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System Theory of Pain and of Opiate Analgesia: No Tolerance to Opiates

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In spite of overwhelming data and unanimous views to the contrary, we hypothesized, 20 years ago, that tolerance does not develop to opiate drugs. The present is the second of two reviews that evaluate this hypothesis in the face of the evidence that is now available. The first review appeared in the December, 1995 issue of *Pharmacological Reviews* (Colpaert, 1995); it concluded that tolerance does not develop to the ability of opiates to produce discriminative effects, which are typically measured in laboratory animals and are homologous to the subjective effects that opiates characteristically produce in humans (Jasinski, 1977).

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The present review concerns tolerance to opiate analgesia (for previous reviews, see: Besson et al., 1978; Cox, 1990; Dickinson, 1991; Duggan and North, 1984; Johnson and Fleming, 1989; Kalant, 1987; Kornetsky, 1987; Mao et al., 1995; Nestler, 1992; Pasternak, 1993; Smith et al., 1988; Yaksh and Noueihed, 1985). Specifically, we will evaluate evidence relating to (*a*) the hypothesis that no tolerance develops to the action of opiates that allows these compounds to produce analgesia, and (*b*) a System Theory that defines in an abstract manner the mechanisms whereby the physiological systems that control pain are able to detect nociceptive stimuli and permit opiates to exert analgesic effects.

In this article, we will conclude show that tolerance does not develop to the action of opiates on pain systems and that tolerance is not a pharmacological property of the opiates. It will also appear that the simple assumptions of System Theory can account for the many, diverse and complex features of apparent tolerance to, and also of dependence on, opiates. These features are proposed to reflect the operating characteristics of the nociceptive and other physiological systems, the function of which is coregulated by opiate receptors and their endogenous ligands.

I. Origin of No-Tolerance Theory

A. No Tolerance to Opiate Drug Discrimination

In a typical drug discrimination (DD)[a] experiment, laboratory animals are trained to discriminate the injection of a particular dose (the training dose) of a particular drug (the training drug; D) from saline (S) injection. For example (Colpaert et al., 1976a), food-deprived rats can be trained to press one of two levers for food in daily, 15-min sessions; arrangements are made so that, at some time before the sessions, the animals are injected with either D or S. After D injection, the animal is required to press one lever (the drug lever (DL)) to obtain food, and presses on the other lever do not yield food. After S injection, the animal now is required to press the other lever (saline lever (SL)), and presses on the DL then are inconsequential. Training is implemented until the animal reliably selects the appropriate lever after injections of either D or S. Once trained, the animals can be used to conduct tests of stimulus generalization. To this end, the animal is administered, before the test session, a test treatment that can be either saline, the training dose, any other dose of the training drug, or indeed any dose of any other drug. In the test session, it is determined which of the two levers, DL or SL, the animal selects. If the test treatment makes the animal select the DL, then it is considered that stimulus generalization occurred between it and D; it is inferred that the test treatment produced a stimulus similar to that produced by D. If the test treatment makes the animal select the SL, then it is considered that it did not produce a stimulus that is qualitatively similar to that produced by D. In this manner, laboratory animals—and, also, humans—can be trained to discriminate any of a large variety of drugs from saline (e.g., Colpaert and Slangen, 1982), including morphine and other opiates. Drug discriminations typically demonstrate a remarkable degree of pharmacological specificity: for example, animals trained to discriminate an opiate from saline will only show generalization with other opiates, whereas any nonopiate compound will make them select the SL. The generalization is reversed by opiate antagonists only and is specifically mediated by well defined opiate receptors.

In a study (Colpaert et al., 1976b) examining tolerance to opiate DD, rats were trained to discriminate 0.04 mg/kg of the opiate analgesic fentanyl (Janssen et al., 1963) from saline, and tests were conducted with various fentanyl test doses to obtain the fentanyl dose-response curve, or stimulus generalization gradient. The morphine gradient was similarly determined. The dose-response data further allowed us to find the ED_{50} test doses at which fentanyl and morphine generalized with the 0.04 mg/kg training dose of fentanyl. The gradients of fentanyl and morphine were determined repeatedly throughout a 17-week period, during which regular training sessions and, thus, injections of the fentanyl training dose continued to be administered. Despite the continuation of these injections, and although the apparent analgesic effect of fentanyl had been diminished, the gradients of both fentanyl and morphine remained unchanged, and their ED_{50} values for stimulus generalization failed to increase. We concluded from these findings (Colpaert et al., 1976b; see also: Colpaert et al., 1978a) that tolerance does not develop to opiate DD. This conclusion has been contradicted unanimously by numerous studies from other laboratories (for reviews, see: Young, 1990, 1991; Young and Sannerud, 1989), but a recent examination of the evidence available to date (Colpaert, 1995) has nonetheless allowed us to maintain our original conclusion.

B. Opiate Drug Discrimination and Opiate Analgesia

The extensive studies that have been made of opiate DD (for reviews, see: Colpaert, 1977, 1978a, 1982; Herling and Woods, 1981; Holtzman, 1982) have revealed that the pharmacological features of opiate DD are remarkably similar to those of opiate analgesia. Specifically, and as indicated above, both are produced by opi-

Abbreviations: DD, drug discrimination; D, training drug; S, saline; DL/SL, saline lever, drug lever; NSAID, nonsteroidal anti-inflammatory drug; DAGO, D-Ala^2-MePhe^4-Glyol^5-enkephalin; DSLET, Tyr-d-Ser-Gly-Phe-Leu-Thr; $PaCO_2$, partial pressure of carbon dioxide in arterial gas; PV, paraventricularis thalami; 5-HT, hydroxytryptamine; 5-HIAA, hydroxyindoleacetic acid; nVT, ventrobasal thalamic nucleus; A.U., arbitrary units; ACTH, adrenocorticotropic hormone; NK, neurokinin; STs, System Theory system; S-R, stimulus-response.

ate agonists, antagonized by opiate antagonists and stereoselective (Colpaert, 1978a). The doses at which opiates produce discriminative and analgesic effects in the rat correlate highly (Colpaert et al., 1976c), and both actions are mediated by the same type(s) of opiate receptors located in the central nervous system. Partial opiate agonists produce only partial generalization with a high efficacy agonist (Colpaert et al., 1976d; Colpaert and Janssen, 1984, 1986), and do so at doses that also produce only partial analgesic effects (Colpaert et al., 1976d). The time course whereby fentanyl produces generalization is similar, if not identical, to that whereby it produces analgesia in experimentally naive rats (Colpaert et al., 1978b). This far-reaching similarity thus posed the following problem: if opiate DD and opiate analgesia are pharmacologically similar, how then is it possible that tolerance develops to the analgesic but not, as we argue, to the discriminative effects of opiates?

The latter question is all the more intriguing, as tolerance is a pharmacologically defined phenomenon (e.g., Fernandes et al., 1977a; Nies, 1990); opiate tolerance therefore is commonly regarded as a pharmacological property of the opiates (e.g., Cox, 1990; Johnson and Fleming, 1989; Sjogren and Eriksen, 1994), and its operation across the different physiological systems mediating different opiate effects must be expected to demonstrate at least some generality. Various hypothetical answers to this question can, of course, be imagined. But parsimony has led us to consider the possibility that the problem itself might be false; the problem disappears if one is prepared to entertain the admittedly surprising hypothesis that tolerance also does not develop to opiate analgesia.

However, tolerance is believed to develop to almost all effects of opiates (hence the wording "opiate tolerance"; e.g., Cox and Werling, 1991). There seems to be no reasonable doubt that opiates can produce analgesia (hence the wording "opiate analgesia"), and countless experimental studies have presumably documented and characterized the concept that tolerance develops to opiate analgesia (Cox and Werling, 1991; Trujillo and Akil, 1991).

Therefore, in entertaining the hypothesis that tolerance does also not develop to opiate analgesia, the challenge upon us has been to devise a theory that maintains that tolerance does not develop to opiates, while at the same time allowing that the *apparent* effects of opiates can diminish when the drugs are applied repeatedly and/or for a long period of time. Among the many different effects that opiates produce (e.g., Ling et al., 1989), the theory that we devised (Colpaert, 1978b) for that purpose specifically addressed the analgesic effects of opiates, opiate analgesia constituting the most extensively studied and most mechanically useful of the effects of opiates.

II. System Theory of Opiates and Pain

The theory that we devised specifies how a nociceptive stimulus can be detected and how an opiate can diminish this detection (Colpaert, 1978b). It defines in an abstract manner the mechanisms whereby the physiological systems of nociception process pain stimuli and is hence referred to as a System Theory. One explicit assumption that is being made is that tolerance does not develop to the action, here referred to as the primary action, whereby endogenous or exogenous opiates can diminish the detection of a nociceptive stimulus. As indicated above, this assumption was made to test its feasibility; note, however, that it also constitutes a zero hypothesis and is therefore most parsimonious. The mechanisms defined by System Theory were also devised so as to be most simple, making the least possible assumptions. The theory is represented graphically in figure 1 and will be elaborated further in a later section (IV.A.); table 1 provides a glossary of the symbols that are used in describing the theory.

Any endogenous or exogenous event (here termed adequate *stimulation* or *stimulus*) that ultimately causes pain possesses a magnitude, represented by x along a physical variable, here termed φ_α (e.g., the temperature of a thermal stimulus). This magnitude x is larger than the magnitude n that the variable assumes normally, i.e., most of the time. For the acute stimulus to ultimately cause pain, it must have some impact on some relevant physiological variable (φ_o; e.g., the firing rate of a primary afferent or of any other downstream neuron in a polysynaptic afferent pathway). This impact is represented by the projection from φ_α to φ_o, yielding a magnitude x′ along φ_o. An account of the System's operation through time (τ) will be provided below (section IV.A.1.); suffice it here to specify that the input channel that the physiological variable constitutes assumes some value at any time. How can x′ now be detected, i.e., be found different from the values that φ_o assumes at other times[1]? One simple manner in which this could be done is for the System to establish some integration of the values that φ_o has assumed during a given, sample, period of most recently preceding time (hence ι_τ; e.g., over the past 40 units of time). In a normal organism (panel A in fig. 1) to which no stimulus has been presented over this sample period, the temporal integration ι_τ will correspond with the projection from magnitude n along the physical variable. Having thus obtained ι_τ, x′ can now be detected by finding the difference δ' that exists between x′ and ι_τ. The values ι_τ and δ are being

[1] The reader may find it helpful to consider the analogy of an observer who continuously monitors a digital display reporting from a remote sensor. The number being displayed can assume any of a range of values and can, but does not necessarily change from one point of time to the next. The observer's problem thus is to determine, at any point of time, whether the number that is currently on display differs from what he usually sees and, hence, to determine that a special event (a stimulus) has likely impacted on the sensor.

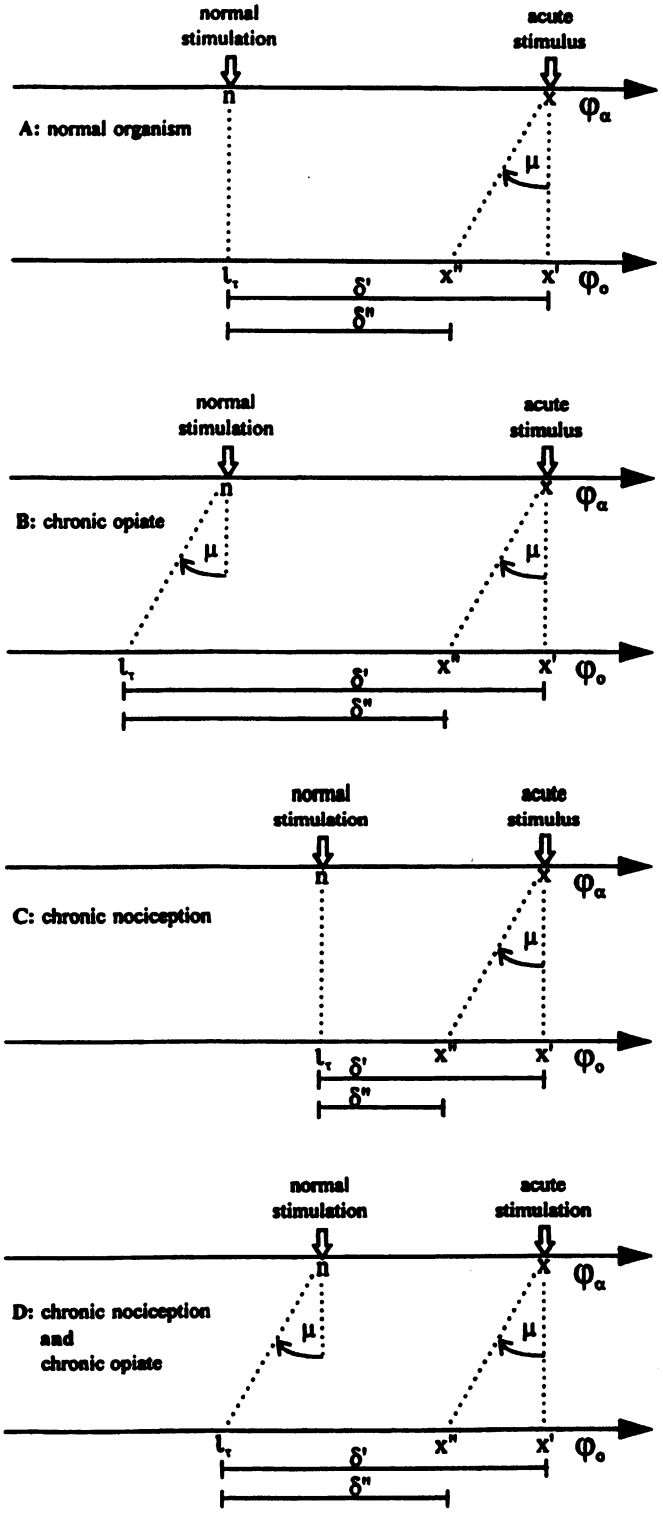

FIG. 1. Graphical representation of theoretical mechanisms whereby nociceptive stimuli can be detected and whereby this detection can be diminished by opiates. The different panels consider different conditions, i.e., that of a normal organism (A); that of chronic exposure to an opiate (B); that of chronic exposure to nociceptive stimulation (C) and that of chronic exposure to both an opiate and nociceptive stimulation (D). In each condition, pain is examined: pain that can be perceived upon the application of an acute stimulus in the absence (single prime) or presence (double prime) of acutely injected morphine.

TABLE 1
Glossary of symbols used

Symbol	Definition
e_τ	effect of an opiate as found by the ratio δ'/δ''
e_s	effect of an opiate as found by the subtraction $\delta' - \delta''$
n	the value which φ_α normally assumes
w	weight of φ_o in Equation 2
x	a particular value of φ_α
x′	value of φ_o when φ_α assumes the value x in the absence of a test dose of an opiate
x″	value of φ_o when φ_α assumes the value x in the presence of a test dose of an opiate
δ	delta; magnitude of pain sensation; found by Equation 4
δ′	δ produced by a test stimulus in the absence of a test dose of an opiate
δ″	δ produced by a test stimulus in the presence of a test dose of an opiate
ι_τ	*iota tau*; temporal integration of φ_o; found by Equation 2
μ	*mu*; dose or concentration of an opiate agonist
τ	*tau*; time
φ_α	*phi alpha*; physical activity, adequate stimulation
φ_o	*phi omicron*; physiological activity; found by Equation 1

determined continuously, thus allowing the System to detect any physical stimulus at any time, and making it yield a pain intensity that can vary; this perceived intensity is proportional to δ and can thus vary with the magnitude of the physical stimulus.

By what mechanism can an opiate, given acutely before the acute stimulus, now diminish the pain intensity that the acute stimulus x otherwise produces? The simplest possible manner whereby this can occur would be for the opiate to make x no longer yield x′, but a value x″ that is smaller than x′. Note that the projection from φ_α to φ_o has thus shifted by an arc μ; because morphine's analgesic effects are dose-dependent, we will assume that μ is, simply, proportional to dose[2]. In the presence of dose μ of morphine, then, the difference, δ″, between ι_τ and the projection, now x″, generated by x is smaller than the value δ′, which this difference would otherwise assume. The diminution of this difference from a value δ′ to the smaller value δ″ represents morphine's analgesic effect. Note that this diminution can be observed by an experimenter but is not itself a parameter of the

[2] With opiate receptor agonists other than morphine, μ will also be proportional to dose, albeit that the relationship between μ and dose will for every agonist in turn depend on its efficacy, i.e., on the intrinsic activity that it produces at the receptor. The principles of molecular pharmacology (Ariëns, 1964) would imply this relationship to be relatively flat and the maximal effect to be relatively small with low efficacy agonists; with higher efficacy agonists, the relationship will be steeper and the maximal effect larger.

System; unlike System parameters, it will therefore not be represented by a Greek letter. Let the experimenter arbitrarily choose to quantify the diminution by the ratio of δ' to δ''; thus, the opiate's analgesic effect is found from a ratio[3], represented by the symbol e_r, so that $e_r = \delta'/\delta''$. In the arbitrary units of figure 1, panel A, e_r thus assumes a value of 1.33. As a result, we have a System that can detect an acute nociceptive stimulus, and that allows morphine to exert a dose-dependent analgesic effect; this effect occurs as the result of some primary action of morphine whereby the physiological impact of a physically defined stimulus is simply diminished.

Now let us examine how the System would operate when morphine is being administered chronically: in particular, when morphine is being administered, at a dose μ, over a period of time long enough to cover the System's sample period (panel B in figure 1). In specifying morphine's mechanism of action above, it was assumed that the opiate causes a shift to the left, by an arc μ, of the projection from φ_α to φ_o; this shift applied to x, and parsimony would lead one to have it also apply to any value of φ_α, including the value n. Thus, having applied the dose μ of morphine, during an entire sample period, will make the resulting ι_τ now be moved to the left by an arc μ along the φ_o axis. Importantly, note that this shift is effectively by an arc μ; *we explicitly assume here that no tolerance developed to morphine's primary action*. Specifically, we assume that despite its chronic administration, the same dose of morphine remained capable throughout of generating the arc μ, rather than any arc smaller than μ. Let us now discontinue the chronic administration of morphine and administer the acute stimulus. As in a normal organism, x will again yield x′; however, the difference δ' between ι_τ and x′ will now be larger than it is in a normal organism. The System's operation here thus predicts that chronic morphine should induce *hyperalgesia*. Let us then, in this organism that has been exposed to chronic morphine, again administer acutely both the dose μ of morphine and the acute stimulus. And let us again assume, as we did above, that despite its previous, chronic administration, *no tolerance* developed to the ability of (dose μ of) morphine to cause the arc μ when re-applied acutely. The δ'' that the stimulus in the presence of acutely administered morphine now generates is larger than it is in the normal organism, indicating that the intensity of reported pain after acute morphine is also larger. In addition, e_r has become 1.25 and, thus, smaller than what it was in the normal organism. In other words, we now have a System that *assumes that tolerance does not develop to morphine's primary physiological action*, and at the same time explains that morphine's *apparent effect*, measured downstream from the primary action, *is diminished* (which can be rephrased to indicate that *apparent tolerance* developed). The System thus fully satisfies our initial objectives in devising this theory.

Let us now go on and examine this System's operation in a condition that is also of clinical interest, i.e., that of chronic pain. Presumably, the events that cause chronic pain make the input that most of the time is given to the System, and is here termed normal, larger than what it is in pain-free conditions. In panel C of figure 1, n has thus moved rightward along the φ_α axis, and so does ι_τ along the φ_o axis as a consequence. Application of the same acute stimulus of value x again yields x′, but the difference δ' between x′ and ι_τ is now smaller than it was in the normal organism. We therefore predict that chronic nociceptive stimulation is associated with *hypoalgesia*. The acute administration of dose μ of morphine, followed by the acute stimulus, will as always yield x″. However, δ'' is now smaller, and e_r is now larger (i.e., 1.48) than it was in the normal organism. We therefore predict, unexpectedly, that chronic pain is associated with an apparent *increase* of morphine's analgesic effect. This *apparent inverse tolerance* occurred while, again, *no change* was assumed to occur to morphine's primary physiological action.

