, 9 pairs of observations became available (3 subjects per stimulus multiplied by 3 stimulus types, mood data being excluded).

When averaging over stimulus types, scores were converted to ranks to make comparisons between the three types of stimulation possible. All correlations are based on data from the saline day only.

"Partialling" in the text to follow refers to the calculation of the partial correlation coefficient (cf. Cohen & Cohen, 1969) between post-run hormone levels and post-run verbal reports from which the mean effects of either the pre-run verbal report or hormone level have been statistically removed. These coefficients allow tests of hormone/verbal report relationships uniquely attributable to the run.

Cold Pressor. The relationship of plasma hormone levels to the time to report FP (Faint Pain), the minimum pain level on the rating scale, is shown in Table 18. The absolute levels of post-run PRL were directly related to reduced pain report. Partialling pre-run verbal report attenuated this relationship, however, indicating that absolute levels of PRL can be accounted for by the baseline relationship of PRL and verbal report (r= .48). The relative increase in PRL was, however, significantly related to longer FP report times and this relationship was unaffected by partialling pre-run verbal report. Partialling pre-run hormone levels had no effect on either of these relationships. There were no other significant pain report/hormone correlations. These data demonstrate that increases in plasma PRL levels are a reliable correlate of reduced post-run sensitivity to cold stimuli. Subjects showing the greatest post-run analgesia had the greatest increase in plasma PRL levels.

Ischemic Test. Table 19 shows ischemic pain report and hormone

Table 18. Correlations between PRL, GH, BEir and ACTH levels and the time (sec) to report the cold water stimulus as Faintly Painful (FP).

	PRL	GH	BEir	ACTH
		Pre-run		
Pre-run FP	.09	.41	.10	.06
		Post-run		
Pre-run FP	.46	-.02	.24	-.06
Post-run FP	.60**	.14	.29	-.15
Partials				
Pre FP	.45	-.10	-.26	-.11
Pre HORM	.73**	.18	.21	-.31
	PRL-DIF	GH-DIF	BEir-DIF	ACTH-DIF
Pre-run FP	.57*	-.13	.16	-.13
Post-run FP	.73**	.10	.02	-.32
Partials				
Pre FP	.57*	.39	-.21	-.39
Pre HORM	.73**	.18	.21	-.31

* $\underline{P} < .10$

** $\underline{P} < .05$

Table 19. Correlations between PRL, GH, BEir and ACTH levels and ischemic verbal report (VR) (averaged over the 11-15th min) (N= 12).

	PRL	GH	BEir	ACTH
		Pre-run		
Pre-run VR	.48	.06	-.39	-.08
		Post-run		
Pre-run VR	.36	-.49	-.17	.04
Post-run VR	.49	-.40	-.06	.18
Partials				
Pre-run VR	.45	.16	.25	.37
Pre-run HORM	.14	-.38	.10	.18
	PRL-DIF	GH-DIF	BEir-DIF	ACTH-DIF
Pre-run VR	.15	-.44	.12	.14
Post-run VR	.25	-.39	.29	.18
Partials				
Pre-run VR	.34	-.14	.50	.17
Pre-run HORM	.14	-.38	.10	.18

* $\underline{P} < .10$

** $\underline{P} < .05$

correlations. While none reached significance, some are still worthy of note. Both pre- and post-run levels of PRL were directly related to their respective measures of pain report, such that pain reports were higher in subjects with higher PRL levels. This relationship was attenuated by partialling pre-run PRL levels, indicating that post-run verbal report is related to post-run PRL in a manner similar to pre-run PRL. This suggests a relationship between PRL levels and tonic control of ischemic pain report but fails to support the presence of run-specific effects. Post-run, absolute GH levels as well as increments were inversely related to ischemic pain report, more pain associated with lower GH levels. Both of these relationships of post-run verbal report to GH were attenuated by partialling out pre-run verbal report. This suggests the absence of a run-specific relationship between GH levels and verbal report, but, like PRL, may indicate a tonic relation between verbal report and GH levels. Thus, the ischemic test suggested a baseline relation of hypoalgesia to low PRL levels but failed to show a run effect. Other hormone levels were unrelated to ischemic pain report.

Thermal Pain Test. Pre-run, plasma PRL levels were inversely related to discriminability of the high intensity stimulus pair, and positively related to low-intensity report criterion (see Table 20). Thus, lower PRL levels were associated with better baseline discriminability of the high pair and more reports of low pair stimulus presence. There were no other significant zero-order correlations between verbal report and plasma hormone levels. However, when pre-run verbal report was partialled out, greater stoicism in report of the high pair was related

Table 20. Correlations and partial correlations between PRL, GH, BEir and ACTH levels and indices of thermal discriminability (high intensity pair, HIPA, low intensity pair, LOPA) and report criterion (HIB, LOB) pre-run and post-run (N= 12).