Let us go even further and examine the System's operation in yet another, clinically interesting, condition, i.e., that in which a chronic pain is being treated, chronically, with morphine. Let us set up this condition such that the dose of morphine and the time over which it is applied constitute a perfect match of the intensity and the duration, respectively, of the event that causes the chronic pain. In preparing panels B and C, we in fact have already anticipated this match. Let the so-called normal input in panel D thus be the same as that of panel C. The value n generated by this input is thus the same as that in panel C and represents chronic nociceptive stimulation. However, because the dose μ of morphine is administered at the same time, the projection from φ_α to φ_o is deflected by the arc μ. Naturally, we continue to assume that no tolerance develops to morphine. After having stopped the chronic conditions, we again apply the same acute stimulus, yielding x′. But δ' now is larger than it was in panel C, and smaller than it was in panel B; it is, in fact, identical to what it was in panel A. We thus predict that chronic pain acts to antagonize the hyperalgesia otherwise associated with chronic morphine and that chronic morphine acts to antagonize the hypoalgesia otherwise associated with chronic nociceptive stimulation. Let us now again, acutely, administer morphine and, also, the acute stimulus. And, as always, we assume that no tolerance develops to morphine. We see that x″ assumes its invariant position along the φ_o axis, but δ'' is larger than it was in panel C and smaller than it was in panel B; δ'' in fact is identical to what it was in panel A, and so is e_r. We thus predict that *chronic nociceptive stimulation acts to antagonize the apparent tolerance* otherwise associated

[3] Another, equally arbitrary, manner for the experimenter to quantify the same diminution is to subtract δ'' from δ'; the opiate analgesic effect would then be found from a subtraction, represented by the symbol e_s, so that $e_s = \delta' - \delta''$.

with chronic morphine and that *chronic morphine acts to antagonize the apparent inverse tolerance* otherwise associated with chronic nociceptive stimulation. We further specify that, *inasmuch as the chronic morphine matches the chronic nociceptive stimulation, it should be possible to treat chronic pain with chronic morphine without inducing any apparent tolerance*. In particular, and if the match is adequate such as can be the case when the chronic nociceptive stimulation is also stable, it should be possible to treat the chronic pain with a stable dose of morphine that must *not* be increased as its administration continues.

It is useful to emphasize here the importance of adequately establishing this match. A mismatch whereby too little morphine is given will yield unsatisfactory relief of ongoing pain and apparent inverse tolerance. In addition, a mismatch whereby too much morphine is given will generate apparent tolerance.

In conclusion of this section, we have described here a System that is capable of detecting nociceptive stimuli and to let morphine exert apparent analgesic effects that can diminish when morphine is given repeatedly and/or over a prolonged period of time. Importantly, parsimony was exerted in devising this system; it would seem difficult to devise an even less assuming system that would nonetheless be capable of detecting pain and of allowing morphine to exert analgesic effects. Note that morphine's mechanism of action as devised here is not to directly diminish pain; morphine is hypothesized here simply to shift the relationship that otherwise exists between an adequate physical stimulus and the (relevant) neuronal parameter on which that stimulus impacts. This shift is considered to constitute the primary physiological action of morphine. This primary action as such does not diminish pain; it is the operational properties of the System downstream that govern pain perception that will result in the perception (δ) of pain being lesser. It also is not the pharmacological action of morphine that can make the apparent analgesic effects of the opiate be diminished. This diminution thus does not imply that tolerance develops to morphine. In fact, in the framework of our theory, it is *because* we assume that tolerance does not develop to morphine's primary action that the System's operational properties *can* make its apparent analgesic effects diminish.

The theory would appear to at least have the merit of parsimony; its few and unassuming mechanisms are fully summarized in figure 1, panel A. The reasoning developed in panels A and B of figure 1 has done little more than to allow us to maintain that tolerance does not develop to morphine in the face of existing evidence that morphine can generate analgesic effects that can apparently diminish. This reasoning thus has done little more than provide a highly theoretical alternative to the current and unanimously held theory that opiates produce analgesia to which tolerance does develop[4]. But the theorizing that was developed in panels C and D has yielded a number of intriguing and innovative predictions for which no evidence was available, at least not at the time that this theory was proposed (Colpaert, 1978b). The predictions can be summarized as follows: (1) the *chronic* (i.e., repeated and/or prolonged) administration of an *opiate* should (1.1) induce *hyperalgesia* and (1.2) result in an apparently diminished analgesic effect of the opiate (i.e., *apparent tolerance*); (2) conditions that are inducive of *chronic pain* should (2.1) be associated with *hypoalgesia* and (2.2) find the apparent analgesic effect of an opiate to have increased relative to that in normal subjects (i.e., *apparent inverse tolerance*); (3) when the chronic opiate co-exists with chronic nociceptive stimulation, then they should counteract each other (3.1) in generating hyper- and hypoalgesia, respectively, and (3.2) in generating apparent tolerance and apparent inverse tolerance, respectively; (4) the latter predictions can be specified further to indicate that, *inasmuch as the chronic opiate and the chronic nociceptive stimulation constitute an adequate match* of each other, *it should be possible to treat chronic pain with opiate compounds in a lasting manner*.

Prediction 1.2 is the only prediction that our theory has definitely in common with current theory of opiate tolerance and opiate analgesia. However, unlike our theory, current theory fails to account for several other predictions and, in fact, conflicts with some predictions (i.e., 3.2 and 4). The predictions thus offer a possibility to test the two theories; they in addition are potentially of important clinical relevance. We thus have undertaken to experimentally verify these predictions, particularly 3.2 and 4. These and other studies are discussed in the following section.

III. Tests of the Theory

A. Experimental Evidence

Different putative animal models of pain and opiates were used in the initial studies (Colpaert, 1978c, 1979; Colpaert et al., 1978c, 1980a; see also Colpaert, 1978b) that we conducted to test the hypothesis that nociceptive stimulation counteracts the development of apparent tolerance to opiate analgesia. The studies also tested the further hypotheses specified in section II.

One series of studies (Colpaert et al., 1978c, 1980a) used the fairly short-acting opiate, fentanyl (Janssen et al., 1963) and applied mechanical stimulation of the hind paws in rats as a method to produce brief but repeated nociceptive stimulation. The studies further used tail withdrawal from 55°C water as an assay (Janssen et al., 1963) to assess the magnitude of opiate analgesia. The studies found that the opiate and the nociceptive stimulation caused hyper- and hypoalgesia,

[4] Note, however, that a stimulus processing system that formalizes the classical theory has so far not been articulated.

respectively. The studies also found that repeated fentanyl injections diminished, whereas repeated nociceptive stimulation enhanced, fentanyl's apparent analgesic effects in the tail withdrawal assay. Finally, the repeated fentanyl injections and the repeated nociceptive stimulations counteracted each other in determining the magnitude of the fentanyl analgesia; thus, the repeated nociceptive stimulation counteracted the development of apparent tolerance to opiate analgesia. The findings thus verified the hypotheses in experimental conditions that used brief episodes of nociceptive stimulation. A further experiment (Colpaert et al., 1980a) showed that the mere exposure to the nociceptive stimulus that was used in the analgesic testing procedure sufficed to make fentanyl produce an apparently enhanced analgesic effect; this enhancement was dose-dependent, being larger with low than with higher doses of fentanyl.

Another series of studies (Colpaert, 1978c, 1979) undertook to verify the same hypotheses under conditions of chronic pain. An animal model of chronic pain was not available at that time, and we undertook to use adjuvant arthritis as a potential, albeit not at that time validated, model. Adjuvant arthritis is a pathology that can be produced in rats by inoculation, into the tail base, with *mycobacterium butyricum* and that has pathological and biochemical features that resemble human rheumatic disease (Calvino et al., 1987a; Jones and Ward 1963, 1966; Pearson, 1956, 1963; Rosenthale and Capetola, 1982; Ward and Jones, 1962). Adjuvant arthritis has long been in use as a screening assay for anti-arthritic drugs (Awouters et al., 1975; Rainsford, 1982). In these studies, then, it was attempted to match the putative chronic pain associated with adjuvant arthritis with bezitramide, an opiate possessing a particularly long duration of action on oral administration (Janssen et al., 1971). The tail-withdrawal procedure was again implemented to assay the apparent magnitude of opiate analgesia. It was found that the adjuvant arthritis produced hypoalgesia and an enhanced analgesic effect of (apparent inverse tolerance to) bezitramide and, also, of morphine. The twice daily administration during 1 week of 1.25 mg/kg of bezitramide produced in normal animals hyperalgesia and a diminished analgesic effect of (apparent tolerance to) bezitramide and, also, of morphine. The exposure of other animals to both adjuvant arthritis and to chronic bezitramide showed the putative chronic pain and the chronically administered opiate to counteract each other. In particular, the apparent tolerance to bezitramide's analgesic effects no longer developed in rats with adjuvant arthritis. These data (Colpaert, 1979) thus offered the first (experimental) evidence that chronic pain can be treated with opiates such that apparent tolerance to the opiate's analgesic effects does not develop. There are, however, two caveats to the latter conclusions. Firstly, we had used adjuvant arthritis as an animal model of chronic pain, but it remained to be established that adjuvant arthritis in the rat is effectively associated with anything resembling a phenomenon that, even in human patients, is very difficult to define. Secondly, if adjuvant arthritis were found to effectively generate chronic pain in rats, then it would remain to be demonstrated that an opiate can attenuate this chronic pain. This is what we set out to do in the research effort that is being considered in section III.B.

These caveats notwithstanding, the studies (Colpaert, 1979; Colpaert et al., 1980a) thus coherently verified each of the different predictions that were generated by our theory (section II.); the data were obtained while using different methods of nociceptive stimulation and while implementing different opiates. In the remainder of the present section, we will consider further experimental studies and findings that have subsequently been obtained in our and other laboratories.

In addition to the effects we observed in a rat tail withdrawal assay (Colpaert, 1978c, 1979), considerable other evidence has been reported that shows opiates to produce hyperalgesia (prediction 1.1). Thus, in rats, systemic injections (Kayan et al., 1971) or subcutaneous implantation of pellets of morphine (Tilson et al., 1973) generated hyperalgesia as measured in a hot plate and a flinch-jump procedure, respectively (see also: Kim et al., 1990; Wilcox et al., 1979). In mice, repeated morphine injections over 7 days enhanced the writhing response to intraperitoneal acetic acid (Inoki et al., 1990; Ohnishi et al., 1990), and foot-lick and jump responses to a 50°C hot plate were increased after a 7-day infusion of the κ-agonist U 50,488 (Teskey and Kavaliers, 1991). Similar observations have been made in guinea pigs (Mulé et al., 1968) and cats (Kayan and Mitchell, 1968). In humans, continuous intrathecal (Morley et al., 1992) or systemic (Andrews, 1943; Sjogren et al., 1993) infusions of morphine have produced hyperalgesia; the magnitude of these effects has been so as to cause an allodynia that has also been referred to as "paradoxical pain" or "overwhelming pain syndrome" (Morley et al., 1992; see also: Glavina and Robertshaw, 1988; Potter et al., 1989; Sjogren and Eriksen, 1994). Tentative explanations of this hyperalgesia have involved increased calcium entry (Inoki et al., 1990) and the morphine metabolite, morphine-3-glucoronide (Sjogren et al., 1993).

There is, of course, overwhelming experimental evidence that chronic administration of opiates, to pain-free animals, can produce an apparently diminished analgesic effect of the opiate (prediction 1.2); this evidence has been the subject of different review articles (Cox, 1990; Pasternak, 1993; Redmond and Krystal, 1984; Trujillo and Akil, 1991) and will not be reconsidered here.

That one nociceptive stimulation can reduce the algesic effect of another stimulation, i.e., induce hypoalgesia (prediction 2.1), in fact constitutes a long-recognized phenomenon that has variously been referred to as coun-

terirritation (e.g., Sigurdsson and Maixner, 1994), diffuse noxious inhibitory controls (Le Bars et al., 1979), autoanalgesia (Yonehara et al., 1983) or antinociception (Yashpal et al., 1995). Nociceptive counterirritation has been applied for centuries to treat pain of various etiologies (Parsons and Goetzl, 1945; Ward-Tetley, 1956). The phenomenon has been amply demonstrated and characterized in experimental studies using measures or reports of acute pain in animal and human subjects (for review, see Basbaum and Fields, 1984; Roby-Brami et al., 1987; Rodgers and Randall, 1988; Willer et al., 1984) and, importantly, in chronic pain patients (Lipman, et al., 1987). In addition to this behavioral evidence, nociception-induced hypoalgesia has also been extensively documented by electrophysiological methods (Alarcon and Cervero, 1990; Bouhassira et al., 1987; Dickinson and Le Bars, 1983; Fleischmann and Urca, 1989; Fu et al., 1990; Laird and Cervero, 1989; Le Bars et al., 1981, 1992; Morton et al., 1987; Ness and Gebhart, 1991a, 1991b; Salter and Henry, 1990a, 1990b; Talbot et al., 1989). Furthermore, sensory stimulation, including modalities that are nociceptive, increases the expression of the immediate-early gene, Fos protein product of the c-*fos* proto-oncogene (Hunt et al., 1987; for reviews, see Fitzgerald, 1990; Morgan and Curran, 1991), and the increased c-Fos expression that repetitive hindpaw pinch otherwise induced in rat lumbar spinal nociresponsive neurons was recently found (Morgan et al., 1994) to be inhibited by another, spatially remote nociceptive stimulus (i.e., immersion of the tail in 50°C water). Note that the latter study used methods of nociceptive stimulation that were similar to those we used in some of the initial studies verifying the various predictions of our theory (Colpaert et al., 1978c, 1980a). The available evidence demonstrating hypoalgesia from counterirritation thus covers a vast array of both nociceptive stimulations and of methods to assay algesic effects (Roby-Brami et al., 1987; Willer et al., 1984). Note, however, that the phenomenon might not be universal, although it remains unclear why exceptions occur (Sigurdsson and Maixner, 1994). That the phenomenon would not be universal does not detract from the system portrayed in figure 1. Rather, it suggests that any number of such systems may exist at different levels of anatomical organization to converge at yet higher levels; the multiple systems may be arranged in serial and/or parallel configurations. Note that a single system suffices to predict hypoalgesia from counterirritation using two stimulations that are remote in time but identical in their anatomical site of impact; and some such arrangement as that referred to above would be required anyway if the system's output is not only to detect pain, but also to identify its nature and site of impact. Interestingly, some evidence (Yashpal et al., 1995) suggests that cutaneous nociceptive input originating from different dermatomal levels converges at a suprasegmental level to generate instances of heterosegmental hypoalgesia that involve C-fibers and receptors for substance P and opiates (see also Bouhassira et al., 1995).

Prediction 2.2 requires that nociceptive stimulation should act to increase the apparent analgesic effects of opiates (induce apparent inverse tolerance). Implementing adjuvant arthritis as in our initial studies (Colpaert, 1978c, 1979) to induce nociceptive stimulation, Guilbaud (co-author of many of the references in this section) and colleagues have extensively confirmed this prediction with additional opiates as well as with different methods to assay their analgesic effects. That is, using vocalization in response to mechanical pressure applied to the paw, and in comparison with control animals, apparently enhanced analgesic effects were found in arthritic rats with morphine (Kayser and Guilbaud, 1983, 1985, 1990), and with other opiates including the μ-agonist D-Ala^2-MePhe^4-Glyol^5-enkephalin (DAGO), the δ-agonist Tyr-d-Ser-Gly-Phe-Leu-Thr (DSLET), the κ-agonist U-50,488H (Neil et al., 1986), and the partial agonists tramadol, nalbuphine and buprenorphine (Kayser et al., 1991). This apparent inverse tolerance was also observed with kelatorphan, an inhibitor of multiple enkephalin-degrading enzymes (Kayser et al., 1989), but not with the enkephalinase inhibitors thiorphan (Kayser and Guilbaud, 1983) and acetorphan (Kayser et al., 1989). Morphine seemed (Kayser and Guilbaud, 1990) to produce less of an enhanced analgesic effect (in arthritic rats) on paw withdrawal as compared with the vocalization induced by mechanical stimulation. Also, in rats with adjuvant arthritis that received a subcutaneous implantation of morphine pellets, Lérida et al. (1987) found morphine's peak analgesic effect in a tail flick assay to be larger in the arthritic as compared with normal animals. In addition to this evidence obtained in arthritic rats, previous exposure to a hot plate enhanced morphine's analgesic effects both in drug-naive rats and in animals that allegedly had been rendered tolerant to morphine (Sherman et al., 1982). Using mechanical stimulation to generate nociceptive stimulation and tail withdrawal from heat to assay analgesic drug effects, we (Van den Hoogen et al., 1989) reported enhanced analgesic effects of epidurally injected sufentanil, suggesting that apparent inverse tolerance can be obtained at spinal opiate receptors. In rats in which local inflammation of one hindpaw was induced with either Freund's adjuvant or carrageenan, enhanced analgesic effects have been reported with morphine, with the κ agonist U-50,488H and, also, with the partial α_2-adrenergic agonist clonidine (Hylden et al., 1991; Joris et al., 1990; Stein et al., 1988a). The enhancement of analgesic effects was limited to the inflamed and did not occur with the presumably normal, contralateral, paw; the data suggest an involvement of peripheral opiate receptors located on local terminals of primary afferents (Stein et al., 1988a, b) and noradrenergic pathways (Hylden et al., 1991) in ipsilateral lumbar segments of the spinal cord. Also, a comparison was made (McLaughlin and Dewey,

1994) of opiate analgesic effects in tests involving brief, so-called (Dennis and Melzack, 1979) phasic or longer, so-called tonic nociceptive stimulation. The tests being used were tail flick, hot plate and formalin-induced inflammation, respectively. The findings again indicated opiates (i.e., morphine, meperidine, fentanyl, buprenorphine) to produce greater analgesic effects in the presence of the tonic as compared with the phasic stimulations (McLaughlin and Dewey, 1994).

Other than ours (Colpaert, 1979; Colpaert et al., 1980a), no further studies appear to have addressed the prediction (3.1) that nociceptive stimulation and opiates should counteract each other in generating hypo- and hyperalgesia, respectively. Interestingly, however, Neil et al. (1986) (see table 1 of this reference) treated arthritic rats repeatedly with either saline or morphine, and did find the morphine-treated animals to have a lower threshold for mechanically induced vocalization.