	PRL	GH	BEir	ACTH
		Pre-run		
Pre-run				
HIPA	-.58**	.07	.47	.05
HIB	.28	.01	.05	.24
LOPA	-.14	-.06	.12	.14
LOB	.63**	-.33	.09	-.04
		Post-run		
Post-run				
HIPA	.22	-.26	-.14	.11
HIB	.24	-.05	-.11	.29
LOPA	-.07	.05	-.07	-.41
LOB	.45	.31	.42	-.20
	Post-run (partial pre-run VR/ pre-run hormone)			
Post-run				
HIPA	.21/.39	-.25/-.09	-.16/-.06	.06/-.29
HIB	-.02/.31	-.27/-.09	.63**/-.09	-.27/-.19
LOPA	.11/.12	-.02/ .14	-.02/-.14	-.45/-.05
LOB	.02/.23	.19/ .32	.24/ .35	-.31/ .49

* $\underline{P}$< .10

** $\underline{P}$< .05

to lower levels of BEir, a suppressive effect of pre-run verbal report. Table 21 shows that there were no significant correlations between the post-run change in plasma hormone levels and pre- or post-run indices of verbal report. There were no run-specific correlations between verbal report and either absolute or relative change in hormone levels.

In summary, the pain data show three different effects: 1) hypoalgesia was related only to the change in PRL levels, such that greater PRL increases were associated with reduced levels of verbal report to cold stimuli; 2) higher levels of ischemic verbal report were related to high PRL levels both pre- and post-run; and 3) at baseline, low PRL levels were associated with high thermal discriminability of noxious stimuli and a conservative criterion for reporting the presence of low intensities. While the first finding shows a covariance of post-run verbal report and PRL, the second finding shows a predictive relation of post-run verbal report from pre-run PRL; the last indicates only a baseline relation. Interestingly, only PRL levels were related to variation in the verbal report of pain.

Effect of Test Time on Verbal Report/Hormone Relationships.

Results presented above related pain report collapsed over test time to hormone levels. Results below relate pre- and post-run pain report collapsed over pain test to pre-, post-, and post- minus pre-run hormone difference scores at each of the four lag times. To achieve comparability of the three pain measures, each subjects ratings were transformed to a rank score (1 through 12), where low ranks indicate

Table 21. Correlations and partial correlations between PRL, GH, BEir and ACTH changes in level and thermal discriminability (HIPA, LOPA) and report criterion (HIB, LOB) pre-run and post-run (N= 12).

	PRL-DIF	GH-DIF	BEir-DIF	ACTH-DIF
		Pre-run		
Pre-run				
HIPA	.23	.04	-.42	-.45
LOPA	-.29	.12	-.17	-.23
HIB	.21	.08	.22	.44
LOB	.39	.30	.29	.06
		Post-run		
Post-run				
HIPA	.36	-.37	.08	-.14
LOPA	.06	0	-.23	-.49
HIB	.31	-.05	-.03	.24
LOB	.31	.27	.10	-.20
		Post-run (Partial pre-run VR/ pre-run hormone)		
Post-run				
HIPA	.42/.39	-.36/-.08	.01/-.06	-.25/-.13
LOPA	.28/.12	-.09/ .14	-.16/-.14	-.45/-.49
HIB	.25/.31	.21/-.09	-.39/-.09	-.25/ .25
LOB	.04/.23	.08/.32	-.17/ .35	-.36/-.20

* $\underline{P} < .10$

** $\underline{P} < .05$

lower levels of verbal report or post-run reductions of pain report. For the cold pressor test, the time to report FP was used as the rank variable and for the ischemic test, the pain report average at the 11-15 min ischemic duration. For the thermal test, each of the P(A) and B scores at the high (PAHI, BHI) and low intensities (PALO, BLO) were used as ranking variables. This required a total of four separate analyses, combining each of the four thermal measures successively with the cold and ischemic rank data.

At the 20 min lag, the lowest levels of pain report were associated with lowest absolute levels of ACTH (Table 23) and with smaller increments in plasma ACTH level (Table 25). This effect was greater when BLO or PAHI lag variables were used than PALO or BHI and were unaffected by partialling either pre-run verbal report or ACTH levels (Tables 24 and 26), indicating a run-specific effect. These data support the hypothesis that a common opioid mechanism underlies alterations of pain report and plasma ACTH levels.

There was a trend associating absolute levels as well as increments in PRL levels (Tables 23 and 25, respectively). These effects were somewhat attenuated by partialling out pre-run pain report or hormone levels (Tables 23 and 26), but still suggest a run-specific effect. Higher levels of PRL were found in those subjects who reported the least amount of post-run pain, effects consistent with a common

Table 22. Pre-run correlations between PRL, GH, BEir and ACTH levels and verbal report of pain (collapsed over test stimulus) by thermal index and test lag (min) (N= 9).

Verbal Report		PRL	GH	BEir	ACTH
PAHI	lag 20	-.20	-.46	-.09	-.16
	lag 30	-.01	.02	-.31	-.38
	lag 40	-.33	.13	.16	-.03
	lag 50	.16	.10	-.07	0
PALO	lag 20	-.20	-.46	-.09	-.16
	lag 30	-.01	.02	-.31	-.38
	lag 40	-.33	.13	.16	-.03
	lag 50	.16	.10	-.07	0
BHI	lag 20	.03	-.40	-.20	-.51
	lag 30	.01	.11	-.66*	-.26
	lag 40	.06	-.22	.13	-.29
	lag 50	.01	.31	-.36	-.02
BLO	lag 20	-.43	-.52	-.24	-.20
	lag 30	-.15	.23	-.46	-.37
	lag 40	-.04	-.03	.19	.12
	lag 50	0	.37	-.49	-.06

* $\underline{P} < .10$

** $\underline{P} < .05$

Table 23. Post-run correlations between PRL, GH, BEir and ACTH levels and verbal report of pain (collapsed over test stimulus) by thermal index and test lag (min) (N= 9).

Verbal Report		PRL	GH	BEir	ACTH
PAHI	lag 20	-.44	-.35	-.41	.76**
	lag 30	.39	-.19	.13	-.35
	lag 40	.25	-.08	.45	.39
	lag 50	.34	-.46	-.33	-.15
PALO	lag 20	-.39	.21	.34	.35
	lag 30	-.14	-.42	-.29	-.30
	lag 40	.16	-.12	.14	.04
	lag 50	.37	-.31	-.33	-.32
BHI	lag 20	-.47	.24	.30	.36
	lag 30	.06	-.19	-.07	-.29
	lag 40	.23	-.13	-.05	.04
	lag 50	.26	-.42	-.26	-.15
BLO	lag 20	-.54	-.29	-.30	.78**
	lag 30	-.33	-.42	-.38	-.20
	lag 40	.21	.17	.35	.26
	lag 50	.21	-.52	-.31	-.02

* $\underline{P} < .10$

** $\underline{P} < .05$

Table 24. Post-run partial correlations between PRL, GH, BEir and ACTH levels and verbal report of pain (collapsed over test stimuli) by thermal index and test lag (min) (N= 9).

Verbal Report		PRL	GH	BEir	ACTH
PAHI	lag 20	-.32/-.24	-.36/-.49	-.33/-.31	.75**/.74**
	lag 30	.44/ .39	.11/-.12	.53/ .14	.15 /-.40
	lag 40	.37/ .21	-.12/ .17	.31/ .50	.40 / .29
	lag 50	.03/ .24	-.21/-.44	.17/-.25	.63* /-.32
PALO	lag 20	.12/-.58	-.19/ .14	.34/ .46	.41/ .57
	lag 30	.11/-.21	-.30/-.33	-.22/-.17	-.25/-.09
	lag 40	.07/ .13	-.21/-.24	0 / .11	-.31/ .09
	lag 50	.62*/ .34	.55/-.23	.24/-.33	.11/-.60
BHI	lag 20	-.35/-.60	.08/ .13	.47/ .38	.55/ .54
	lag 30	.67*/-.10	.16/-.11	.59/ .19	.01/ -.25
	lag 40	.69*/-.08	.20/-.39	-.08/-.10	.38/ .07
	lag 50	.33/ .10	.25/-.34	.36/-.20	.50/-.32
BLO	lag 20	-.36/-.44	-.44/-.46	0 /-.16	.88**/.80**
	lag 30	.41/-.43	-.02/-.33	.33/-.28	.06 / .06
	lag 40	.59/ .17	.15/ .04	-.24/ .31	.08 / .14
	lag 50	.45/ .16	.04/-.53	.07/-.16	.56 /-.10

* $\underline{P} < .10$

** $\underline{P} < .05$

Table 25. Post-run correlations between PRL, GH, BEir and ACTH change in levels (POST- minus PRE-RUN) and the verbal report of pain (collapsed over test stimuli) by thermal index and test lag (min) (N= 9).

Verbal Report		PRL-DIF	GH-DIF	BEir-DIF	ACTH-DIF
PAHI	lag 20	-.43	-.21	.22	.74**
	lag 30	.38	-.23	.13	-.45
	lag 40	.23	-.22	.58*	.28
	lag 50	.28	-.46	-.07	-.34
PALO	lag 20	-.51	.25	.53	.57*
	lag 30	-.19	-.47	.02	-.06
	lag 40	.14	-.04	.04	.09
	lag 50	.40	-.34	-.28	-.63*
BHI	lag 20	-.58*	.29	.44	.57*
	lag 30	-.06	-.23	.31	-.27
	lag 40	.02	.03	-.17	.08
	lag 50	.11	-.45	-.08	-.34
BLO	lag 20	-.58*	-.14	.26	.80**
	lag 30	-.40	-.47	-.01	.11
	lag 40	.19	.25	.21	.14
	lag 50	.19	-.50	.13	-.11

* $\underline{P} < .10$

** $\underline{P} < .05$

Table 26. Post-run partial correlations between PRL, GH, BEir and ACTH change in levels (POST- minus PRE-RUN) and the verbal report of pain (collapsed over test stimuli) by thermal index and test lag (min) (N= 9).