Finally, predictions 3.2 and 4 require that chronic opiates and chronic nociceptive stimulation should counteract each other in generating apparent tolerance and apparent inverse tolerance, respectively, to the analgesic effects of opiates. Abbott et al. (1981) treated rats for 5 days with either morphine or saline and thereafter tested the magnitude of morphine's analgesic effects against paw elevation induced by subcutaneous injection of formalin. The formalin injections presumably produced pain for a duration of time that was comparable to that we had used in one study (Colpaert et al., 1980a) but shorter than that in another (Colpaert, 1979) study. The findings did not reveal any difference in the magnitude of the analgesic effects of a single dose of morphine and led the authors to suggest that no tolerance occurred in the formalin test (Abbott et al., 1981). However, the single dose of morphine reduced the pain score to the zero floor in all groups, so that any possible difference might have been rendered undetectable. Note also that in the latter study (Abbott et al., 1981), the chronic opiate treatment was not administered along with chronic nociceptive stimulation before the time that analgesic testing was carried out; the data therefore are perhaps more relevant to the inverse apparent tolerance that our theory predicts should occur with tonic nociceptive stimulation. Repeated coadministration of morphine and of formalin in rats was carried out, however, in another study that subsequently assayed morphine's analgesic effects in both the formalin and the tail-flick tests (Vaccarino et al., 1993). The data thus obtained elegantly confirmed, in both tests, that the apparent tolerance that otherwise occurred after repeated morphine injections, was counteracted when these morphine injections were co-administered with repeated formalin injections (Vaccarino et al., 1993). Mohibur-Rahman et al. (1993) repeatedly coadministered, in mice, 10 mg/kg of morphine with injections of either formalin, Freund's adjuvant (in the hind paw) or acetic acid (intraperitoneally); morphine's analgesic effects were subsequently assayed in tail-pinch, tail flick, and acetic acid-writhing procedures. The nociceptive stimulations counteracted the development of apparent tolerance to morphine's analgesic effects when formalin was used, but less so when either the adjuvant or acetic acid were used. The authors contend that the nociceptive stimulants differed in their intensity and duration of action, with formalin likely producing the largest nociceptive effects. These findings (Mohibur-Rahman et al., 1993) thus support the predictions in demonstrating that the extent to which nociceptive stimulation counteracts the apparent tolerance that otherwise occurs to a fixed (i.e., 10 mg/kg) dose of morphine is a function of the intensity and duration of the nociceptive stimulation. Kayser and Guilbaud (1985) misinterpreted our earlier findings (Colpaert, 1978c, 1979) to suggest that apparent tolerance to opiate analgesia cannot develop in arthritic rats. This interpretation is obviously incorrect, and the data in their study, in fact, perfectly confirmed the theory's prediction. Specifically, arthritic and control rats were given repeated, subcutaneous injections of up to 160 mg/kg of morphine, and morphine's analgesic effects were subsequently assayed in a paw pressure-vocalization test. The data showed morphine analgesia to be larger in arthritic than in control rats, and this was true both in animals that had or had not received chronic morphine. Thus, apparent tolerance was counteracted by the arthritis, and the apparent inverse tolerance that was otherwise associated with arthritis was counteracted by repeated morphine injections. Also, the apparent magnitude of morphine's analgesic effect in arthritic rats that had received chronic morphine was smaller than that in nonarthritic chronic-saline animals at some, albeit not at all, of the doses of morphine that were tested. Our theory would suggest this to be attributable to a mismatch between the chronic morphine and the nociceptive stimulation that presumably is associated with adjuvant arthritis. The up to 160 mg/kg doses of chronic morphine that were used are considerably higher indeed than the 2.5 to 40 mg/kg doses of subcutaneous morphine that appear to be required (Colpaert et al., 1987) to match the intensity of the chronic pain of arthritic rats. The Kayser and Guilbaud (1985) study thus produced data that are remarkably consistent with our theory (see also: Kayser et al., 1986). Further data from the same laboratory confirmed chronic morphine to counteract the apparent inverse tolerance that otherwise occurs in arthritic rats with morphine and, also, DAGO (Neil et al., 1986). The apparent tolerance that opiates can, of course, produce in arthritic rats, was smaller with tramadol than it was with morphine (Kayser et al., 1991); this suggests tramadol to exert smaller intrinsic activity at opiate receptors and to perhaps thus offer a closer match of the chronic pain of adjuvant arthritis. Finally, Lérida et al. (1987) also found apparent tolerance to the analgesic effects of subcutaneously implanted morphine pellets to develop to a lesser extent

in arthritic as compared with control rats. Thus, the available data confirm the hypothesized, mutual, counteraction of opiates and nociceptive stimulation in generating apparent tolerance and inverse tolerance, respectively. It would be extremely useful, however, for further research to obtain systematic, parametric, data characterizing the intensity and duration of nociceptive stimulation in its interacting with various doses of opiates as they match, and can mismatch, the nociceptive stimulation while impairing its algesic effects.

It should be noted here that the studies by Guilbaud and colleagues used vocalization to paw pressure to assay analgesic drug effects in arthritic rats. In arthritic rats, the limbs are severely inflamed and, of course, markedly hyperalgesic. The analgesic assay thus involves the use of a hyperalgesic response that complicates the analysis. It is perhaps for this reason that this preparation has yielded such remarkable findings as putative hyperalgesia produced by low doses of morphine (Kayser et al., 1987) that generated apparent inverse tolerance when administered to nonarthritic animals (Kayser et al., 1986). Equally puzzling are findings, also obtained under these conditions, that doses of naloxone that reportedly produce analgesic effects, perhaps because of weak intrinsic activity, when given alone (Kayser and Guilbaud, 1981), antagonize the analgesic effects of higher doses of morphine (Kayser and Guilbaud, 1983). No coherent explanation of these intriguing findings has been offered, and the data have not as yet been reproduced in other laboratories; a recent report failed to reveal any effect of naloxone on electrical discharges of nociceptive (group III or group IV) afferents from the acutely inflamed knee joint of the cat (Schepelman et al., 1995). Further study of the role of opiate receptors located in peripheral, especially in inflamed, tissues (Stein, 1993) may perhaps elucidate these findings. The use of a response that expresses inflammatory hyperalgesia may similarly have confounded the outcome of the first of a series of three experiments that attempted to verify whether chronic nociceptive stimulation alters apparent tolerance to morphine (Gutstein et al., 1995). The experiments used a unilateral injection of complete Freund's adjuvant in the rat hindpaw, thus inducing inflammation and hyperalgesia, albeit no demonstrated chronic pain. Nine days after this injection, morphine or placebo pellets were implanted, and pain responses were examined in a tail flick assay. The findings indicated that the morphine-implanted animals had shorter latencies, leading the authors to suggest that chronic pain enhances the development of apparent tolerance to opiate analgesia. My interpretation of these data would be that the model perhaps generated marked, inflammatory hyperalgesia, but too little chronic pain to constitute an adequate match of the chronic morphine, which therefore produced hyperalgesia in the tail flick assay. The second and third experiments in this series effectively confirmed inflamed animals to demonstrate hyperalgesia in the tail flick assay (Gutstein et al., 1995).

In conclusion, it appears that a considerable body of experimental evidence confirms the various predictions of our theory. For as far as these predictions concern chronic pain, adjuvant arthritis in the rat has been the only model of chronic pain (Colpaert, 1978b, 1978c, 1979) on which these data are based. The following section therefore addresses the validity of adjuvant arthritis as an animal model of chronic pain.

B. Adjuvant Polyarthritis

The 1978 proposition of adjuvant arthritis in the rat as an animal model of chronic pain set a daunting challenge (Colpaert, 1978b, c; see also Colpaert, 1979). To objectively demonstrate and reliably measure pain in humans is a difficult enough task that is typically handled by applying psychometric analyzes to the subject's subjective pain ratings (Beecher, 1957, 1959; Chapman et al., 1985; Merskey, 1976); this reliance on the subject's self-report persists to date (e.g., Hammond, 1991). To obtain pain ratings from animals has naturally been impossible, and all animal research on pain has in fact relied, explicitly or implicitly, on a convention that the physiologist Sherrington (1906) proposed and made acceptable early in this century. Specifically, Sherrington proposed that a stimulus be considered painful if it produces what he called the pseudo-affective response; the latter was defined as a number of plurisegmental reflexes, or behaviors, involving somatic muscle as well as a number of branchial and autonomic responses such as hyperpnea and hypertension (see also: Cannon, 1929; Sternbach, 1968). The acceptance of (elements of) the pseudo-affective response as both a demonstration and measure of pain has since allowed researchers to propose and experimentally study in animals nociceptive stimuli and putative pains, the duration of which has ranged from a few milliseconds (Carmon et al., 1976) to approximately 2 hours (Dubuisson and Dennis, 1977). The putative, experimental, pains in animals that have thus been introduced have been qualified (Dennis and Melzack, 1979) as being tonic and phasic, respectively. Sherrington's pseudo-affective response consisted, of course, of those reactions that in humans are correlated with acute, subjectively reported pains and which can be measured, in an objective and quantified manner, by methods that do not rely on any subjective report.

Herein lies the limitation of Sherrington's otherwise ingenious proposal; it concerned acute pains but could not, and was not intended to, apply to chronic pains. Indeed, chronic pain in humans is not, and certainly not consistently, associated[5] with the externally observable

[5] Note, however, that hyperventilation may constitute an exception; we will see later in this section that hyperventilation occurs in response to both acute and to chronic pains, and may, perhaps uniquely, offer a measure of pains throughout the full range of their duration (phasic, tonic, chronic).

signs that Sherrington defined as the pseudo-affective response. In the uncharted territory of chronic pain, Sherrington thus left animal research without any guidance as to how to demonstrate and measure the pain. In the case of adjuvant arthritis, this rather enormous difficulty was compounded by another problem. Rats with adjuvant arthritis present with massive and widespread inflammation involving various tissues (Jones and Ward, 1966); by definition and in empirical fact, the inflammation is associated with an equally widespread hyperalgesia (Rosenthale and Capetola, 1982). Any attempt to demonstrate chronic pain in rats with adjuvant arthritis should avoid the implication of inflamed tissues. Indeed, hyperalgesia refers to the phenomenon whereby an acute stimulation yields a greater-than-normal algesic response (Swingle, 1974; Winter and Flataker, 1965); it by no means ensures that any pain is present in the absence of this (superimposed) stimulation. It thus would be misleading to infer the presence of chronic pain in arthritic rats from hyperalgesic responses induced by an acute stimulation that is superimposed upon the inflammation.

In a decade-long effort to demonstrate the presence of and measure chronic pain in rats with adjuvant arthritis, we have adopted three different approaches. Adjuvant arthritis being a long-lasting, ondulating disease, special care was taken in many of these studies to characterize the evolution of various parameters as a function of time; observations were thus made every 7 days for periods of up to 11 weeks.

A first approach followed experimental demonstrations by the behaviorist Skinner (1938) that organisms increase behaviors that are instrumental in either obtaining appetitive stimuli (i.e., reward) or in avoiding aversive stimuli (e.g., electric shock). Pain presumably being aversive, we thus hypothesized (Colpaert et al., 1980b, 1982) that a manipulation that produces analgesia (e.g., an analgesic compound) should induce this instrumental behavior in animals exposed to pain, while being ineffectual in normal animals. Specifically, if arthritic rats are in chronic pain, then they should self-administer more of an analgesic than do control animals. The studies examined this hypothesis with suprofen, a nonsteroidal anti-inflammatory drug (NSAID), and the opiate fentanyl, and found self-administration to be enhanced in arthritic rats with both compounds (Colpaert et al., 1980b, 1982). Kupers and Gybels (1995) elegantly confirmed the enhanced self-administration of fentanyl in arthritic rats and, also, that this enhancement peaks in week 3 after the inoculation (Colpaert et al., 1982). Note that the paradigm that was used in those studies requires that the animal learns, through conditioning, to associate the taste of the drinking solution containing the analgesic, with its analgesic effect; this learning process is known as conditioned *taste* preference (Garcia et al., 1955). One of the variants of this learning process is conditioned *place* preference (Cappell et al., 1973); using this latter variant, arthritic rats also exhibited enhanced place preference with morphine (Sufka, 1994). Shippenberg et al. (1988) found that, 7 days after inoculation with *mycobacterium butyricum* into the plantar surface of the right hind limb, morphine produced a place preference in thus inflamed rats, but its magnitude was similar to, not higher than, that of normal controls. Note, however, that at this point of time, rats had developed inflammation and hyperalgesia, but undoubtedly *not* the chronic pain that in polyarthritic rats is most prominent 3 weeks after inoculation in the tail base (Colpaert, 1987). The latter time was also that at which the fentanyl self-administration by polyarthritic rats peaked in the first study of this nature (Colpaert et al., 1982). The protocol used in our initial studies (Colpaert et al., 1980b, 1982) of substance self-administration in arthritic rats was designed to (*a*) generate as little as possible self-administration driven by non-analgesic effects (e.g., drug-produced reward or euphoria) in normal control animals and (*b*) associate the perceptual effects (i.e., taste) of the orally available compounds with their putative analgesic effects. Using a protocol where normal rats do intravenously self-administer morphine, presumably driven by euphoria, Lyness et al. (1989) found that arthritic rats self-administered morphine less, rather than more, as compared with normal controls. The latter finding is open to different possible explanations. One is that opiates are less addictive in arthritic rats (Lyness et al., 1989); this hypothesis would be compatible with an earlier suggestion that some drive states may be depressed in these animals (Colpaert, 1987). Another possible explanation, however, is that any limb movement is acutely painful in arthritic rats (Chery-Croze et al., 1985; Colpaert, 1987); the morphine self-administration in the Lyness et al. (1989) study required the execution of (fixed ratio 10) bar pressing that itself may have been painful in, and thus avoided by, rats with adjuvant arthritis.

The second approach that has been taken in efforts to validate the adjuvant arthritis model can be viewed as an analogy to Sherrington's method. That is, in humans, the autonomic responses of sympathetic hyperactivity that accompany (subjectively reported) acute pain decrease as the (subjectively reported) pain becomes chronic, and vegetative signs (e.g., disturbances in sleep, food intake and weight control), and irritability, often appear (Procacci et al., 1979; Reuler et al., 1980; Sternbach, 1984). The approach thus consisted of determining whether those physiological and behavioral features that occur in humans, and that can be assessed objectively, may also occur in arthritic rats. The evidence that has thus been obtained (Colpaert et al., 1982) in arthritic rats indicates that the animals lose weight and become irritable, but it remains difficult to attribute specifically these findings to the presence of chronic pain (for detailed discussion, see Colpaert, 1987). However,

findings in humans showed that chronic pain from heterogenous etiologies is accompanied by chronic hyperventilation (Glynn et al., 1981). It had long been recognized that hyperpnea accompanies acute pain in animals (Sherrington, 1906) and humans (Comroe et al., 1962), and ventilation is often taken as an index to monitor the depth of anesthesia in spontaneously breathing patients (Clutton-Brock, 1957). Acute pain may in fact stimulate respiration so as to counteract the respiratory depressant effects of forane (Eger et al., 1972) and morphine (Borgbjerg et al., 1996; Hanks et al., 1981). Also, the threshold for acute nociception to induce pain can be raised in volunteers by active hyperventilation (Clutton-Brock, 1957), and passive hyperventilation at some stage has been used (Geddes and Gray, 1959; Gray and Rees, 1952) as a technique of anesthesia[6]. The findings by Glynn et al. (1981) thus seemed to imply hyperventilation to constitute an exceptional sign of pain: this is, to our knowledge, the only objective, externally accessible sign that has been documented to accompany both acute and chronic pains in humans. We have been unable so far to monitor, for 11-week periods in arthritic rats, arterial pO_2 and pCO_2 without the procedure itself compromising the measurement. Failing this, a noninvasive whole-body plethysmographic technique was developed (Colpaert and Van den Hoogen, 1983a) allowing frequency, absolute tidal volume and minute volume of respiration to be obtained from freely moving rodents; the technique derives from a barometric method that was originally devised to measure ventilation in newborn infants (Drorbaugh and Fenn, 1955). Using this technique, then, it was found (Colpaert and Van den Hoogen, 1983a) that arthritic rats hyperventilate; the hyperventilation followed a time course after the inoculation that parallels the arthritic disease process (Colpaert and Van den Hoogen, 1983b; see also Wang and Sagen, 1995).

Further studies examining arthritic hyperventilation as an expression of chronic pain analyzed the possible role in this hyperventilation of substance P, which acts as a neurotransmitter in primary afferents processing nociceptive stimuli (Henry, 1976; Hökfelt et al., 1975; Lembeck and Zetler, 1962). Thus, it was found that in arthritic rats, levels of substance P are increased in the sciatic nerve (Lembeck et al., 1981) as well as in the saphenous nerve, dorsal root ganglia, dorsal roots and dorsal spinal cord (Colpaert et al., 1983; Schoenen et al., 1985). Furthermore, capsaicin had been documented to first enhance the release and then deplete for long periods of time substance P from primary afferents (Bucsics and Lembeck, 1981; Gamse et al., 1980; Theriault et al., 1979). Paralleling these capsaicin effects on substance P release, we found (Bervoets and Colpaert, 1984) intrathecal capsaicin in arthritic rats to first further increase and then to decrease the hyperventilation. Corroborating further the role of substance P in the respiratory response to pain, intrathecal capsaicin in nonarthritic rats also induced hyperventilation (Bervoets and Colpaert, 1984; see also Cruwys et al., 1995).

A third approach to validating the adjuvant arthritis model has consisted of determining whether arthritic rats demonstrate behavioral or other changes that can possibly be interpreted as expressions of chronic pain. As mentioned above, arthritic rats present with a weight loss (Calvino et al., 1987a; Colpaert et al., 1980b, 1982), possibly resulting from decreased food intake (De Castro-Costa et al., 1981) and also with decreased locomotor and other behavioral activities (Calvino et al., 1987a; De Castro-Costa et al., 1981). The hypomobility is further decreased, rather than reversed, by morphine (De Castro-Costa et al., 1981), but morphine also depresses, nonspecifically, various behaviors in pain-free animals (e.g., Picker and Yarbrough, 1991). Consistent with a possible role of chronic pain in these effects, surgical section of the spinothalamic and spinoreticulothalamic pathways partly attenuated the weight loss and hypoactivity of arthritic rats (Dardick et al., 1986). Aggregated arthritic rats hypervocalize (Colpaert et al., 1982), and this hypervocalization is responsive to analgesic drugs (Okuyama and Aihara, 1984a; Pircio et al., 1975). However, little or no hypervocalization occurs in arthritic rats that are housed singly, and vocalization in arthritic rats can also be induced by touching and handling the animals (Colpaert et al., 1982; De Castro-Costa et al., 1981). Thus, confining several arthritic rats to a limited space may provoke the animals to move and to hence acutely stimulate in a mechanical manner the inflamed, hyperalgesic, tissue of afflicted limb joints. The hypervocalization may thus represent an acute pain that occurs when inflamed hyperalgesic tissue is acutely stimulated, and there is no further evidence that it would reflect chronic pain. De Castro-Costa et al. (1981) found scratching to be increased in arthritic rats and proposed it to express chronic pain. However, a considerable body of evidence (Colpaert, 1987) converges to indicate that the chronic pain of arthritic rats is particularly severe 2 to 3 weeks after the inoculation, although secondary, acute pains from persistent inflammation and hyperalgesia might continue to occur for about 8 weeks (see later in this section). A major difficulty with accepting scratching as a sign of chronic pain in arthritic rats is that it reaches a peak at weeks 4 to 5 postinoculation (Calvino et al., 1987a; De Castro-Costa et al., 1981, 1987) and, thus, later than the time at which the chronic pain is most intense. Morphine depresses the scratching behavior of arthritic rats (De Castro-Costa et al., 1981) but, as mentioned before in this section, morphine also nonspecifically depresses various other behaviors in pain-free animals. The NSAID acetylsalicylic acid similarly decreased arthritic scratching (De Castro-

[6] However, after such maneuvers as thoracic surgery, breathing itself may cause pain and ventilation might become depressed (Buckley, 1985), the resulting hypoxia being responsive to analgesic treatments (Flecknell et al., 1991).