Verbal Report		PRL-DIF	GH-DIF	BEir-DIF	ACTH-DIF
PAHI	lag 20	-.30/-.38	-.28/-.45	.33/-.11	.72**/.74**
	lag 30	.38/ .35	-.01/-.13	.32/ .14	-.19 /-.45
	lag 40	.24/ .20	-.26/ .16	.50/ .60*	.24 / .30
	lag 50	-.26/ .23	-.23/-.46	.66*/-.28	.58* /-.34
PALO	lag 20	-.29/-.53	-.23/ .14	.50/ .47	.51 / .65*
	lag 30	.07/-.20	-.36/-.34	.18/-.28	.12 /-.08
	lag 40	.46/ .12	-.18/-.24	-.03/ .11	-.20 / .09
	lag 50	.46/ .37	.54/-.23	-.19/-.33	-.40 /-.63*
BHI	lag 20	-.40/-.59	.03/ .14	.51/ .39	.61* / .64*
	lag 30	.55/-.11	.03/-.12	.66*/.02	-.24 /-.27
	lag 40	.34/-.09	.36/-.39	-.13/-.13	.02 / .08
	lag 50	-.27/ .05	.21/-.33	.21/-.22	.31 /-.33
BLO	lag 20	-.44/-.54	-.38/-.42	.53/-.01	.86**/.81**
	lag 30	.22/-.40	-.20/-.33	.70*/-.42	.17 /.10
	lag 40	.49/ .16	.36/ .04	-.35/ .33	-.19 /.15
	lag 50	.37/ .17	.20/-.56	.42/-.25	.43 /-.11

* $\underline{P} < .10$

** $\underline{P} < .05$

underlying opioid mechanism of action.

Mood Scales.

PRL. Pre-run (see Table 27), PRL levels were positively related to ratings of joy, pleasure, and cooperation. However, post-run verbal reports were independent of both absolute levels (Table 28) and increases in post-run PRL levels (Table 30). Partialling out pre-run ratings of euphoria resulted in an inverse relation between post-run PRL levels and verbal report, suggesting a suppression of this relationship by pre-run verbal report. These data demonstrate an association of larger increases in post-run euphoria with lower PRL levels, effects inconsistent with increased opioid activity at the pituitary. Thus, while pre-run ratings of mood were consistent with expectations of opioid activity, post-run relationships do not support an opioid-mediated mechanism of the obtained mood elevation.

GH. Pre-run, GH levels were unrelated to the verbal report of mood (Table 27). Post-run, a positive trend relating plasma GH to ratings of alienation was found (Table 28). This was found when either pre-run verbal report or pre-run hormone levels were partialled (Table 29). Further, increasing post-run levels of GH were positively related to ratings of alienation (Table 28); this relation, also unaffected by partialling either pre-run verbal report or GH (Table 31) indicates a run-specific dose-response relation of alienation to GH levels. This relationship is consistent with increased post-run opioid activity, which might be expected to concurrently elevate GH levels and lead to

Table 27. Pre-run correlations of mood ratings and levels of PRL, GH, BEir and ACTH (N= 12).

Scale	PRL	GH	BEir	ACTH
Apprehension	-.32	.42	.26	-.20
Conscientious	.05	-.36	.06	-.13
Anxiety	.24	-.16	.50*	.01
Optimistic/Pleased	.34	.28	-.52*	.27
Alertness	.39	0	-.63**	-.19
Euphoria	.36	.43	-.59**	.23
Alienation	.16	-.31	.34	-.03
Joy	.51*	.33	-.54*	.24
Pleasant	.62**	.11	-.59**	.20
Cooperation	.54*	-.01	.06	-.11

* $\underline{P} < .10$

** $\underline{P} < .05$

Table 28. Correlations of post-run mood ratings and levels of PRL, GH, BEir and ACTH (N= 12).

Scale	PRL	GH	BEir	ACTH
Apprehension	-.45	-.27	-.32	.09
Conscientiousness	.02	-.01	.02	.59**
Anxiety	.02	.39	.29	-.06
Optimism/Pleasure	.33	-.10	.06	.09
Alertness	.01	-.36	-.03	.44
Euphoria	-.06	-.13	.23	-.04
Alienation	.25	.58*	.30	-.24
Joy	.08	.01	-.28	.03
Pleasant	.09	-.06	-.31	-.05
Cooperation	.35	-.19	.14	.15

* $\underline{P} < .10$

** $\underline{P} < .05$

Table 29. Post-run partial correlations of mood ratings and levels of PRL, GH, BEir and ACTH (N= 12).

Scale	Partial (pre VR/pre hormone) PRL	GH	BEir	ACTH
Apprehension	-.09/-.36	-.21/-.19	-.44/-.41	.16/ .25
Conscientious	-.07/-.15	0 / .07	.05/ .09	.59**/ .63**
Anxiety	-.07/-.01	.36/ .26	.25/ .24	-.02/ .21
Optimism	.39/-.07	-.13/ .06	.01/ .14	-.20/ .01
Alertness	.11/-.40	-.21/-.25	.18/ .25	.24/ .56*
Euphoria	-.60*/-.09	-.18/ .15	.10/ .36	-.29/-.04
Alienation	-.11/ .50*	.72**/.54*	.42/ .20	.10/-.58*
Joy	-.28/ .05	0 / .20	.19/ .51*	-.21/-.02
Pleasant	-.38/-.05	.04/ .26	.09/ .57*	-.33/ .03
Cooperation	.36/-.09	-.13/ .16	-.23/ .14	-.09/ .32

* $\underline{P} < .10$

** $\underline{P} < .05$

Table 30. Post-run correlations of mood ratings and the (POST- minus PRE-RUN) change in levels of PRL, GH, Beir and ACTH (N= 12).

Scale	PRL-DIF	GH-DIF	BEir-DIF	ACTH-DIF
Apprehension	-.41	-.30	-.46	.25
Conscientious	-.10	-.06	.17	.60**
Anxiety	0	.46	.09	.22
Optimism	.07	-.19	.23	.01
Alert	-.26	-.41	.46	.56*
Euphoria	-.09	-.29	.46	-.05
Alienation	.44	.58*	-.03	-.57*
Joy	.07	.14	.61**	-.02
Pleasant	0	-.06	.66**	.03
Cooperation	.07	.19	.12	.32

* $\underline{P} < .10$

** $\underline{P} < .05$

Table 31. Post-run partial correlations of mood ratings and and change in level of of PRL, GH, BEir and ACTH (N= 12).

Scale	PRL-DIF	GH-DIF	BEir-DIF	ACTH-DIF
Apprehension	-.08/-.36	-.14/-.19	-.45/-.52*	.18/.26
Conscientious	-.22/-.15	-.09/ .07	.22/ .15	.58*/ .62**
Anxiety	-.10/-.01	.44/ .26	.07/ .18	.28/ .25
Optimism	.26/-.07	-.19/ .06	-.08/ .19	-.19/ 0
Alert	.03/-.40	-.32/-.25	.45/ .44	.15/ .60*
Euphoria	-.42/-.09	-.30/ .15	-.08/ .47	-.07/-.07
Alienation	.11/ .50*	.66**/.54*	.19/ 0	-.29/-.59**
Joy	-.15/ .05	-.09/ .20	.42/.62**	-.09/-.02
Pleasant	-.18/-.05	-.10/ .26	.26/.66**	-.25/ .03
Cooperation	.33/-.09	-.03/ .16	-.15/ .13	-.04/ .32

* $\underline{P} < .10$

** $\underline{P} < .05$

dissociative (mind/body separation) phenomena.

BEir. Higher pre-run BEir levels were related to higher ratings of worry about being hurt, lower ratings of feeling pleasant, less likely to have a good run, less alert and attentive, less euphoric, and less joyful (see Table 27). While dysphoric effects are consistent with reduced central opioid activity plasma hormone levels would be expected to increase with reduced central activity. Post-run BEir increases (Table 30) were positively related to ratings of joy and pleasure, effects which were attenuated by controlling pre-run verbal report, but not pre-run BEir (Table 31). Thus, while two of the three "happiness" scales showed a positive dose-response relation to BEir levels, this effect was partially accounted for by the pre-run relation of joy and pleasure with BEir. Thus, neither pre- nor post-run data support a relationship between changes in central opioid activity and the report of mood.

ACTH. Pre-run, ACTH levels and verbal report of mood were independent (Table 27). Post-run plasma ACTH levels were positively related to ratings of concern over doing well (conscientiousness) (Table 28); this association was unaffected by partialling either pre-run verbal report or ACTH levels, indicating that higher conscientiousness ratings were run-specifically related to higher levels of ACTH (Table 29). Table 28 shows that increases in post-run plasma ACTH levels were positively related to: (1) ratings of concern over doing well, which was unaffected by partialling pre-run verbal report or ACTH (Table 31); (2) ratings of attention, which were attenuated by partialling pre-run verbal report but not ACTH; and, (3) inversely related to ratings of

alienation, which were also attenuated by controlling pre-run verbal report but not ACTH. Thus, conscientiousness was run-specifically related to both the absolute levels of and increases in ACTH levels, while the relation of ACTH change to attentiveness and alienation could be accounted for by baseline measures.