Costa et al., 1987), but others have failed to obtain similar results with aspirin or other NSAIDs (Mohrland and Johnson, 1983). Also, the NSAIDs suprofen and indomethacin, as well as dexamethasone and cortisone acetate, exerted little or no effect on the hyperventilation of arthritic rats (Colpaert et al., 1987). In mice, scratching can be induced by pruritogenic substances, but not by the presumably pain-producing substances capsaicin and formalin (Kuraishi et al., 1995). Note also that, in humans, NSAIDs (when given alone) have very limited effectiveness in relieving the pain of rheumatoid arthritis (e.g., Ruoff, 1982). Chronic administration of the antidepressants amitriptyline and imipramine reduced arthritic scratching in one study (Butler et al., 1985), but this reduction was associated with a reduction of the pathology, and the findings are difficult to interpret (Butler et al., 1985). Kupers et al. (1988) found that scratching in arthritic rats can be depressed by electrical stimulation of the nucleus paraventricularis thalami (PV), a maneuver which in some instances seems to alleviate pain in humans (Gybels et al., 1980; Meyerson, 1983). The PV stimulation further produced apparent analgesic effects in tail-flick and hot-plate procedures, although the effects thus obtained in these different procedures did not correlate (Kupers et al., 1988). However, the PV stimulation that decreased scratching also decreased biting and grooming and increased sniffing and running (Kupers et al., 1988). It would be interesting for further studies to determine whether morphine, acetylsalicylic acid, other NSAIDs and corticosteroids can mimick the effects of PV stimulation in arthritic rats (i.e., decrease scratching, biting and grooming, and increase sniffing and running); it would also be of interest to determine how these compounds and PV stimulation affect the same behaviors in pain-free animals. Whether scratching in arthritic rats reflects chronic pain thus remains a matter of some debate (Colpaert, 1987; De Castro-Costa et al., 1981, 1987; Kupers et al., 1988). One potential way to reconcile the different findings derives from the fact that the self-administration of fentanyl and suprofen by arthritic rats occurs at periods of time that do overlap, but this self-administration peaks at times that differ (i.e., weeks 2–3 and weeks 4–7, respectively; Colpaert et al., 1980b, 1982). Two stages have tentatively been identified (see fig. 1 in Colpaert, 1987) in terms of the pains that may evolve in rats after inoculation with *mycobacterium butyricum*. One consists of a severe, chronic, opiate-responsive pain that is little, if at all, susceptible to NSAIDs and may therefore be noninflammatory in nature; it occurs during weeks 2 and 3 postinoculation and abates over weeks 4 and 5. From week 4 onward, and for a further period of about 3 to 4 weeks in all, arthritic animals resume various behaviors and activities while inflammation and hyperalgesia persist; thus may arise acute, repeated, inflammation-induced hyperalgesic pains which are relatively mild, responsive to NSAIDs, and perhaps absent while the animal is immobile. The time at which scratching in arthritic rats reaches peak (Calvino et al., 1987a; De Castro-Costa et al., 1981) coincides with this second stage. Finally, different behavioral responses demonstrating the hyperalgesia of the various inflamed tissues in arthritic rats have, of course, been reported, and these responses can readily be counteracted by both NSAIDs and opiates (e.g., Capetola et al., 1980; Hirose and Jyoyama, 1971; Rainsford, 1982; Winter et al., 1979). However, these latter studies invariably have induced acute responses to acute pains that do not exist in the absence of the acutely superimposed stimulation and thus do not constitute evidence of chronic pain in arthritic rats. It is unfortunate that a confusion often continues to be made in the literature between these acute pains from inflamed, hyperalgesic, and acutely stimulated tissues on the one hand, and the chronic pain that may perhaps exist in arthritic rats.

Various biochemical and histochemical changes also occur in arthritic rats. As mentioned above, levels of substance P are enhanced in sciatic nerve, saphenous nerve and in the L4 and L5 dorsal sections of the lumbar spinal cord (Chery-Croze et al., 1985; Colpaert et al., 1983; Lembeck et al., 1981). The effects of capsaicin on spinal cord levels of substance P (Colpaert et al., 1983) and on the ventilation (Bervoets and Colpaert, 1984) are consistent with the possibility that substance P mediates the putative chronic pain of arthritic rats. The time-course of spinal cord substance P levels has also been studied (Schoenen et al., 1985); the qualitative data thus obtained on days 15, 30 and 60 after inoculation are perhaps compatible with the time course of chronic pain (see Colpaert, 1987), but quantitative data obtained with a higher temporal resolution are required to characterize this relationship more precisely. Levels of substance P also increase in the plasma and cerebrospinal fluid of rats with adjuvant arthritis, but these increases did not parallel the time course of behavioral manifestations of inflammatory hyperalgesia (Calvino et al., 1994). A decrease of substance P levels has been reported in ventral sections of lumbar spinal cord, presumably containing gray matter fibers projecting to motoneuron cell bodies (Chery-Croze et al., 1985).

At both 15 and 21 days after inoculation, total serum tryptophan levels decrease, while plasma-free tryptophan levels increase (Weil-Fugazza et al., 1980). Forebrain as well as spinal cord levels of tryptophan, 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) increase at day 15, but return to control or near-control levels on day 21 (Weil-Fugazza et al., 1980; see also Sofia and Vassar, 1974). The complex time course of these changes (Godefroy et al., 1987; Schoenen et al., 1985; Weil-Fugazza et al., 1980) thus is not simply parallel to that of the putative chronic pain of arthritic rats (Colpaert, 1987). It also remains to be established whether the increased levels of 5-HT in the brain and

spinal cord are associated with any changes in 5-HT release (Weil-Fugazza et al., 1984). Finally, at 16 days after inoculation, morphine further enhances the increased levels of tryptophan and 5-HIAA, but not of 5-HT, in the brain and spinal cord of arthritic rats (Weil-Fugazza et al., 1979).

Other findings have demonstrated increased levels of the mitochondrial enzyme, succinic dehydrogenase (Schoenen et al., 1985), of cholecystokinin (Chery-Croze et al., 1985) and of norepinephrine and uric acid (Weil-Fugazza et al., 1986) in the lumbar spinal cord of arthritic rats. There also is considerable evidence (Besselin et al., 1980, 1984; Faccini et al., 1984; Millan et al., 1985a, b, c, 1986a, b; Yonehara et al., 1983) of marked changes in endogenous opiate systems of the brain and of the spinal cord. However, detailed studies of the time course and physiological specificity of these various changes are lacking, and the data so far available do not permit one to unambiguously relate these findings to the chronic pain as opposed to the mere inflammation or, for that matter, to the stress and depression of drive states that perhaps also occur in arthritic rats (Colpaert, 1987).

Electrophysiological experiments have examined the responsiveness of afferent fibers contained in an articular ramus innervating an inflamed ankle joint of arthritic rats. As compared with control animals, fibers of pentobarbitone-anesthetized arthritic animals, 3 to 4 weeks after the inoculation, showed a lowered threshold for mechanical stimulation (Guilbaud et al., 1985a) and the occurrence of background activity that was responsive to aspirin (Guilbaud et al., 1985b). In unconscious arthritic rats that underwent ischemic decerebration by bilateral carotid ligation, 15 to 43 days after inoculation, unit activity of dorsal horn neurons in response to cutaneous stimulations was also enhanced (Menetrey and Besson, 1982). That is, superficial dorsal horn cells were identified exhibiting background activity and enhanced responsivity to mild, acute, mechanical stimulation; some neurons in deeper areas responded similarly to otherwise nonnoxious stimuli (Menetrey and Besson, 1982). A further study (Calvino et al., 1987b) similarly identified atypical, dorsal horn convergent neurons, the segmental electrophysiological characteristics of which were changed; the size of their excitatory receptive fields was enlarged, and their responsiveness to transcutaneous electrical stimulation was enhanced (3 to 5 weeks after inoculation, under halothane anesthesia; Calvino et al., 1987b). Furthermore, unitary responses of neurons in the ventrobasal thalamic nucleus (nVT) to somatic, acute stimulations applied to the receptive fields of inflamed tissues were also enhanced in arthritic rats (3 to 4 weeks after inoculation, under halothane anesthesia; Gautron and Guilbaud, 1982). Of 168 cells studied, only 20 were activated exclusively by intense cutaneous stimulation, whereas an atypical proportion of 108 cells were excited by mild stimulations. Somatosensory neurons of the posterior intralaminar region of the thalamus showed similar characteristics (Kayser and Guilbaud, 1984). The NSAIDs aspirin (Guilbaud et al., 1982) and indomethacin (Okuyama and Aihara, 1984b) as well as morphine (Kayser et al., 1983; Okuyama and Aihara, 1984b) depressed these responses of nVT neurons to peripheral stimulation under otherwise similar experimental conditions. Finally, unusual responsivity to peripheral, acute stimulation of inflamed tissue has also been found in single, layer V neurons of the first somatosensory cortex (3 to 5 weeks after inoculation in halothane anesthetized arthritic rats; Lamour et al., 1983), with most of the neurons being driven by joint movement and/or moderate pressure applied to the skin.

The available electrophysiological evidence thus consistently demonstrates unusual unit response characteristics of articular afferent fibers, spinal dorsal horn and thalamic and cortical neurons. However, the precise relationship of these findings to the chronic pain of arthritic animals remains to be clarified. All of these findings have, of necessity, been obtained in unconscious, usually anesthetized, and at times decerebrated, animals, and it is unclear how chronic pain can be studied at all under these conditions. The most unassuming definitions of pain require the subject to consciously report about its subjective effect (Beecher, 1957, 1959); to accept findings in unconscious subjects as evidence of pain would thus require that first there be defined and accepted measurements of pain that no longer require these to be validated by whatever such confirmation as can be obtained in conscious subjects. Also, these electrophysiological studies have been concerned with acute responses to acutely applied stimulations of inflamed, hyperalgesic tissues that may possibly be unrelated to chronic pain. Indeed, chronicity is perhaps not necessary for these altered response characteristics to be obtained; Coggeshall et al. (1983) found that during acute inflammation of the knee joint in cats, afferent fibers developed background activity, enhanced sensitivity to mechanical cutaneous stimulation and a normally absent responsiveness to joint movement. The susceptibility to aspirin of these altered response characteristics, as demonstrated at the levels of articular fibers and thalamic neurons, constitutes further support for these characteristics to merely reflect acute inflammation. Indeed, any electrophysiological differences between arthritic rats and preparations involving acutely inflamed tissues remain to be demonstrated.

As indicated in section III.A., various modalities of acute nociceptive stimulation enhance c-Fos expression in different afferent systems (Fitzgerald, 1990; Morgan and Curran, 1991), and enhanced c-Fos expression has also been documented in the spinal cord of arthritic rats (Basbaum et al., 1988; Weihe et al., 1990). A detailed study (Abbadie and Besson, 1992; see also Abbadie et al., 1994; Sagen and Wang, 1995) confirmed c-Fos expression to be enhanced in sacral, lower thoracic and cervical segments, the highest levels being found in the lumbar

L3 and L4 segments. Measurements were made 1, 2, 3, 11 and 22 weeks after inoculation, the highest value being obtained at week 3. Whether the latter represents peak was left uncertain, and it would be interesting for further work to characterize time points that are intermediate between weeks 3 and 11. Like the self-administration of analgesic compounds (Colpaert et al., 1980b, 1982) and enhanced ventilation (Colpaert and Van den Hoogen, 1983a, 1983b), enhanced c-Fos expression occurred in the absence of any additional, experimenter-produced stimulation. However, the c-Fos expression was still markedly elevated 11 weeks after inoculation, i.e., at a time when the self-administration of analgesic drugs and hyperventilation have reached levels so low as to be indistinguishable from that of nonarthritic controls. Also, enhanced expression of c-Fos in the dorsal horn occurs with nonnociceptive as well as with nociceptive sensory stimulation (Hunt et al., 1987), cautioning further against any direct relationship between c-Fos expression and chronic pain in arthritic rats. Abbadie and Besson (1993) found no effect of a single dose of morphine on c-Fos expression in lumbar spinal cord neurons in arthritic rats; the single morphine treatment did, however, counteract the further increase of c-Fos expression produced by acute mechanical stimulation of the inflamed ankle joints. As pointed out by the authors (Abbadie and Besson, 1993), it would be interesting for further work to examine the effects on c-Fos expression of an opiate that would be administered chronically throughout the 2-week period during which arthritic rats are in severe chronic pain. Finally, c-Fos expression in the dorsal horn, L4-L5 segments of the rat spinal cord is also enhanced in the acute carrageenan model of inflammatory hyperalgesia and, in this model, is responsive to NSAIDs (Buritova et al., 1995).

The evidence reviewed here suggests that the polyarthritis induced by Freund's adjuvant is effectively associated with chronic pain (Colpaert, 1979, 1987). Theories of behavior (Skinner, 1938) would predict an analgesic compound to more powerfully reinforce the self-administration of the analgesic in subjects exposed to pain than in pain-free subjects. This was confirmed by studies using the NSAID suprofen (Colpaert et al., 1980b) and the opiate fentanyl (Colpaert et al., 1982). Also, like chronic pain patients (Glynn et al., 1981), arthritic rats hyperventilate (Colpaert and van den Hoogen, 1983a, b), and hyperventilation may constitute one of the very few, if not only, objective sign of both acute and chronic pain that can be measured by noninvasive methods. Finally, arthritic rats present with various behavioral, biochemical and electrophysiological anomalies, some of which may perhaps relate to chronic pain; parameters of particular interest for further research include increased levels of substance P in primary afferents, increased scratching behavior, enhanced c-Fos expression in lumbar spinal cord neurons and the altered electrophysiological characteristics of neurons throughout afferent pathways. Each of those various, individual findings that have been reported in attempts to validate adjuvant arthritis as an animal model of chronic pain can alternatively be explained by one or several other hypotheses. However, the hypothesis that rats with adjuvant arthritis suffer chronic pain is uniquely parsimonious in accounting for all of these findings and in explaining the remarkable coherence that exists in the temporal pattern with which they occur (Colpaert, 1987). It is therefore reasonable to conclude that rats with adjuvant arthritis are effectively in chronic pain.

The latter conclusion thus justifies, a posteriori, the use we originally made in studies of opiate tolerance (Colpaert, 1978c, 1979) of adjuvant arthritis as an animal model of chronic pain. However, those studies specifically tested our System Theory of opiates and pain (section II.), and in so doing implicitly assumed opiates to be efficacious against the chronic pain of adjuvant arthritis. It thus remained to be demonstrated that the latter is the case. De Castro-Costa et al. (1981) found the enhanced scratching of arthritic rats to be depressed by morphine, but the specificity of this finding warrants further investigation. The enhanced self-administration of fentanyl by arthritic rats (Colpaert et al., 1982) is clearly suggestive of fentanyl exerting analgesic effects, but alternative explanations are possible (Colpaert, 1987). Perhaps most pertinent, then, is that morphine counteracts the hyperventilation of arthritic rats (Colpaert et al., 1987). This opiate effect, in arthritic rats breathing air, was specific, in that nonopiate drugs failed to decrease arthritic hyperventilation except when also producing hypnosis (as was the case with 160 mg/kg of chlordiazepoxide, see Colpaert et al., 1987). The opiate effect also was specific in that morphine at these doses did not decrease the respiration of nonarthritic rats breathing air (Colpaert et al., 1987). Morphine at these doses can depress the respiration of normal rats, but only if the animals are challenged with CO_2 (Van den Hoogen and Colpaert, 1986). The latter findings are coherent with opiates, in normal organisms, decreasing the apparent sensitivity of central chemoreceptors to changes in arterial pH that are due to changes in partial pressure of carbon dioxide in arterial gas ($PaCO_2$) (Mueller et al., 1982). It would thus appear that opiates can effectively relieve the severe chronic pain of rats with adjuvant arthritis.

C. Clinical Chronic Pain

The present section will be concerned with the development of tolerance to opiate analgesia in patients with chronic pain. Despite, and perhaps because of, the overwhelming belief that tolerance develops to opiate analgesia, few studies have sought to formally examine the issue in humans. Apparent tolerance to analgesia (Rossbach, 1880) and to a range of other opiate effects (Light et al., 1930; Martin and Jasinski, 1969; see also Martin, 1977) was first documented in studies conducted in opi-

ate-dependent subjects. In one study (Houde et al., 1966; see also Houde, 1985), cancer patients received graded single doses of morphine before and after 2 weeks of regular morphine treatment; a rightward shift occurred in the dose-response curve of the single doses for producing pain relief. Also, it has been found that the use of high doses of opiates in cancer patients is associated with a relatively rapid increase in opiate dose (Bruera et al., 1989; Mercadante et al., 1992) and that a relatively smaller analgesic response is correlated with a greater degree of previous opiate use (Thaler et al., 1991; Wallenstein et al., 1990). Others (Mueller et al., 1982) observed that the dose of epidural morphine required to provide adequate pain relief was higher in these patients who had received larger doses of parenteral opiates before the epidural treatment. It would thus appear that apparent tolerance to opiate analgesic effects can develop in humans, including in patients who suffer pain. These observations are compatible with System Theory and, also, with the classical theory that tolerance develops to opiates.

Of course, no study has formally examined in humans our prediction that apparent tolerance to opiate analgesic effects should not occur if the opiate that is being administered offers an adequate match of the to-be-alleviated-pain in terms of both the magnitude and the duration of its effects. However, a wealth of retrospective surveys and partially controlled studies report that the dose of opiates that is required in chronic pain patients to alleviate pain may remain constant for years on end. Observations to this effect have been made with both parenteral (e.g., Kaiko et al., 1981; Kanter et al., 1980) and intrathecal or epidural administration (Arner and Arner, 1985; Driessen et al., 1989; Onofrio and Yaksh, 1990; for particularly eloquent data, see Zenz et al., 1981) of morphine and various other opiates (de Leon-Casasola and Lema, 1994; Portenoy and Foley, 1986). The observations pertain to pains from malignant (e.g., Caputi et al., 1983; Mount et al., 1976; Saunders, 1982; Zenz et al., 1989) or nonmalignant etiologies (e.g., Pappagallo and Campbell, 1994; Portenoy and Foley, 1986) in patients who are either opiate-naive or on methadone maintenance (Kantor et al., 1980; Rubenstein et al., 1976), and used protocols that have either physicians or the patients themselves control the administration of the opiate (Jadad et al., 1992; Ralphs et al., 1994). Importantly, with respect to the adjuvant arthritis animal model of chronic pain, the opiates codeine and propoxyphene have been found to provide sustained analgesia in patients with rheumatoid arthritis (Thurel et al., 1991; Vlok and Van Vuren, 1987), albeit that dropouts occurred because of side effects (Kjaersgaard-Andersen et al., 1990). With long-term use, the increases of the opiate dose that are sometimes required to continue to alleviate pain often seem to be caused by disease progression and aggravation of the pain rather than to tolerance (Arner et al., 1988; Collin et al., 1993; Foley, 1991; Portenoy, 1994b; Twycross, 1974), and some pains may or may not respond well to opiates, regardless of the patient's drug history (e.g., Fitzgibbon and Galer, 1994; Kupers et al., 1991; Markley, 1994; Portenoy et al., 1990). Such increases of dose are definitely not the rule, however; for example, Taub (1982) describes 313 patients in whom no escalation of opiate dose was encountered during periods of treatment lasting up to 6 years. Early, pioneering, efforts to relieve clinical chronic pain have established progressive protocols that carefully titrate the opiate dose to the individual patient's pain (Mount et al., 1976; Twycross 1974, 1978; Twycross and Wald, 1976). These protocols are likely to in effect establish the matching between opiate and pain that our theory requires (section II.) for apparent tolerance to opiate analgesic effects to be avoided. The implementation, more or less faithful, of these protocols has in recent years given rise to authoritative clinicians firmly expressing the opinion that opiate-responsive chronic pain can effectively be treated with opiates, for open-ended periods of time, in the absence of any apparent tolerance to the opiate's analgesic effects (for reviews, see Foley, 1991; Portenoy, 1994a, b; Twycross and McQuay, 1989; Zenz et al., 1992). That oral morphine is successful in over 90%, but not all, of cancer patients (Zylicz and Twycross, 1991) may perhaps be attributable to the matching not always being entirely adequate in terms of both the intensity (dose) and the duration of the opiate being used.

The clinical evidence cited above is limited. For obvious ethical reasons, methodologically rigorous, completely controlled studies of opiate analgesia and of pain sensitivity in volunteers who do not and in patients who do suffer chronic pain have not been conducted. However, the current analysis of such evidence as there is, and recent clinical opinion, is consistent with the predictions that System Theory makes about the relationship between nociceptive stimulation and apparent tolerance. In fact, none of the clinical observations and findings argues against any of these predictions. Most importantly to the patient suffering chronic pain, it would indeed appear that apparent tolerance to opiate analgesia does not develop, and that the chronic pain can effectively be treated, if the opiate treatment adequately matches the pain. Inasmuch as the development of tolerance to opiate analgesia constitutes the most difficult problem in providing clinical pain relief (e.g., Kelemen, 1973), this problem would now seem, in principle, to have been resolved.