IV. DISCUSSION

The intense stress of the run was demonstrated by performance at 85% of maximal aerobic effort and significant increases in plasma levels of the stress hormones BEir, ACTH, GH, and PRL. Under saline treatment, discriminability of thermal stimuli was reduced post-run. This hypoalgesic effect was roughly equivalent to that produced by morphine sulfate (10 mg IV), which reduced P(A) from .82 to .75 15 min after injection (Yang et al., 1979). The reduced discriminability may indicate reduced central input of thermal information and was not the result of a shift in attitude towards reporting pain. The ischemic test also showed post-run hypoalgesia under the saline condition, an effect only somewhat smaller in magnitude than that produced by 20 min inhalation of 33% nitrous oxide (Yang et al., 1980). Both effects lasted for approximately 25 min post-run. In contrast, verbal report of less than painful ischemic stimulation was unaffected by the run and thermal discriminabiity of non-painful sensation was reduced at a different time period (greater than 40 min post-run). This argues against attribution of these effects to a general reduction of attention, and suggests a specific alteration of pain sensations. Run-induced thermal and ischemic hypoalgesia appear to be mediated by different mechanisms; naloxone reversed effects on ischemic but not on thermal test stimuli. This suggests that endogenous opioid mechanisms are only involved in the modulation of ischemic pain, but indicates that both opioid and nonopioid antinociceptive systems (Watkins and Mayer, 1982; Terman,

Shavit, Lewis, Cannon and Liebeskind, 1984) were activated by the run.

It is not clear why there was no change in response to cold stimulation. While it was initially thought that ischemic and cold stimulation would yield similar results because both are "deep" stimuli (as opposed to superficial thermal stimulation), and thus based in the paleospinothalamic system. Present data suggest this conceptualization is insufficient. These stimuli may still be processed through the same neural substrate but be differently affected by stress; if, for example, cold stimulation were more intense than ischemic and exceeded the damping ability of stress-induced pain inhibitory mechanisms. To test this hypothesis would require matching the intensity of these stimuli (by using a refrigeration-controlled water bath) rather than using the constant temperature (and extremely aversive) ice-water bath. This raises the more general, and controversial, issue of what the adequate stimulus for pain is when cold is applied. At least two major possibilities exist: (1) cold receptors in veins signal the stimulus (cf. Fruhstorfer and Lindblom, 1983); and (2) cold stimuli cause vasoconstriction, the secondary effects of which cause pain (eg, through reduced perfusion and subsequent ischemia (Abramson, 1967).

While a change in pain sensitivity might be expected with alterations in body temperature, this is not a factor in the present results. Thumb temperatures collected as part of the cold stimulation procedure indicate a return to pre-run temperature levels by the time test procedures began (approximately 20 min post-run). Increased temperature may, however, have played a role in elevating hormone levels, which were acquired only 5-10 min post-run; temperature

recordings at that time are not, however, available.

Both joy and euphoria scale ratings were elevated post-run under saline treatment. This effect was reversed by naloxone, a result consistent with mediation of mood elevation by an endogenous opioid system. By contrast, other measures showed the subjects anxiety and attention were unaltered post-run. Mood elevation appeared at 30 and 40 min post-run, after the hypoalgesic effect had ceased; this difference may reflect the stress-induced activation of different nerual systems. This conclusion is supported by correlational analyses of post-run mood and pain reports. Joy ratings were unrelated to pain reports and euphoria ratings were related only to ischemic ratings ($r = .57$, $P < .05$). The direction of this relationship was, however, contrary to the predictions of a common opioid mechanism; hyperalgesia was related, if at all, to increased euphoria ratings. Since both post-run ischemic pain insensitivity and euphoria rating increases were reversed by naloxone, this correlation suggests pain and mood are regulated by independent opioid mechanisms.

Elevated ratings on cooperation and conscientiousness scales, seen at all post-run lags, were not reversed by naloxone, suggesting that running also affected non-opioid systems. This conclusion is supported by the naloxone-insensitive reduction in thermal discriminability noted above, and with a previous finding of run-induced naloxone-insensitive mood changes (Markoff et al., 1982).

While all subjects were familiar with runner's high, and some with the possibility of a run-induced hypoalgesia, there are a number of reasons to conclude that the results were not due to the effect of

expectation. First, neither hypoalgesia nor euphoria were found under the naloxone condition. Since there are no subjective effects at the dose of naloxone used (Volavka, James, Reker, Pollock and Cho, 1979), it is improbable that the subjects could have selectively reduced their pain reports only under saline conditions. Second, mood effects did not appear until 30 min post-run; we would expect an obliging subject to report this during the first time period. Third, an expectation hypothesis would predict a reduced pain report and improved mood at all test lags. Finally, there was no shift in the pain report criterion, B, an index known to be sensitive to shifts in expectation. For example, Clark (1969) has shown a significant increase in the pain report criterion to thermal stimuli, while discriminability remained constant when strong suggestion of the analgesic effect of a placebo was given.

It remains to discuss possible relations among the pain, mood, and hormone effects with reference to a common causal mechanism. To summarize the major results: (1) For the ischemic test stimulus, an opioid-mediated (i.e., naloxone-reversible) post-run hypoalgesia was found. (2) For the thermal test stimulus, an opioid-insensitive hypoalgesia was found. (3) Increased post-run ratings of joy and euphoria were reversed by naloxone, consistent with opioid mediation. Previous research (reviewed in the Introduction, pp. 15-28) indicates that increased central opioid activity at the pituitary level releases PRL and GH and inhibits release of BE and ACTH. Therefore, (4) higher post-run levels of PRL and GH are explicable by an opioid mechanism but BE and ACTH increases are not. Clearly, therefore, not all effects are attributable to opioid mechanisms.

Additional information comes from correlations between pain and mood variables, on the one hand, and hormone variables, on the other. If both types of variables are influenced by a common mechanism, one would expect correlations between them. Correlations between pain measures averages over stimulus type at each lag time with hormonal changes will be considered first. At the 20 min lag (where both thermal and ischemic hypoalgesia was maximal), subjects reporting the least pain had the smallest increments in ACTH, consistent with a opioid mediator. Also at the 20 min lag, reduced post-run reports of pain were associated with higher levels of PRL. This effect is also consistent with opioid-mediation: more central opioid activity would be expected to decrease pain sensitivity and facilitate pituitary PRL release. Thus, covariation of hormonal changes and pain report are consistent with a common opioid mechanism of action at short post-run intervals.

Correlational analyses of each stimulus type collapsed over lag times provide less consistent findings which are not generally attributable to joint opioid effects: (1) Hypoalgesia to cold stimulation was run-specifically related to increased PRL levels, evidence of a dose-dependent opioid effect. However, since there was no significant post-run reduction in pain sensitivity on this test stimulus, the meaning of this correlation is unclear. On the ischemic test, where post-run hypoalgesia was found to be opioid sensitive, lower PRL levels were found in those subjects who had more post-run analgesia, contrary to an hypothesis of a common opioid mediator. For the thermal stimulus, lower PRL levels were associated with high discriminability and stoical pain report criteria. If lower PRL levels reflect reduced

central (pituitary) opioid activity, higher discriminability is a reasonable correlate of this activity, but more stoical report criteria (fewer pain reports) are not. Further, these thermal pain relations were noted only at baseline, thus were not a result of run-induced alterations in neurotransmitter function. No consistent relationship of pain sensitivity to GH, BEir, or ACTH levels were found. These data consistently suggest a relationship of PRL levels to pain report but do not consistently support an underlying opioid system mediating these effects.

To summarize, collapsing over type of pain stimulus yields correlations which are consistent with mutual opioid mediation of hormonal changes and pain sensitivity, viz., concurrent hypoalgesia and reduced levels of ACTH and increased levels of PRL at 20 min. By contrast, data averaged over time but providing separate correlations for each pain test show a consistent relationship to PRL levels, although the direction of these correlations consistently suggest an opioid mechanism. Both of these sets of correlations may, however, be expected to provide only minimal estimates of covariation between these variables since they average together positive and neutral, or negative, relationships. For example, at the 20 min lag, the ischemic but not thermal or cold tests showed opioid mediation. When these three tests are collapsed, we might assume that indications of opioid mediation are a primary result of the ischemic data. In spite of this, the pain sensitivity/pituitary function relationship is consistent with alterations in opioid activity. The time course of these effects is also compatible with the short half-life of BE (approximately 20 min). Thus,

it is quite reasonable to find greater consistency when averaging test stimuli at each time period than when looking at each stimulus over time.

Mood alterations and hormone levels were uncorrelated, inconsistent with the hypothesis that these changes may be attributed to a common opioid mechanism. Two mood scales were consistently related to hormone levels: (1) post-run GH levels, both absolute levels and increments, increased with ratings of alienation, both effects consistent with opiate actions. This scale did not, however, show a pre- vs. post-run change under saline conditions which one would expect if opioid activity were increased. (2) Greater concern with doing well was associated with both higher absolute levels and increases in post-run ACTH levels. Further, while there was a trend in the direction of greater post-run conscientiousness, this change was naloxone-insensitive, suggesting that the ACTH/conscientiousness relationship is independent of opioid processes. (3) BEir was related, pre-run, to dysphoric ratings on a number of scales (see Table 22). This may reflect general levels of stress: being in a new environment, a "pain experiment", with unfamiliar people and apparatus, etc. Post-run, higher BEir increases were related to higher ratings of joy and pleasure (somewhat attenuated by partialling pre-run ratings). However, this relationship is opposite to what one would expect since higher central opioid activity elevates mood and reduces pituitary BE release. This suggests an independence of factors affecting mood and pituitary hormone levels.