IV. System Theory and Opiate Drug Action

In this section, we will describe a mathematically formalized model of the System Theory that was presented above in a verbal manner. We will also examine to what extent System Theory can accommodate the major features of putative tolerance to opiate analgesia as they have been identified empirically by experimental

studies. Finally, we will explore how System Theory can apply to opiate effects other than analgesia.

A. Formal System Theory

As specified above (section II.; fig. 1), physical stimuli impacting on a particular input channel possess a magnitude that is defined along a physical variable termed φ_α. Transduction occurs such that the physical stimulation φ_α causes a physiological activity φ_o. This transduction will be assumed here to be simply linear, but it is changed in the presence of an opiate agonist, the dose of which is termed μ. For example, in the presence of a dose of 14 arbitrary units (A.U.) of morphine, a φ_α of 20 A.U. no longer causes a φ_o value of 20 A.U. but a lower value that is found by subtraction, i.e., 20 −14 = 6. Equation 1 applies at all points of time:

$$\varphi_o = \varphi_\alpha - \mu. \qquad [1]$$

The predictions and data that are discussed below are all derived from numerical, computer-generated, simulations. The values of φ_α and of the doses of morphine that are used in these simulations belong to the geometrical series. . . 2.5, 3.5, 5, 7, 10, 14, 20,. . . . The System will often be challenged by a standard test stimulus of 20 A.U. and be administered a standard test dose of morphine of 14 A.U. As indicated in section II, the System will compute a temporally integrated value, termed ι_τ, of all physiological activity φ_o that has occurred over a past, sample period of time that precedes immediately the current point of time. In what follows, the sample period used to obtain ι_τ will typically span 40 (arbitrary) units of time; ι_τ is continuously computed as the moving average of the physiological activity φ_o that occurred over the preceding, discrete 40 units of time. In so doing, φ_o is weighted, however, so that more recent inputs have a greater impact than inputs that are more remote in time. The weight being accorded decreases linearly from 1.00 to 0.01 over the sample period. Thus, the φ_o value at the one time unit that immediately precedes the current time point, is multiplied by 1.00; the φ_o value that occurred 40 units of time before the current time point, is multiplied by 0.01. φ_o values occurring between these points of time are multiplied by multipliers that decay linearly from 1.00 to 0.01 (see fig. 2, insert). At all points of time, current ι_τ (i.e., ι_τ at time zero, or τ_o) is thus determined following Equation 2:

$$\iota_\tau(\tau_o) = \frac{1}{40} \sum_{k=-40}^{-1} w_k \cdot \varphi_o(\tau_k) \qquad [2]$$

in which the weight w_k of φ_o is found as

$$w_k = \frac{33k + 1333}{1300}.$$

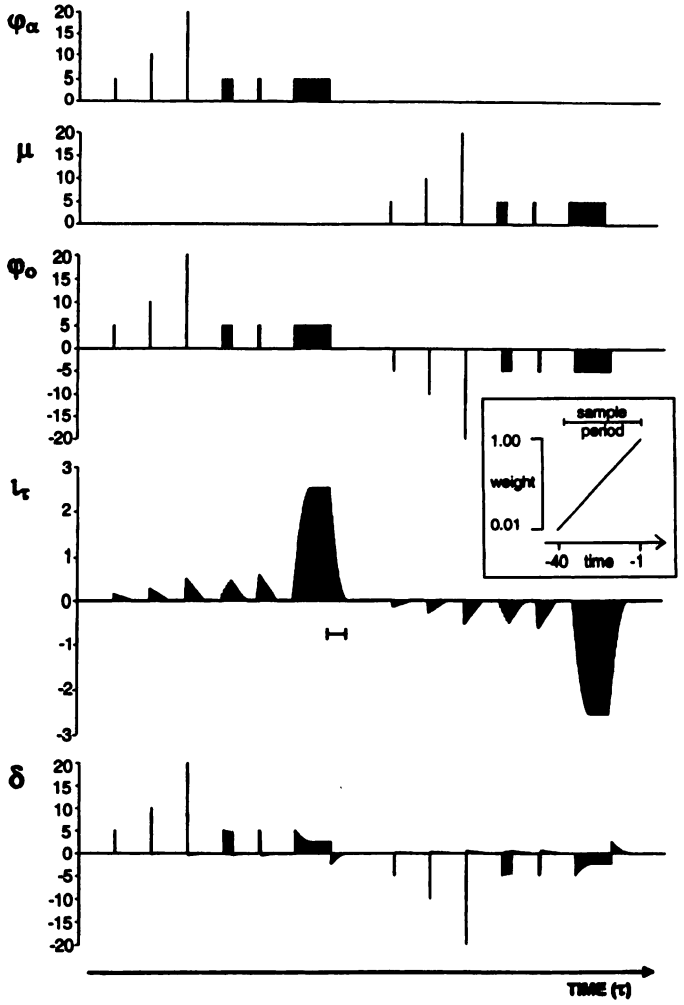

FIG. 2. Temporal dynamics of ι_τ. The data demonstrate how physical stimulations (φ_α) or doses of morphine (μ) of varying magnitudes, frequency and duration determine physiological activity (φ_o) and its temporal integration ι_τ. Pain sensation is represented by the difference δ between φ_o and ι_τ. All ordinates express arbitrary units (A.U.); the abscissa represents time, also in A.U. The insert specifies how, in the computation of ι_τ, the weight that is being attributed to φ_o varies as a function of time. The calibration marks the sample period of ι_τ: i.e., 40 units of time. Data were obtained from computer simulations of the operations of System Theory.

The difference δ will be found by subtracting ι_τ from φ_o, and Equation 3 also applies at all points of time:

$$\delta = \varphi_o - \iota_\tau. \qquad [3]$$

Analgesia produced by morphine will typically be determined by finding the δ produced by the stimulus of 20 A.U. of φ_α in the absence (i.e., δ') and in the presence (i.e., δ'') of a 14 A.U. dose of morphine; it will be calculated as the ratio e_r of δ' to δ'' (i.e., $e_r = \delta'/\delta''$). Unlike φ_o, ι_τ and δ, the analgesia index e_r is not a parameter of the System. As noted in section II., e_r is an index that the experimenter can arbitrarily choose to compute from data on δ; it is *not* being determined at every point of time.

1. Operating characteristics of ι_τ. A full comprehension of System Theory requires one to appreciate the dynamic features of the System's parameters, especially ι_τ, as they vary over time. Figure 2 specifies how ι_τ changes over time as the System is being challenged with various stimuli and injections of morphine.

Initially, no stimulus is being presented, and the physical activity φ_α is set at zero. We will assume that only one particular modality of φ_α generates physiological activity[7] so that initially, φ_o and ι_τ are at zero, each parameter being expressed in terms of its own arbitrary units.

A first stimulus lasting one unit of time is presented; the stimulus has a magnitude of 5 A.U. along φ_α and yields a physiological activity that also is of magnitude 5 A.U. (along φ_o). Even this short and small stimulus causes ι_τ to increase (i.e., to 0.12 A.U.); ι_τ then decays to reach zero again after a period of time that is equal to the sample period, i.e. 40 units of time after the presentation of the stimulus. The larger stimuli, of magnitudes 10 and 20 A.U. of φ_α, cause ι_τ values that are larger (i.e., 0.25 and 0.50 A.U., respectively) but decay within the same (40 units long) period of time. The repeated (i.e., five times, once every 5 time units) or longer-lasting (i.e., during 5 time units) of the magnitude 5 stimulus causes increases in ι_τ that are larger than that produced by a single, 1-time-unit-long presentation of the stimulus (i.e., to 0.47 and 0.59 A.U., respectively). Prolonged (i.e., during 80 time units) stimulation at the same 5 A.U. intensity of φ_α causes an even larger increase in ι_τ; the latter increase reaches asymptote (at 2.52 A.U.) after 40 time units have expired since the onset of stimulation; ι_τ then remains at asymptote until the stimulation is discontinued. It subsequently decays to reach zero again, 40 time units after the stimulation has been discontinued. It thus appears that any stimulus, however short and small, causes ι_τ to increase. The peak value reached by ι_τ depends on the intensity, frequency and duration of the stimulation. Upon discontinuation of the stimulus, ι_τ decays to zero after a lapse of time that is equal to the sample period.

In the absence of stimulation, the application of an opiate such as morphine has effects on φ_o and on ι_τ that are a mirror image of those of stimulation. That is, morphine decreases rather than increases ι_τ; it does so in a manner that similarly depends on the magnitude of its dose, and on the frequency and duration of its application. Any administration of morphine, however small its dose and however short its duration, causes ι_τ to decrease, albeit slowly. Like those of stimulation, the effects of morphine on ι_τ decay so that ι_τ reaches zero again 40 time units after the discontinuation of morphine administration.

[7] This assumption is being made here for the sake of simplicity; in a variant of the present model, it would also be possible to assume that different modalities of φ_α can generate a single modality of φ_o.

The lower panel in figure 2 represents the difference δ that at any point of time can be found according to the equation $\delta = \varphi_o - \iota_\tau$. Discrete stimuli cause increases in δ; δ represents the physiological sensation of the (physical) stimuli (i.e., pain): it can be coupled to an effector system and then also represents this effector's activity (i.e., the pain response). In what follows, we will systematically consider positive values of δ and the activity of an effector system that is linearly coupled to positive δ values. No consideration will be given to negative δ values, and to the activity of a possible, second, effector system[8] that could conceivably be coupled to negative δ values.

The simulations represented in figure 2 thus exemplify the dynamic changes that occur with ι_τ when the System is challenged by either stimulation or morphine. The following section will specify some of the consequences that such changes in ι_τ have to the responses of the System in conditions of chronic pain and chronic opiate treatment.

2. Algesia and opiate analgesia. Figure 1 demonstrated, in verbal terms, how System Theory generated predictions concerning the effects of nociceptive stimulation and of opiates, on the responsiveness to acute nociceptive stimulation (algesia) and on the apparent magnitude of opiate analgesia. Figure 3 presents a computer-generated simulation of the System's operation as a function of time, and this while the System is being challenged with the events depicted in figure 1.

The simulation examines the magnitude of δ (perceived pain intensity) in response to an acute, test stimulus that lasts 1 unit of time and is of φ_α magnitude 20; ι_τ is being computed as specified above. The stimulus is being presented in the absence (single prime, left panels) and in the presence (double prime, right panels) of a test dose of morphine. The test dose is delivered simultaneously with the stimulus; it, too, lasts only 1 unit of time and is of magnitude 14, thus decreasing by 14 the activity φ_o generated by any current stimulation φ_α.

In a normal organism (panels A), ι_τ is at zero, and the test stimulus induces a δ of magnitude 20 in the absence (panel A′) and of magnitude 6 (because $20 - 14 = 6$) in the presence (panel A″) of the test dose. Chronic admin-

[8] Such an effector system might nonetheless be of interest. The effector system coupled to positive values of δ will appear to account for apparent tolerance and the enhancement of some responses. However, the enhancement of other responses that is characteristic of the so-called sensitization that opiates can also produce (Babbini and Davis, 1972; Goudie and Emmett-Oglesby, 1989; Locke and Holtzman, 1986; Rauhala et al., 1995) can similarly be generated by effector systems that are coupled to negative values of δ, of ι_τ, or to entities derived therefrom. Negative values of δ may at this stage be as difficult to imagine in physiological terms as it would be to imagine Kelvin's zero temperature after having accepted the Celsius zero. However, electrophysiological evidence will be considered later (section IV.D.) that opiates can depress the spontaneous activity of nociceptive afferents, and it has been suggested (Costa and Herz, 1989; Costa et al., 1990) that such ligands as ICI 174864 can activate δ opiate receptors in a so-called inverse manner.

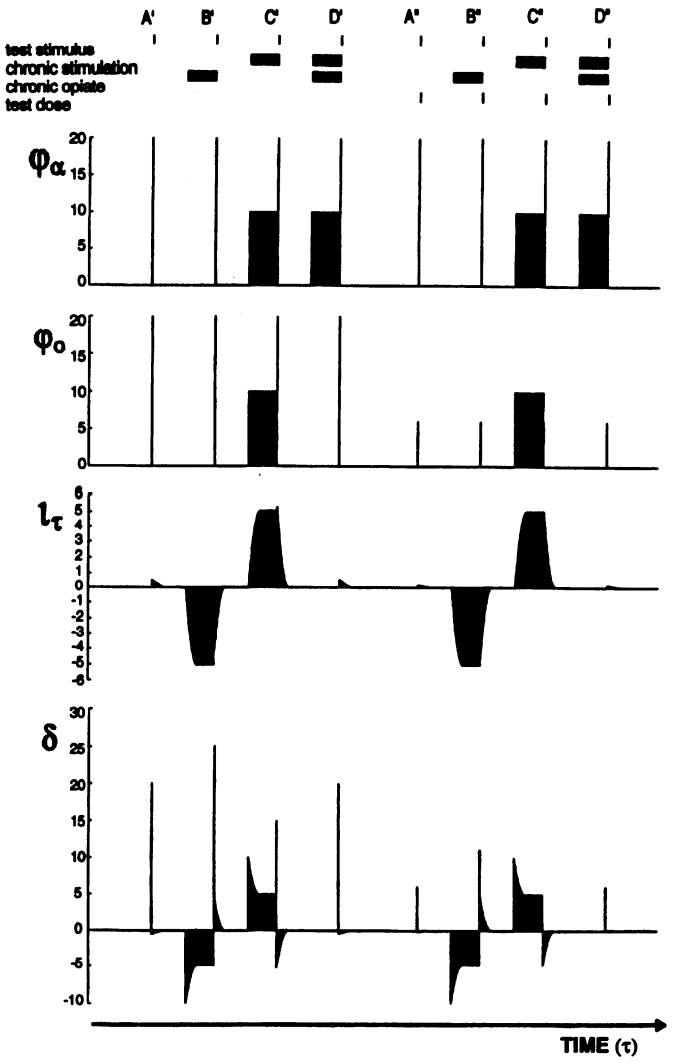

FIG. 3. Operating characteristics of the System: algesia and opiate analgesia in the four conditions (A to D) specified in figure 1. The computer simulation examined the effects of a standardized, acute, test stimulus in the absence (single prime, left panels) and presence (double prime, right panels) of an acutely administered test dose of morphine. Four conditions are being considered: i.e., the normal condition (A), that of an organism having received an opiate chronically (B), that of an organism having received chronic nociceptive stimulation (C), and that of an organism having received chronically both an opiate and nociceptive stimulation (D).

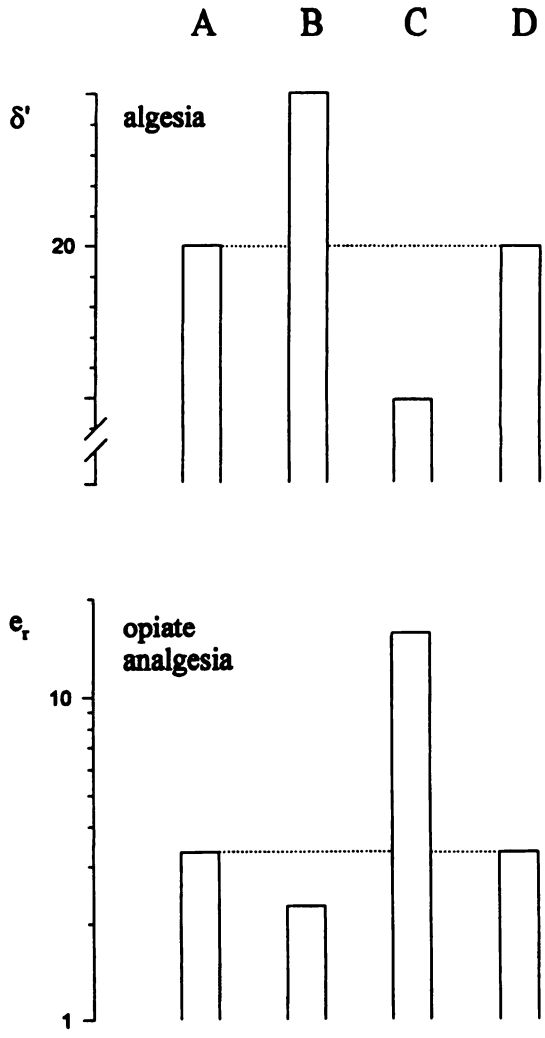

FIG. 4. Numerical values of pain sensitivity (δ′) and of morphine's apparent analgesic effects (e_r) generated by the computer simulation specified in figure 3. δ′ and e_r were studied in the normal condition (A), as well as in conditions of chronic opiate treatment (B), of chronic nociceptive stimulation (C), and in a condition in which these two latter chronic treatments were combined (D).

istration of an opiate (during 100 units of time; of magnitude 10) as in panels B, and of nociceptive input (also during 100 units of time; of magnitude 10) as in panels C, causes ι_τ to decrease and increase, respectively. The chronic coadministration of both an opiate and nociceptive stimulation as in panels D′ and D″ fails to affect ι_τ. Figure 4 displays the numerical values that were thus generated for δ and e_r (i.e., the ratio of δ′ to δ″). The data indicate the System, in a mathematically formalized manner, to predict that chronic opiate treatment and chronic nociceptive stimulation induce hypo- and hyperalgesia, respectively; the data also show the pain response to be normal when these two, matching, conditions are combined. The data further formalize the predictions that chronic opiate treatment and chronic nociceptive stimulation induce apparent tolerance and apparent inverse tolerance, respectively; and that the apparent magnitude of opiate analgesic effects is normal if the two, matching, conditions are combined.

In conclusion, the simulations presented in figure 3 demonstrate that it is possible to mathematically formalize, as in the present model, the predictions that were initially made from the verbal formulation of System Theory that was provided in section II. The numerical predictions derived from this formal model (fig. 4), in fact, fairly faithfully reproduce empirical data that were obtained in experiments that examined the effects of chronic pain and of chronic opiate drug administration, on pain sensitivity and on apparent opiate analgesia in arthritic rats (see fig. 3 in Colpaert, 1978b).

3. Matching and mismatching. One prediction of our theory that merits particularly to be elucidated further is that apparent tolerance to an opiate's analgesic effects should not develop, inasmuch as the opiate action constitutes an *appropriate match* of the nociceptive stimulation. In condition D of figure 3, we have fed the system with both a chronic nociceptive stimulation and a chronic opiate treatment the magnitudes of which were perfectly equivalent; both also had an identical duration and were synchronous. A perfect match was thus established between the nociceptive stimulation and the opiate. Figure 5 exemplifies matches, but also articulates several mismatches.

The simulations portrayed in figure 5 determined the response δ to a test stimulus of magnitude 20 in the absence (δ') and presence (δ'') of a test dose of morphine of magnitude 14. Before doing so, the system was exposed to chronic stimulation and to chronic opiate treatments that were of magnitudes 10 or 20 and lasted 40 units of time or longer. The chronic stimulation and the chronic opiate treatment coincided in some, but not in other, cases. The magnitude e_r of the apparent analgesia produced by the test dose of morphine was again found as the ratio of δ' to δ''. The e_r values thus found are provided for each simulation.

The normal magnitude of the morphine test dose being 3.33, one mismatch causing apparent tolerance (i.e., an e_r value smaller than 3.33) is one whereby the dose of the chronic opiate was larger than that required to merely offset the nociceptive stimulation. A matching dose that is administered too early or too late (but that in either case outlasts the nociceptive stimulation long enough) similarly generates apparent tolerance (fig. 5, upper panels).

One mismatch that generates apparent inverse tolerance (i.e., an e_r value larger than 3.33), and this despite the chronic administration of an opiate, is one where the intensity of nociceptive stimulation is larger than that which can be offset by the opiate. Also, a matching intensity of nociceptive stimulation that begins either too early or too late (but in either case outlasts the chronic opiate long enough) again generates apparent inverse tolerance (fig. 5, lower panels).

It thus appears that *intensity*, *duration* and *relative timing* constitute the three variables that govern the matching and possible mismatching that can occur between (chronic) nociceptive stimulation and (chronic) opiate treatment. These three variables determine the magnitude of the opiate's apparent analgesic effects (i.e., e_r); this magnitude can either be normal (as is the case with any matches) or can differ from that seen in untreated organisms (apparent tolerance or apparent inverse tolerance, as is the case with mismatches).

Although it in this manner seems that matches and mismatches can be assembled readily, it will in empirical conditions appear more difficult to construct perfect matches; this is because of inertia. That is, especially in conditions where whole organisms are concerned, the physiological action of the opiate typically will not have an abrupt onset and offset; most likely, it will be dynamic as a function of time. Thus, figure 6 portrays how, in whole organisms, inertia resulting from such dispositional factors as distribution, metabolism and elimination causes the intensity of opiate drug action to evolve as a function of time. Inertia causes the relationship

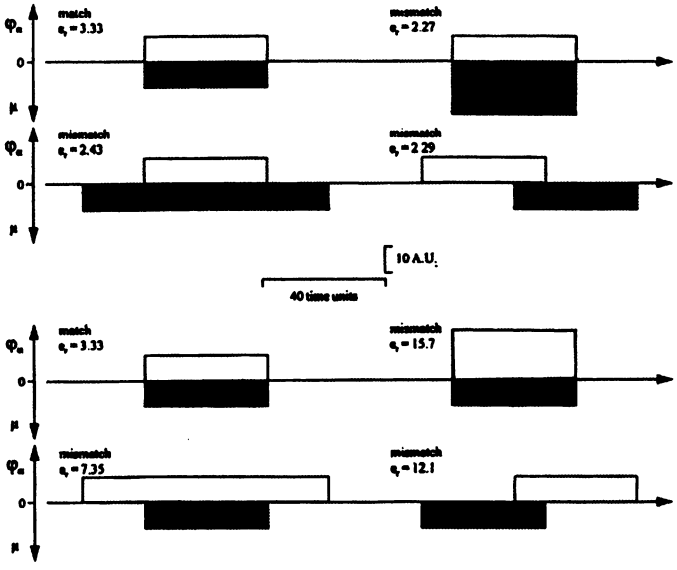

FIG. 5. Matches and mismatches between chronic nociceptive stimulation and the chronic administration of an opiate. The various conditions use nociceptive stimulations that are of (φ_α) magnitude 10 or twice as large; they also use doses of a chronic opiate that are of magnitude 10 or twice as large. The magnitude of e_r (i.e., δ'/δ'') was found, as in figure 3, for a morphine test dose of magnitude 14 that was coadministered with a test stimulus of magnitude 20; both were delivered immediately after the discontinuation of the chronic treatment. The measurements (not shown) were carried out using computer simulations. The upper two panels feature mismatching conditions that yield apparent tolerance; the lower two panels feature mismatching conditions that yield apparent inverse tolerance.

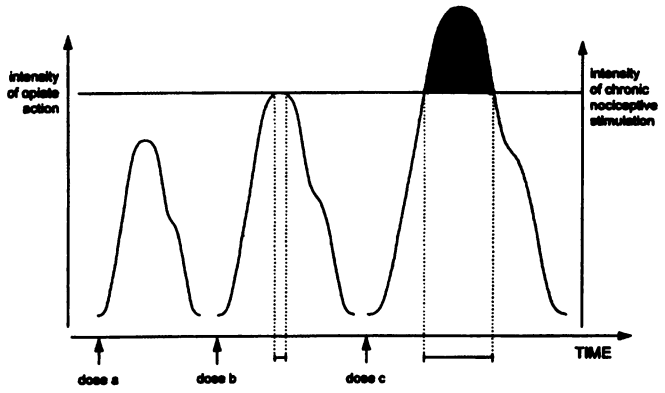

FIG. 6. Relationship between the dose (a to c) of an in vivo administered opiate and the intensity of its action as a function of time (left ordinate). Right ordinate: intensity of a chronic nociceptive stimulation. Vertical projections delineate the time during which the intensity of the opiate drug action is adequate to offset the chronic nociceptive stimulation.

between this latter intensity and time to assume a shape that is not rectangular but bell-like; empirical time-action data (e.g., Wolff et al., 1940) typically show the curve to be skewed in the manner depicted in figure 6. Thus, dose "a" causes some effect, but the intensity of the opiate drug action that it produces is insufficient to offset the nociceptive stimulation. The maximal intensity of opiate action produced by dose b does match the nociceptive stimulation and thus causes apparent analgesia, but the latter will likely have a duration too short for it to be found of any practical significance. Dose c does cause apparent analgesia for an appreciable length of time, but it generates an overshoot both in amplitude and in width that in System Theory will contribute to generate apparent tolerance. Thus, the inertia that occurs, especially in whole organisms, makes it difficult to construct matches; most difficult to generate are matches that allow the opiate to relieve entirely and lastingly the pain that would otherwise be associated with chronic nociceptive stimulation. Possible solutions to this problem are more technological than scientific. The most obvious solution is to generate approximately rectangular time-action relationships such as those that, effectively, can be approached by patient-controlled devices of drug delivery (Owen and White, 1992) or rate-controlled formulations such as patches (Lehmann and Zeck, 1992). Thus, matching in empirical conditions is complicated by inertia, but both experimental (Colpaert, 1979) and clinical evidence (section III.C.) suggests that satisfactory matches can be established in whole organisms.

B. Properties of Apparent Tolerance

So far in section IV, we have further elucidated and specified formally how System Theory can make some particular predictions concerning pain sensitivity, or algesia, as well as concerning apparent opiate analgesia. One of these predictions is that *apparent* tolerance to opiate analgesia can effectively be observed under some conditions. Experimental studies of apparent tolerance to opiate analgesia have found this tolerance to possess a number of empirical properties, most of which have in fact been left unexplained. In the present section, we will examine whether System Theory can accommodate, and account for, these empirical properties of apparent tolerance to opiate analgesia.

1. Dose-dependence. Empirical studies (e.g., Duttaroy and Yoburn, 1995; Kayan et al., 1973; Stevens and Yaksh, 1989; Tilson et al., 1973) indicate that the magnitude of apparent tolerance to opiate analgesia is proportional to the dose at which the opiate is being administered so as to induce the apparent tolerance.

In the simulations that were carried out for this purpose, an opiate was applied, as by infusion, for 40 units of time at doses that were either 0 (normal control) or ranged from 5 to 80 A.U. The infusion was not accompanied by any nociceptive stimulation. Immediately after the infusion, a 20 A.U. test stimulus was applied in either the absence (yielding δ') or presence (δ'') of a 14 A.U. test dose of the opiate. The magnitude e_r of the apparent analgesia produced by the test dose was found, as before, as the ratio of δ' to δ''.

The simulation found the normal control magnitude of the analgesia produced by the opiate test dose to be 3.33 (fig. 7, center panel). After the infusion of a 5 A.U. dose of the opiate, e_r decreased to 2.64. As the dose of the infusion was larger, e_r decreased further along an orderly function to reach a value of 1.30 at the 80 A.U. dose. At this latter dose, the apparent tolerance that had thus been induced amounted to 2.6-fold relative to control. The simulation data thus demonstrate System Theory to accommodate, and account for, the dose-dependence of the apparent tolerance that can be produced to the analgesic effects of opiates.

2. Duration-dependence. Empirical studies (Gellert and Holtzman, 1978; Gold et al., 1994; Yoburn et al., 1985) have indicated the apparent tolerance to opiate analgesia to be a function of the duration of the opiate treatment.

In the simulations that were carried out for this purpose, a dose of 10 A.U. of the opiate was applied for a length of time that either was zero (normal control) or ranged from 1 to 160 units of time. Immediately after this treatment, a 20 A.U. test stimulus was applied in either the absence (yielding δ') or the presence (yielding δ'') of a 14 A.U. test dose of the opiate. The magnitude e_r of the apparent analgesia produced by the test dose was found, as before, as the ratio of δ' to δ''.

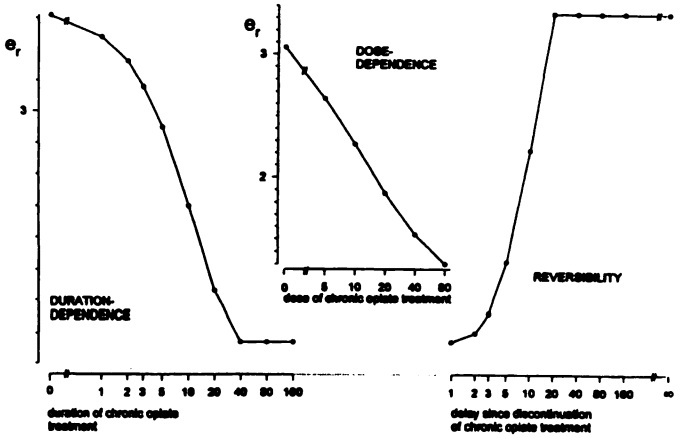

FIG. 7. Dose-dependence, duration-dependence and reversibility of apparent tolerance to opiate analgesia. Data points represent results obtained in three series of computer simulations of experiments that examined in different conditions the magnitude e_r (ordinates) of the analgesia produced by an opiate test dose of 14 A.U. against a test stimulus of 20 A.U. Assuming that tolerance does not develop to opiates, and under the modalities of System Theory, the simulations examined the effects on e_r of the dose (center panel; doses are expressed in A.U.) and of the duration (left panel; time being expressed in A.U. of time) of chronic opiate treatment. The simulations also examined the reversibility (right panel) of apparent tolerance by varying the delay that separated the tests from the discontinuation of chronic opiate treatment.

The simulation again found the normal control magnitude of the analgesia produced by the test dose to be 3.33 (fig. 7, left panel). However, pre-exposure, even for only 1 unit of time, to a dose of 10 A.U. caused e_r to decrease to 3.24. As the duration of this exposure was longer, e_r orderly decreased further to reach a value of 2.27 after an exposure that lasted 40 units of time. This length of time, of course, corresponds to the length of the sample period for ι_r and represents the time for the latter to stabilize. As a consequence, e_r remained at an asymptotic value of 2.27 with any duration of chronic opiate treatment that was longer than 40 time units (i.e., 80 and 160 time units; fig. 7, left panel).

The results from this simulation thus demonstrate System Theory to accommodate, and account for, the dependence of apparent tolerance on the duration of time during which the inducing opiate treatment is administered. The results further indicate this relationship between duration and the magnitude of apparent tolerance to be biphasic. Apparent tolerance initially increases in a manner that is proportional to duration; the proportional relationship applies until a duration is reached that is equal to the System's sample period. Beyond this duration, apparent tolerance remains at an asymptotic value. The fact that the magnitude of apparent tolerance to opiate analgesia is first proportional to duration and then reaches an asymptotic value, has been reported by studies examining morphine's analgesic effects in the rat after exposure to morphine in either a drinking solution (Gellert and Holtzman, 1978) or subcutaneously implanted pellets (Gold et al., 1994). As pointed out earlier in this section, the duration required for the chronic opiate treatment to reach asymptote for apparent tolerance is identical to the System's sample period. By finding this duration, it should thus be possible for experiments to empirically establish the System's sample period.

3. Reversibility. Another empirical property of apparent tolerance to opiate analgesia is its reversibility; once established by an opiate treatment that is then discontinued, tolerance decays with the mere passage of time, and opiate analgesia recovers to a magnitude similar to that in untreated organisms (Cochin and Kornetsky, 1964; Goldstein and Sheehan, 1969; Rauhala et al., 1995; Tilson et al., 1973; Way et al., 1969).

In the simulations that examined reversibility, an asymptotic magnitude of apparent tolerance was induced by exposing the System to an opiate dose of 10 A.U. for 40 units of time. Tests were performed after discontinuation of this chronic opiate treatment, with a delay that varied from 1 to 160 units of time; tests were also performed after a delay that was indefinitely long. The tests again used the 20 A.U. test stimulus that was administered in the absence and in the presence of the 14 A.U. test dose of the opiate.

With a delay of only 1 unit of time separating the tests from the chronic opiate treatment, e_r was only 2.27, indicating that apparent tolerance to opiate analgesia had developed (fig. 7, right panel). The magnitude of this apparent tolerance decreased in an orderly manner (i.e., e_r increased) as the delay increased, reaching the normal control value of 3.33 at a delay that was 40 time units long. Any delays longer than the sample period continued to generate a normal e_r.

The simulation thus indicates the System to both accommodate and explain the reversibility as a function of time of apparent tolerance to opiate analgesia. It also specifies that the delay since the discontinuation of chronic opiate treatment that is necessary for apparent tolerance to decay completely is equal to the System's sample period; it should thus be possible for experiments to empirically establish the System's sample period by identifying this delay. Furthermore, the lapses of time that are required in the left and right panels of fig. 7 for the magnitude of opiate analgesia to reach asymptote, are identical. This latter observation suggests that the time required to induce asymptotic tolerance is the same as that required for the tolerance to completely decay.

4. Dose-dose transposition. One definition of tolerance requires that the exposure to one particular dose causes the effect of that same dose to decrease. A second definition of tolerance requires that the exposure to one particular dose causes a shift to the right of the dose-effect curve. A third definition requires that a higher dose has become necessary to generate the same effect. The three definitions are widely accepted and considered to represent a single and same mechanism (e.g., Cox, 1990). However, for these different definitions to be caused by a single and same mechanism, it must be assumed that dose-dose transposition occurs. That is, it must be assumed that, when tolerance is produced by exposing the organism to one particular dose, this tolerance operates not only vis-à-vis the same dose, but also vis-à-vis other (i.e., lower and higher) doses, thus generating a shift to the right of the dose-effect curve. A large body of empirical data (e.g., Duttaroy and Yoburn, 1995; Stevens and Yaksh, 1989) indicates that such dose-dose transposition does effectively occur in experiments studying apparent tolerance to opiate analgesia; however, the mechanism whereby this transposition occurs has not so far been identified.

In the simulations that were carried out to this effect, a test stimulus (of 20 A.U. amplitude and lasting one unit of time) was administered in the absence as well as in the presence of test doses of the opiate that had a magnitude of either 3.5, 5 or 7 A.U. These tests occurred either immediately after a chronic opiate treatment or after no such treatment had been given (normal control). The chronic opiate treatment consisted of a dose of 5 A.U. that was administered during 40 time units, i.e. the lapse of time required for apparent tolerance to reach asymptote. In this manner, the simulations determined whether under the assumptions of System Theory, transposition of apparent tolerance would occur to test

doses that were smaller or higher (i.e., 3.5 and 7 A.U., respectively) than that (i.e., 5 A.U.) used to induce apparent tolerance.

The data that were thus generated (fig. 8) indicate that, after chronic treatment with a 5 A.U. dose, apparent tolerance not only developed to the same dose, but was also transposed to test doses that were either lower or higher. These results demonstrate the System Theory to generate dose-dose transposition of apparent tolerance, to accommodate the different definitions of tolerance and to identify the mechanism whereby apparent tolerance causes a shift to the right of the dose-effect curve.

5. Modes of induction. Some effects of some drugs (e.g., neophobia; see Goudie et al., 1976) occur on the first administration of the drug and rapidly dissipate thereafter. Some other effects appear only after the drug has been administered for a protracted period of time, and this regardless of the dose being used; examples to this effect are the decrease by β-adrenoceptor antagonists of peripheral vascular resistance (Man in't Veld et al., 1988) and the antidepressant activity of inhibitors of the neuronal uptake of NA and 5-HT (Baldessarini, 1990). It is a characteristic and complex feature, then, of apparent tolerance to opiate analgesia that it can be induced by widely varying modes and can develop in a dynamic manner. Specifically, empirical studies have indicated apparent tolerance to opiate analgesia to occur not only after prolonged exposure (such as by infusion or drug pellet implantation; e. g., Gold et al., 1994; Stevens and Yaksh, 1989) but also after intermittent dosing (e.g., Cochin and Kornetsky, 1964; Duttaroy and Yoburn, 1995) and after a single, acute administration (e.g., Cochin and Kornetsky, 1964; Cox et al., 1968).

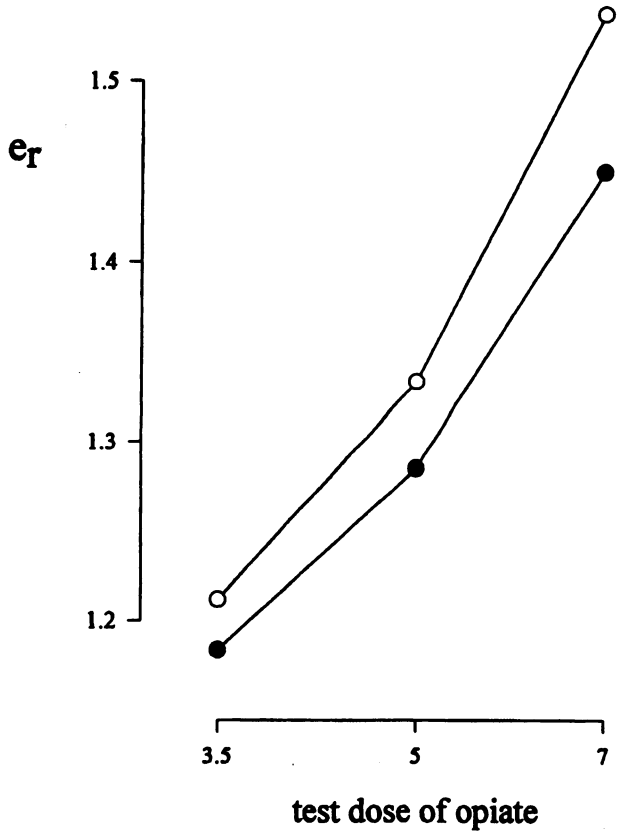

FIG. 8. Dose-dose transposition of apparent tolerance. Data points represent the results from computer simulations that determined whether System Theory can allow for dose-dose transposition of apparent tolerance to opiate analgesia. To this effect, the simulations assessed the magnitude e_r of the analgesia produced by test doses of an opiate that were equal to (i.e., 5 A.U.) or lower and higher than (i.e., 3.5 and 7 A.U.) the 5 A.U. dose that was used to induce apparent tolerance (closed symbols). Open symbols represent control data.

The simulations designed to this effect examined the magnitude e_r of the analgesia produced by an opiate test dose of 14 A.U. against a test stimulus of magnitude 20 A.U. Tests were carried out in control conditions (i.e., without previous exposure to the opiate) or after exposures that were either prolonged (during 40 time units), intermittent (five episodes of 5 time units that were spaced by 5 time units and during which the opiate was applied) or acute (a single episode lasting 5 time units); the opiate dose being applied was 10 A.U. throughout. The data (not shown) indicated the normal control magnitude e_r of analgesia again to be 3.33. Previous exposure to the opiate consistently produced tolerance, whether the exposure was prolonged, intermittent or acute (e_r was 2.27, 2.58 and 2.95, respectively).

The results thus demonstrate that System Theory can accommodate the empirical finding that apparent tolerance to opiate analgesia can be induced by widely differing modes of opiate drug administration. The data further suggest that apparent tolerance develops *during* the action that follows the very first administration of an opiate. As a consequence, it might perhaps prove impossible for any empirical experiment to directly assess with perfect accuracy the amplitude of analgesia produced by even a first opiate drug administration. Indeed, any drug dose that operates at one unit of time will act to distort the magnitude of the apparent analgesia that may be produced at the next time unit. A further difficulty for any empirical study attempting to address this issue is that we do not know at this stage the resolution of time[9] with which the relevant physiological systems operate.