Plasma levels of BEir, ACTH, PRL, and GH were all increased by the run, consistent with the findings of other investigators (Carr et al.,

1979; Colt et al., 1981; Farrell et al., 1982; Fraioli et al., 1980; Frewin et al., 1976; Gambert et al., 1981). Previous work would suggest an integrated hormonal response to stress, particularly with respect to ACTH and BEir levels (Guillemin et al., 1977). The reason for the lack of correlation between these two levels is unclear, but four possibilities suggest themselves: (1) BE and ACTH have different half-lives (ACTH < BE); since hormonal samples were taken after the run, it is possible that hormones were released concurrently but had been cleared differentially before sampling. (2) While the run was an acute stress (the subjects don't train as intensely as 85% of aerobic capacity), it may be conceived as a chronic stressor, because they do run long distances regularly. Since previous studies have not used such highly trained individuals, the present data may be seen in contrast to the effects of an acute exercise stressor. The potential of habitual exercise to alter the hormonal response to an individual stress exposure is supported by studies showing differences in post-run BEir in individuals at various levels of habitual activity (Carr et al., 1979; Colt et al., 1981). (3) The present stressor is purely physical and voluntarily performed. This contrasts with animal studies involving exercise-stress, where the paradigm involved avoidance responding. Weiss and Pohorecky (1984) have shown, in this context, that brain neurotransmitter changes are different in animals that control footshock than yoked controls, who have no control. (4) It is also possible that ACTH and BE are not always released concurrently. Gambert et al. (1981) also failed to find a BE/ACTH correlation in their exercise study, supporting the present findings.

Given the present lack of consistency regarding attribution of mood elevation and pain insensitivity to opioid activity, future work should consider the contribution of other neurotransmitter systems to pain and mood alterations with exercise. One of the best documented brain neurotransmitter alterations is that of NE depletion following learned helplessness paradigms (Miller and Norman, 1979; Weiss et al., 1981). Given the long history of an association of major depression and NE activity (cf. Sachar et al., 1980), as well as more recent demonstrations of NE-mediated pain inihibitory brain stem pathways (Yaksh, 1979), it is reasonable to hypothesize that NE mediates stress-induced mood elevation and pain insensitivity. Indeed, animal work suggests specific sensitivity of some descending brain stem pathways to phenoxybenzamine, a specific alpha-adrenergic antagonist (Kuraishi, Harada and Takagi, 1979). In man, evidence suggests that adrenergic systems mediate pain evoked potential augmenting/reducing phenomena (Buchsbaum, 1984). Similar arguments may be advanced for testing the effects of 5-HT antagonists following stressful manipulations; alterations of 5-HT activity by tricyclic antidepressants are by definition mood-elevating, and increased 5-HT activity in brain stem pathways are pain inhibitory (Basbaum and Fields, 1984; Fields and Basbaum, 1978).

Also on the horizon for future investigations are the effects of exercise intensity and duration on pain sensitivity, mood and associated hormone levels. Exercise intensity has not been sytematically manipulated. If stress is conceptualized as the interaction of a stimulus and an organismic response, it is imperative to have an

objective assessment of the stimulus to avoid confounding of these two factors. In the Black et al. (1979), Haier et al. (1981), and Jungkunz et al. (1983) studies, a constant, low intensity stressor was used. While stressor intensity increases with increasing time of tourniquet ischemia (Chen et al., 1983), that study assessed only one time period during stress. The paradigm used by Willer and colleagues does not allow assessment of effects due to time since their paradigm is dependent on the cumulative effects of successive stress periods. Clearly, stressor intensity is a potentially salient variable regulating the development of hypoalgesia (what, for example, is the threshold of this response?), as well as the degree of stress necessary to achieve maximal development of analgesia. Knowlege of each of these extremes is necessary for the potentially powerful application of SIA to clinical populations. Similarly, stress duration, alone and in combination with stress intensity is an unexplored and potentially salient parameter of stimulus presentation. Parametric studies of stressor intensity and duration are therefore strongly advocated in future work.

In the present study, post-run hormone levels were drawn immediately after the run, while pain and mood testing occurred up to 50 min after this. Therefore, the correlation of hormone levels to behavioral responses derived here might be expected to be reduced, as the half-lives of these hormones are all less than 30 min. Future work should therefore also consider in more detail the time course of alterations in pain, mood, and hormone levels. This would entail the simultaneous monitoring of these variables before, during, and after treadmill or ergometer exercise. In this way, relationships suggested to

be weakly present in this study may be maximized, permitting more reliable inferences about the processes underlying these covariations.

It is also important to note that the stress induced in this study consisted almost solely of physical exertion. This is in contrast, e.g., to the stress of fear experienced by soldiers in battle, the shock of an accident, or even the stress of a mental arithmetic task. To illustrate, consider the difference between the present stressor and a run of similar distance in which the subject is being chased by an armed assailant. The effects on pain sensitivity, therefore, of emotional arousal, by itself or in combination with physical exertion, remain intriguing subjects for future work.

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