6. Other features of apparent tolerance. System Theory also accommodates other features of apparent tolerance to opiate analgesia that have been demonstrated empirically. Thus, cross-tolerance to different opiate drugs (e.g., Cox, 1990) can be accommodated by System Theory by assuming that the action of opiates—whereby the opiate subtracts a portion of φ_α in the transduction to φ_o—is mediated by opiate receptors. This assumption of opiate receptor mediation of course is one that almost

[9] We here have not considered conditions in which opiates would be applied for a length of time that is shorter than the physiological resolution of time.

certainly must be made by any theory of opiate drug action. Obviously, the assumption explains why cross-tolerance can be observed with different opiates activating a same opiate receptor. The assumption also explains how opiate antagonists can prevent the development of apparent tolerance (e.g., Bhargava et al., 1994). This same assumption having been made, and having demonstrated how the System allows apparent tolerance to be dose- and time-dependent (fig. 7), it should further be obvious that System Theory also accommodates the finding that apparent tolerance to opiate analgesia is of similar magnitude when the inductive treatments are equivalent in acutely inducing analgesia (e.g., Duttaroy and Yoburn, 1995). That tolerance can be selective, vis-à-vis one as opposed to another type of opiate receptor (Cox, 1990) can be accounted for in different ways. One way is to assume that, within a single system, the same input φ_α can be transduced similarly by different receptor systems. Another is to assume that the same input φ_α feeds different, single-receptor systems that are arranged in a parallel manner, the outputs of which converge on a similar, second-order system that thus is arranged serially. Finally, evidence indicates that apparent tolerance to opiate analgesia can be conditioned (for review, see Siegel, 1989). Like any theory, System Theory can accommodate this feature by assuming that its operations are conditional on other stimulus events.

C. System Theory Beyond Opiate Analgesia

Up to this point, we have considered System Theory as it concerns the apparent tolerance that opiates can produce to their analgesic effects as the latter are assessed by behavioral experiments in whole organisms. In what follows, we will explore possible expansions of System Theory as it may concern opiate effects other than analgesic that also can be assessed in whole organisms.

1. Differential rate. In addition to analgesia, opiates in whole mammals produce a host of other effects, including so-called respiratory depression, sedation and constipation (Martin, 1984). Apparent tolerance reportedly develops to many, although perhaps not to all, of these effects, but then does so at rates that can differ considerably among those different effects (Bhargava et al., 1994; Fernandes et al., 1977b; Gold et al., 1994; Kayan et al., 1973; Ling et al., 1989; Pasternak, 1988). For example, in humans, apparent tolerance develops rapidly to the respiratory depressant (Fraser et al., 1957) and sedative effects of morphine (Eddy et al., 1957; Twycross, 1974), and more slowly to its emetic and antitussive effects (Eddy et al., 1957). For System Theory to account for the development of apparent tolerance to those various effects of opiates, it must account for these empirical, and unexplained, findings that indicate the rate of the development of apparent tolerance to differ among different effects.

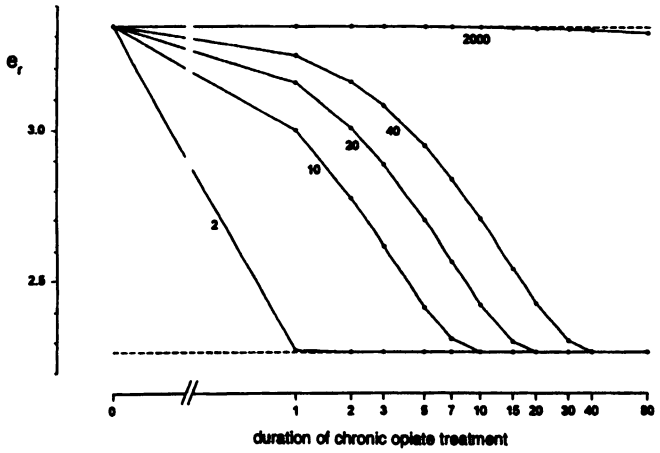

FIG. 9. Differential rate of the development of apparent tolerance to different physiological effects of opiates. The data derive from computer simulations in which different systems having different sample periods and governing different physiological functions that are coregulated by opiate receptors were similarly exposed to a previous opiate treatment that lasted zero time (0; normal control) or had a duration ranging from 1 to 80 time units. The lengths of sample periods varied from 2 to 2000 time units, as specified. Ordinate: magnitude e_r of the analgesic effect produced by a standard test dose of the opiate.

In simulations testing the ability of System Theory to generate differing rates of the development of apparent tolerance, the magnitude (e_r) of the effects of a test dose of 14 A.U. was assessed against a test stimulus of magnitude 20 A.U. The same test stimulus and the same opiate test dose were administered to five different systems that were also exposed, before these tests, to the same opiate treatment. The previous opiate treatment consisted of a 10 A.U. dose of opiate that was administered for lengths of time that ranged from 1 to 80 time units. Control tests were also run, i.e., in the absence of any previous opiate treatment. The five different systems, representing five different physiological systems[10] possessing opiate receptors, differed only in terms of their sample period; the different sample periods had a length of 2, 10, 20, 40 and 2000 time units. Except for the length of their sample period, the different systems were identical; specifically, in the computation of ι_r, the weight being accorded to values of φ_o decayed linearly in each system from 1.00 to 0.01 in the course of the sample period.

The data (fig. 9) indicate that, in the absence of any previous opiate treatment, the test dose of morphine produces an effect that is of the same magnitude for each of the five systems. The data also indicate that previous exposure to an opiate produces apparent tolerance in each of the five different systems. The maximal, i.e., asymptotic, magnitude of apparent tolerance that was

[10] The term *physiological system* is meant here to represent the physiological mechanisms that collectively regulate the relationship that exists between a particular adequate stimulus (e.g., the pH of arterial blood) and the response of a particular effector (e.g., minute volume of respiration).

produced also was the same for the different systems. Asymptotic tolerance was reached, however, after a duration of previous exposure that was equal to the sample period and hence differed among the systems; as a result, apparent tolerance effectively developed at differing rates. The data can also be taken to state that the same duration of previous exposure to the same opiate dose generates a degree of apparent tolerance that can vary from an apparent absence of tolerance to a tolerance that is asymptotic. The results thus demonstrate a manner in which empirical data can be highly misleading. For example, after an exposure of 2 time units, tolerance appears very marked and asymptotic in system 2, partial in system 10, and barely detectable in system 40; with system 2000, it will seem that no tolerance whatsoever developed.

System Theory thus can generate, and explain, data showing apparent tolerance to different effects of an opiate to develop at different rates. To render the System capable of generating differing rates, it has sufficed to simply assume that the physiological systems possessing opiate receptors operate with sample periods that differ. This assumption would seem reasonable; we know the whole organism to more readily survive prolonged disruptions of some such systems (e.g., gastrointestinal motility) than others (e.g., respiration). Note, though, that various other assumptions not discussed here can also generate different rates. An additional implication of these data is that System Theory accounts for yet another empirical feature of apparent tolerance, namely that this tolerance not only develops but also decays (e.g., Rauhala et al., 1995) at rates that differ for different opiate effects.

Current views of opiate tolerance hold that tolerance does not develop to some opiate receptor-mediated effects of opiates (e.g., behavioral stimulant effects: Babbini and Davis, 1972; Esposito and Kornetsky, 1978) and that the different rates at which tolerance develops to other effects result from mechanisms that differ (Abbott et al., 1981). The present simulations more parsimoniously suggest that apparent tolerance develops to all opiate effects that are mediated by opiate receptors, and this by a mechanism that is the same but evolves at different rates.

2. Opiate dependence. Drug dependence is said to occur when the normal functioning of an organism requires the prolonged administration of the drug; this requirement is evidenced by the disruption of function on discontinuation of drug administration or injection of an antagonist (e.g., Cox, 1990). In the different simulations discussed above in which apparent tolerance to opiate analgesia was produced, the System was challenged, after previous exposure to an opiate, with a 20 A.U. test stimulus, and this in the absence (yielding δ') and presence (yielding δ'') of a test dose of the opiate. The tests thus allowed one to obtain the e_r values that we have considered so far in examining apparent tolerance. In these various simulations, however, δ' consistently was larger than the normal control value at any point at which e_r was smaller (i.e., where apparent tolerance had been induced; see later in this section). These aberrant δ' values, reflecting hyperalgesia, are indicative of the System's normal function having been disrupted, and must therefore be taken as evidence of dependence. For higher-than-normal δ' values to reflect dependence is elegantly consistent with empirical evidence; in fact, hyperalgesia has been long identified and used as a measure of opiate dependence (Kayan et al., 1971; Kim et al., 1990; Tilson et al., 1973; Way et al., 1969; Wilcox et al., 1979), albeit that its mechanism has remained elusive (Kayan et al., 1971; Kim et al., 1990; Mao et al., 1995). Like other signs of opiate dependence, hyperalgesia appears either when opiate treatment is discontinued (Kayan et al., 1971; Tilson et al., 1973) or when an opiate antagonist is administered (Martin et al., 1987; Wilcox et al., 1979). We will undertake here to determine whether System Theory also can accommodate the phenomenon of opiate dependence and can explain its mechanisms.

Like apparent tolerance to opiate analgesia, opiate dependence is a function of both the dose and the duration of the opiate treatment that must be administered before tests if dependence is to be found; it also decays as a function of the delay since the discontinuation of the previous opiate treatment (Andrews and Himmelsbach, 1944; Bläsig et al., 1973; Cheney and Goldstein, 1971; Gold et al., 1994; Jaffe, 1980; Kim et al., 1990; Kolb and Himmelsbach, 1938; Tilson et al., 1973; Way et al., 1969). Data from the simulations discussed above (sections IV.B.1. to IV.B.3.) should allow one to determine whether System Theory can generate and explain these major, empirically established properties of opiate dependence. In parallel to figure 7, figure 10 reports the δ' values that were obtained in these simulations.

The normal (control) algesic response δ' to a test stimulus of φ_α magnitude 20 was 20.00 (fig. 10, center panel). Chronic opiate treatment at a dose of 5 A.U. caused δ' to increase (to 22.52 A.U.), and δ' increased further as an orderly function of dose at higher doses. Note that the shape of the dose-response curve that was thus generated suggests that the hyperalgesia induced by opiates can be extremely marked at high doses. Opiate treatment, at a dose of 10 A.U., during no more than a single unit of time, already caused δ' to increase (to 20.25 A.U.; fig. 10, left panel). As the duration of chronic opiate treatment was longer, δ' orderly increased to reach an asymptote, of 25.05 A.U., after a duration of 40 time units. This duration corresponds with the 40-time-unit sample period that was used in calculating ι_r; δ' then remained at this, asymptotic, value at any longer durations of exposure. When assayed immediately after the application during 40 time units of a 10 A.U. dose of opiate, δ' again was at 25.05 units (fig. 7, right panel). As the delay separating the test from the discontinuation of

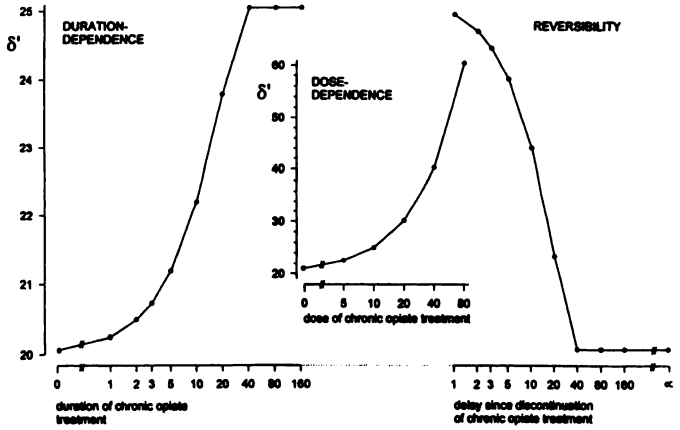

FIG. 10. Opiate dependence: effects of the dose and the duration of previous opiate treatment, and reversibility. Data points represent results obtained in the three series of computer simulations of experiments, the e_r data of which are presented in figure 7. Assuming that tolerance does not develop to opiates, and under the modalities of System Theory, the simulations determined the effects on the response δ′ to an acute nociceptive stimulus, of the dose (center panel; doses are expressed in A.U.) and of the duration (left panel; time being expressed in A.U. of time) of chronic opiate treatment. The simulations also examined the reversibility (right panel) of the effects of chronic opiate treatment on the response δ′ by varying the delay that separated the tests from the discontinuation of chronic opiate treatment.

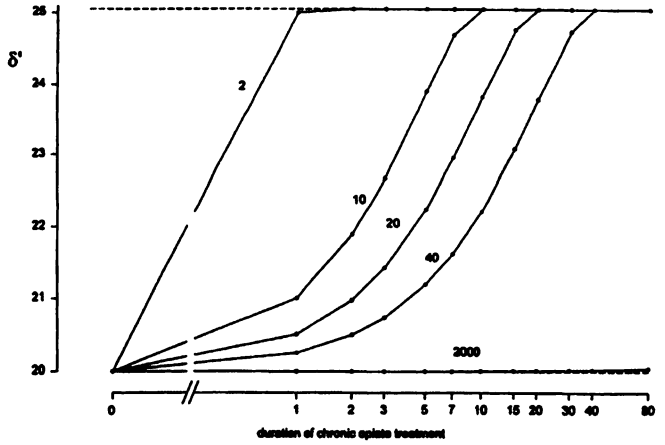

FIG. 11. Differential rate of the development of dependence with different signs of opiate abstinence. The data derive from computer simulations (see also fig. 9) in which different systems having different sample periods and governing different physiological functions that are coregulated by opiate receptors were similarly exposed to a previous opiate treatment that lasted zero time (0; normal control) or had a duration ranging from 1 to 80 time units. The lengths of sample periods varied from 2 to 2000 time units, as specified. Ordinate: magnitude δ′ of the response produced by a standard test stimulus.

chronic opiate treatment grew longer, δ′ orderly decreased to reach a normal, 20.00 A.U., value after a delay of 40 time units. Any longer delays continued to yield normal δ′ values. The simulation data thus demonstrate that System Theory can accommodate and explain the empirical findings cited earlier in this section indicating opiate dependence to be a function of the dose, of the duration, and of the delay since discontinuation, of the opiate treatment that induces dependence.

As with apparent tolerance, empirical studies have shown that opiate dependence can be induced by modes of opiate drug administration as diverse as prolonged, intermittent and acute administration (Bhargava et al., 1994; Gellert and Sparber, 1977; Gold et al., 1994; Kim et al., 1990; Kosersky et al., 1974; Way et al., 1969). The δ′ data obtained from the simulations described in section IV.B.5. indicate (not shown) System Theory to also accommodate these findings. Finally, and again, as with apparent tolerance, the opiate dependence that different physiological or behavioral functions may display has been shown by empirical studies to develop at rates that differ (Bhargava et al., 1994; Gold et al., 1994; Wei et al., 1973). The δ′ data (fig. 11) obtained from the simulations that also generated figure 9 indicate that System Theory accommodates these findings, too.

It thus appears that System Theory can accommodate, and explain, the major properties of opiate dependence that have been identified, albeit never so far explained, by empirical studies. Also, it has long been suggested that both apparent tolerance to and dependence on opiates result from a "common underlying process" (Way et al., 1969; see also Cox, 1990, p. 681); System Theory is the first theory to identify the common mechanism whereby apparent tolerance and dependence likely develop. System Theory also explains why apparent tolerance always occurs when opiate dependence is being induced (Collier, 1980; Gold et al., 1994; Kim et al., 1990; Way et al., 1969) and why the two developments coincide in time (Gellert and Holtzman, 1978). Unlike other accounts (Cox, 1990, p. 682), System Theory further suggests that any opiate treatment, however low its dose and however short its duration, induces dependence of all physiological systems, the regulation of which involves opiate receptors. The rate at which these dependencies develop can, however, be very different with different systems, and so is the magnitude of dependence at any point of time before asymptote is reached for all systems.

Yet another, so far unexplained, empirical finding that System Theory elucidates is that the manifestations of opiate dependence are opposite in sign to opiate effects in drug-naive organisms, misleadingly suggesting that two "opposing processes" (Kim et al., 1990; Koob and Bloom, 1988), "compensatory" (Siegel, 1989), or "opponent responses" (Goudie, 1990) are involved. In our simulations, System Theory made opiates generate both analgesia (e_r) and hyperalgesia (increased δ′) by a single set of mechanisms that can be directly inferred from the System's operation. The System appears to operate similarly in a wide array of other physiological functions, because further symptoms of opiate abstinence such as pupillary dilation, increased respiratory rate, diarrhea and dysphoria (Cheney and Goldstein, 1971; Martin and Eades, 1964; Ritzmann, 1981; Way et al., 1969; Wei et

al., 1973) are opposite in sign to the effects of opiates in drug-naive subjects (Martin, 1984).

It must be pointed out, however, that some authors have argued that analgesia, apparent tolerance and dependence with opiates are dissociated and are based on different mechanisms. Jacquet (1979) theorized that the analgesic effects of and dependence on opiates are mediated by different receptors (i.e., endorphin and adrenocorticotropic hormone (ACTH) receptors, respectively). The theory is based on findings that local injection of $ACTH_{1\text{-}24}$ into the rat midbrain periaquaeductal gray produces no analgesia but can cause signs (e.g., grooming) resembling those of opiate withdrawal. However, it is likely that when these are a consequence of opiate dependence, such signs as grooming occur far downstream of opiate receptor activation and can also be elicited by a variety of different other stimuli. To our knowledge, not a single sign that can occur as a consequence of opiate dependence is one that can be induced in this manner only, grooming being a case in point. Kaneto et al. (1985; see also Kaneto et al., 1973) propose different mechanisms for analgesia and for what was called acute and delayed tolerance on findings that an injection of naloxone prevented the acute (and part of the analgesic effects), but not the delayed, tolerance; however, the studies failed to determine the relative kinetics of the morphine and naloxone that were used. The same authors argue that opiate dependence requires yet another mechanism because the analgesic, but not the dependence-producing, effects of morphine were antagonized by naloxone. System Theory would argue here that the sample period of the systems mediating the withdrawal signs that were assayed in these studies and that did not include hyperalgesia may have differed from that of the pain response that was being monitored to measure analgesic effects. Johnson and Duggan (1984) dissociate tolerance from dependence because of findings in spinal dorsal horn neurons showing that dependent cells remain responsive to the depressant effect of morphine; however, these findings evidently follow the operational characteristics of System Theory. Wüster et al. (1982) obtained marked apparent tolerance but not dependence with opiates in the mouse vas deferens and guinea pig ileum, and speculated regarding different mechanisms (i.e., receptors and effector systems) to be involved. However, a seeming absence of dependence in empirical data might readily reflect problems of measurement (section V.E.). Finally, Kim et al. (1990) contend that different mechanisms may underlie the different signs of opiate withdrawal, because the signs are so varied and because they appear at different times after withdrawal. System Theory accounts for these contentions by considering that opiate receptors are located on a large variety of different physiological systems, the sample periods of which may differ.

3. Opiates and analgesia. Authoritative scientists (Cox, 1990; Fields et al., 1991; Herz, 1993; Martin, 1984; Pasternak, 1993; Reisine, 1995) hold the view that opiates produce analgesia and rightly contend that opiates continue to offer the most effective of available means to alleviate pain. However, the data that were generated by our simulations indicate that, just as reliably and robustly as they induce analgesia (by decreasing δ''; figs. 7, 9), opiates also induce hyperalgesia (i.e., increase δ'; figs. 10, 11). Therefore, for any scientific, albeit perhaps not practical, purpose, it is not entirely adequate to denote opiates as analgesics and to describe their action as analgesia. A less misleading description of their action is to state that opiates scramble the detection of nociceptive stimuli.

By the same token, it is also inappropriate to state, as is commonly being done, that opiates produce such actions as constipation, respiratory depression and euphoria; System Theory, supported by the empirical findings cited above, indicates that, with equal robustness, opiates also produce diarrhea, hyperventilation and dysphoria. There is to be no doubt that opiates are useful clinically in generating analgesic (Jaffe and Martin, 1990) and, also, antidiarrheal effects (Van Bever and Lal, 1976), and that the respiratory depression that opiates also produce (Martin, 1984) is of genuine concern in medical practice. However, the scientific understanding of opiates and organisms probably is not furthered by describing opiates as inducing analgesia, constipation and respiratory depression. System Theory accounts for the available empirical observations by stating that opiates scramble the detection of the exogenous (e.g., nociceptive) and endogenous (e.g., pH of arterial blood) stimuli by physiological functions (e.g., pain, respiration), the regulation of which is codetermined by opiate receptors. Furthermore, in the model that we have considered so far, opiates have scrambled the detection of pain as an indirect consequence of the equation: $\varphi_o = \varphi_\alpha - \mu$. It is perhaps interesting to point out, then, that some of the predictions that System Theory appropriately generates, can also be produced (not shown) when the following equation applies: $\varphi_o = \varphi_\alpha + \mu$ (where the opiate dose acts to add to, rather than subtract from, the physical stimulus).

4. Dependence and tolerance: incompatibility. We have so far found System Theory to establish a relationship between tolerance and dependence that accords with empirical findings. In so doing, a fundamental assumption that we have adhered to is that no pharmacological tolerance develops to opiates; specifically, we have assumed that no tolerance develops to the ability of opiates to subtract some value from the physical stimulus in its transduction to relevant physiological activity. This assumption has proven to be extremely powerful in generating the empirical features of apparent tolerance to and dependence on opiate compounds. It is, nonetheless, le-

gitimate to ask how the System would operate if tolerance to opiates would effectively develop.

In the simulation that was carried out for this purpose (fig. 12), the test stimulus of 20 A.U. magnitude in a normal organism caused a (normal control) δ' of 20.00; testing the same stimulus in the presence of the 14 A.U. test dose of opiate generated a δ'' of 6.00, e_r being 3.33. In an organism that, for 100 time units, was exposed to a chronic opiate treatment of magnitude 10, and *assuming that tolerance does not develop*, the test stimulus, as in previous simulations, caused a δ' of 25.05, indicating that dependence had developed. Testing, under similar conditions, the stimulus in the presence of a 14 A.U. test dose of opiate, and maintaining the assumption that the previous chronic opiate treatment also did not induce tolerance to this test dose, we again, as in previous simulations, obtain a δ'' of 11.05. The resulting ratio e_r of δ' to δ'' is 2.27; it is lower than the normal e_r of 3.33, indicating that apparent tolerance had developed. The same events were simulated again, but **while assuming** this time **that tolerance does develop to opiates**. To this end, a 10 A.U. chronic opiate treatment was again administered; tolerance was simulated by the linear decay of the effect of the chronically administered 10 A.U. dose from 10 to 0 in 10 time units. Testing the 20 A.U. test dose under these conditions yields a δ' of 20 that is normal and thus fails to reveal dependence. Maintaining the assumption that tolerance develops now signifies for the 14 A.U. test dose that its effects are also diminished by 10, so that its effect is now only of 14 − 10 = 4. Testing the 20 A.U. test stimulus in the presence of the 14 A.U. test dose, the effects of which are thus diminished, yields a δ'' of 16; e_r now is 1.25, appropriately indicating that tolerance had developed.

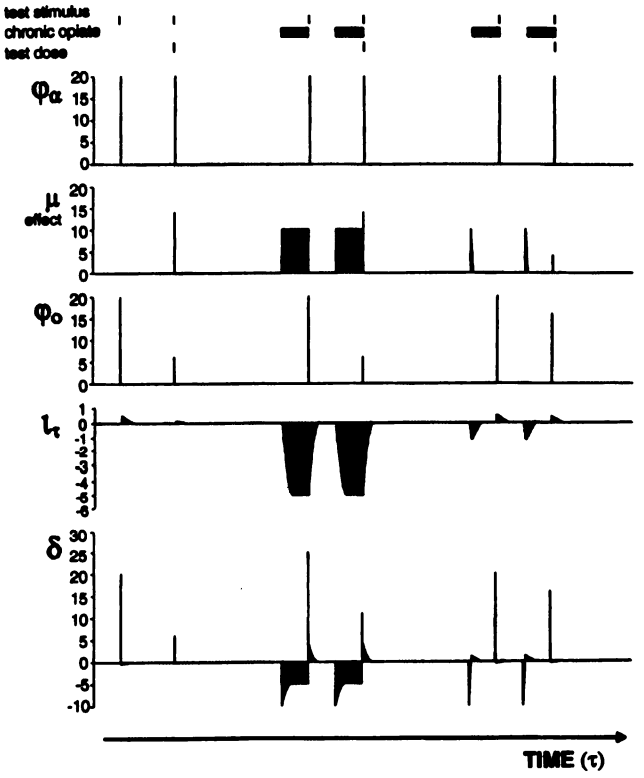

FIG. 12. Operating characteristics of System Theory assuming that tolerance either does or does not develop to opiates. The data derive from computer simulations in which a test stimulus was tested in the presence or absence of a fixed test dose of morphine, thus allowing pain sensitivity and opiate analgesia to be assessed. Tests were run in the absence (left panels) of any previous drug treatment, or after a chronic opiate treatment of 10 A.U. magnitude (center and right panels). In the center panel, it was assumed that tolerance does not develop to opiates, so that the magnitude of the effect of the opiate dose (μ effect) remained the same; the magnitude of the test dose also remained unchanged. In the right panel, it was assumed that tolerance does develop to opiates; as a consequence, the magnitude of the effect of the 10 A.U. dose that was applied chronically decayed from 10 to 0 in 10 units of time. Also, the magnitude of the 14 A.U. test dose that was administered subsequently, was decreased by 10 A.U. (i.e., to 4 A.U.).

It thus appears that, under the operational conditions of System Theory, the assumption that tolerance does develop to the primary action of opiates can adequately generate tolerance to opiate analgesia. However, the assumption fails to generate sustained hyperalgesia and, thus, dependence. Then, in fact, there is no apparent manner in which opiate dependence can occur. In contrast, the assumption that tolerance does not develop to the primary action of opiates appropriately generates hyperalgesia, dependence on the opiate as well as apparent tolerance to its analgesic effects. The System's operation in fact specifies that *dependence developed because tolerance did not*. That is, in our System, an opiate acts to lower ι_τ, and ι_τ can only remain lowered if the opiate's lowering effect is maintained as the treatment is prolonged. The δ' that is enhanced after chronic opiate treatment is larger because the ι_τ in the equation $\delta = \varphi_o - \iota_\tau$ is lower, and not because of any change in φ_o, which remains the same. We therefore conclude that opiate dependence cannot exist if tolerance develops, and that the opiate dependence that, in fact, does exist can develop only because tolerance does not.

As pointed out elsewhere (Colpaert and Shearman, 1988), an eloquent empirical reflection of the fundamental incompatibility between dependence and tolerance seems to be offered by the observation in dependent animals that abstinence symptoms do not occur as long as the opiate maintenance treatment is maintained (Deneau and Seevers, 1964; Gellert and Holtzman, 1978). The observation implies that the maintenance treatment prevents withdrawal symptoms, a prevention that results from a highly specific, stereoselective and naloxone-sensitive opiate action that continues apparently unabated for any length of time that the treatment is maintained. In a careful study (Kreek, 1987) of patients maintained on a single daily methadone dose, no tolerance developed to the ability of this dose to prevent withdrawal. Yet, when the dose was abruptly reduced, a broad spectrum of withdrawal signs appeared.

5. New treatment modalities. In System Theory, transduction of a nociceptive stimulation occurs so that $\varphi_o = \varphi_\alpha - \mu$; φ_o then both feeds ι_τ and gives rise to the sensing of stimulation using the equation $\delta = \varphi_o - \iota_\tau$. One pharmacological intervention whereby analgesia can occur is by detracting from φ_α, as we postulate opiates do *acutely* at the level of transduction. We now know that, in mismatching conditions, the analgesia that is thus produced dissipates as a function of both time and dose (i.e., that apparent tolerance develops) and that, because of inertia, it is difficult in whole organisms to assemble perfect matches. As suggested elsewhere (Colpaert, 1978b), another, theoretical, possibility for the treatment of pain is to **chronically enhance** ι_τ so that δ' is lowered. Because ι_τ depends on φ_o, this could be achieved by a pharmacological agent that mimicks the nociceptive stimulation φ_α, thus acting to enhance φ_o using the equation $\varphi_o = \varphi_\alpha - \mu$. Inasmuch as substance P constitutes a neurotransmitter for primary nociceptive afferents (Budai and Larson, 1996; Ding et al., 1995; Henry, 1976; Hökfelt et al., 1975; Lembeck and Zetler, 1962; Liu and Sandkühler, 1995; Pernow, 1983), the agent would be a **substance P** or neurokinin (NK) **receptor agonist**[11].

In a further simulation (fig. 13), we have examined the effects of administering a substance P receptor agonist while assuming that tolerance does not develop to these agents, either. The simulation repeatedly established the response δ' to a test stimulus of magnitude 20.00. In the absence of pharmacological treatment, the test stimulus caused a δ' of 20 as shown (fig. 13). Treatment was then instituted at an initial dose that was low (i.e., of 5 A.U.); this low level was chosen because, at the earliest time units at which any such agent is applied initially, it should itself cause a pain that we in the simulation did not wish to be intense.

The 5 A.U. dose was maintained for 100 time units, thus allowing ι_τ ample time to increase and, after 40 time units, to in fact reach asymptote. At this point, the test stimulus caused a δ' that no longer was 20.00, but was a lower value (i.e., 17.47 A.U.). The dose of the chronically administered substance P receptor agonist was then increased stepwise (i.e., to 7, 10, 14 and 20 A.U., respectively) and caused δ' to decrease as an orderly function of this dose. The simulation thus suggests that chronic treatment with substance P receptor agonists causes dose-dependent analgesic effects. Although such agents may themselves be algesic, the strategy of progressively increasing doses should make it possible for them to generate analgesia without the agent itself causing significant pain, the latter being defined as by the dotted line in figure 13 (lower panel); System Theory here can rely on empirical findings. Indeed, it has long been demonstrated (Frederickson et al., 1978; Pernow, 1983) that substance P and other NK receptors agonists can produce analgesia, albeit this finding has been left unexplained (Levine et al., 1993; Pernow, 1983). The present account (see also Colpaert, 1978b) elucidates this observation and suggests a new avenue for the treatment of pain.

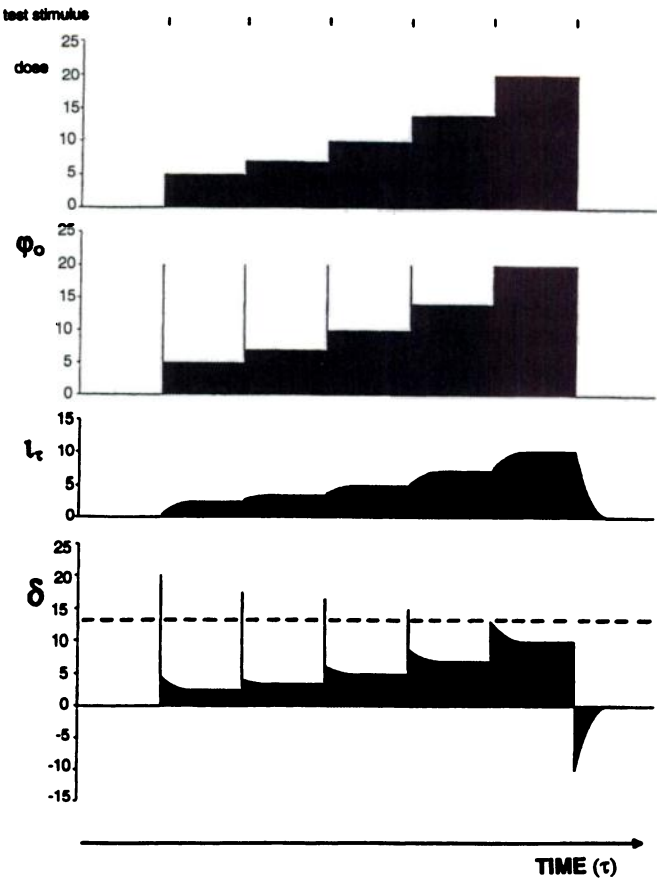

FIG. 13. Effects on pain sensitivity of the chronic administration at incremental doses of a substance P receptor agonist. Data were derived from a computer simulation that tested the pain response δ to a standard test stimulus. Tests were conducted after episodes lasting 100 time units and during which the dose being administered of a hypothetical substance P receptor agonist was incremented from 5 to 20 A.U. The dotted, horizontal, line in the lower panel identifies the critical value of δ, i.e., the threshold value above which δ is associated with substantial pain.

The suggestion, by System Theory, that nociceptive stimulation or agents mimicking its effects can cause analgesia, raises a further issue. The theory indeed suggests that monotonously maintained stimulation causes a pain that initially is large but then at least partly decays (figs. 2, 13). This would imply that, in the presence of a constant nociceptive stimulation, chronic pain cannot exist (if by "chronic pain" one means a pain that remains of a same intensity through time). It is interesting, then, that clinical pains of diverse etiologies demonstrate (e.g., Bruera et al., 1992; Folkard et al., 1976; Pollen and Schmidt, 1979) variations as a function of time that cannot readily be attributed (Strian et al.,

[11] This proposition is, of course, paradoxical to the considerable research efforts that are currently being undertaken to define substance P receptor antagonists for pain relief (e.g., Yashpal et al., 1995).

1989) to the small diurnal variations in pain perception that also can be observed in healthy volunteers.

Another, theoretical, manner in which ι_τ chronically can be enhanced is by pharmacological agents, the action of which would be the inverse of the action of opiates. Opiates act as agonists at opiate receptors; the pharmacological agents being proposed here would be **inverse opiate agonists**. In the equation $\varphi_o = \varphi_\alpha - \mu$, the dose μ_i of an inverse opiate agonist carries a negative sign so that $\varphi_o = \varphi_\alpha - (-\mu_i) = \varphi_\alpha + \mu_i$. The inverse opiate agonist[12] thus would act to dose-dependently increase φ_o and, also, ι_τ. However, and in contrast to those of a substance P agonist, the effects of an inverse opiate agonist are, in our System at least, additive to any existing activity φ_α.

Thus, if the inverse opiate agonist continues to be present at the (poorly predictable) time of nociceptive stimulation, then it would act to restore the response δ' to this stimulation and make the System fail to take advantage of the increased ι_τ[13]. Inverse opiate agonists would nonetheless increase ι_τ and counteract whatever opiate dependence (i.e., supernormal δ') that previously had been installed by opiate agonists. Substance P receptor agonists would act similarly, but then only in those physiological systems (such as the pain system) where substance P acts as a neurotransmitter. The inverse opiate agonists would have the unique property of being able to increase ι_τ for all the physiological systems that are coregulated by opiate receptors and therefore can be rendered opiate-dependent.

In conclusion, two de novo treatment modalities are being proposed for future research to realize and examine. One is the chronic administration, in incremental doses, of agonists at substance P receptors, for the treatment of recurrent pains. The pains being targeted most particularly are those that are associated with rheumatoid arthritis; the empirical studies that have most importantly verified our theoretical positions have indeed been carried out in the rat with adjuvant polyarthritis (section III.). A second treatment modality is the chronic administration, also in incremental doses, of inverse opiate agonists for the treatment of opiate dependence.

D. System Theory Beyond Whole Organisms

Putative tolerance to opiates was initially observed using noninvasive techniques in humans (Light et al., 1930; Rossbach, 1880), and its very definition (e.g., Cox, 1990) and properties (section IV.B.) were similarly derived from observations in whole organisms. It appears from the preceding sections that System Theory offers a uniquely parsimonious and coherent explanation of the many features that define and have been found empirically to characterize apparent tolerance to, and also dependence on, opiates in whole organisms.

Whereas System Theory would operate thus at the highly integrated level of whole organisms, other research has sought and identified the features of tolerance and dependence at less-integrated, higher-resolution levels of analysis. Specifically, several of these features also can be observed in such cell assemblies as the myenteric plexus of the guinea pig ileum, in individual neurons in situ as well as in cultured cells, and with second-messenger systems (see Collier, 1980). Studies at these levels have naturally generated numerous hypotheses concerning the putative mechanisms of the dependence and presumed tolerance that occur in whole organisms. Among these hypotheses (for excellent, comprehensive reviews see Cox, 1990; Johnson and Fleming, 1989; Nestler, 1992) are (*a*) receptor down-regulation and reconfiguration, (*b*) receptor sensitization and desensitization, (*c*) uncoupling of receptors from G proteins, (*d*) chronic partial depolarization, (*e*) changes in gene expression and (*f*) altered responsivity to neurotransmitters (Clouet and Iwatsubo, 1975; Cox and Werling, 1991; Hughes and Dragunow, 1995; Koob and Bloom, 1988; Redmond and Krystal, 1984; Takemori, 1975; Trujillo and Akil, 1991). Although these hypotheses have had the important merit of stimulating a most considerable research effort, the putative cellular and molecular mechanisms of opiate tolerance, and dependence, remain poorly understood (Collin and Cesselin, 1991; Cox, 1990; Ménard et al., 1995; Rauhala et al., 1995; Stanfa et al., 1994). However, and as with most other opiate research, the studies at these levels have been guided by the fundamental notion that tolerance develops to opiates and have attempted to identify the changes that should make this tolerance possible. These changes, however poorly defined to date (Koob and Bloom, 1988), are generally thought to represent adaptive, or "homeostatic," changes in the function of effector systems (Collin and Cesselin, 1991; Cox, 1990; Cox and Werling, 1991; Johnson and Fleming, 1989; Takemori, 1975; Trujillo and Akil, 1991). However, if, as we argue, tolerance to opiates does not develop, then it becomes understandable why these adaptive cellular and molecular changes have remained elusive[14]. Indeed, perhaps no such changes exist, and System Theory may operate instead. In what follows, we will briefly discuss some findings, relating to opiate analgesia, that suggest System Theory may also operate at these higher-resolution levels of analysis.

It is generally accepted that opiates exert their analgesic effects by interacting with opiate receptors (i.e., μ-, κ- and δ-receptors; Reisine, 1995) for which endogenous

[12] Inverse μ opiate agonists have never so far been described and may not currently exist. However, inverse agonists have been described at other receptors (Milligan et al., 1995), including ICI 174864, a putative inverse agonist at δ opiate receptors (Costa and Herz, 1989; Costa et al., 1990).

[13] Indeed, the temporal dynamics of the analgesia produced by inverse opiate agonists in inert systems would be similar to those of the hyperalgesia produced by opiates.

[14] For an eloquent example, see Johnson and Duggan, 1984.

peptide ligands exist (i.e., the enkephalins, dynorphins and endorphins; Herz, 1993). These receptors are located on neuronal cell membranes of the peripheral, spinal and brain systems that control nociception (Besson and Chaouch, 1987; Fields and Basbaum, 1994; Melzack and Wall, 1965). Although opiates may also interact with the descending, modulatory systems that originate in the brain (Fields and Basbaum, 1994; Melzack and Wall, 1965) and with an ascending spino-supraspinal pathway (Gear and Levine, 1995), their action on dorsal horn neurons (Le Bars et al., 1976a, 1976b) constitutes a most likely and now extensively documented (Duggan and North, 1984; Haigler, 1987), electrophysiologically defined mechanism of the powerful analgesia (Yaksh and Rudy, 1977; Yaksh and Noueihed, 1985) that opiates can produce by a spinal mechanism. Indeed, the spinal dorsal horn is where the first synapse is located in the transmission of nociceptive information from the peripheral to the central nervous system.

One key assumption that is being made by System Theory, then, is that opiates act indiscriminately; the (inhibitory) effect of morphine on the transduction of φ_α is the same, regardless of whether the φ_α represents an experimenter-controlled stimulus or normally ongoing, so-called background activity (fig. 1). The operation, in spinal dorsal horn neurons, of System Theory would thus require opiates to depress not only their excitation induced by impulses in primary afferents, but also their spontaneous activity. Electrophysiological evidence suggests this to be the case; Kitahata et al. (1974) found intravenous morphine to inhibit the spontaneous firing of (laminar I and V) cat dorsal horn neurons, this inhibition being antagonized by naloxone (Toyooka et al., 1977). Also, intravenous morphine also inhibits the excitation of dorsal horn neurons by electrical stimulation of slowly conducting (Aδ and C) fibers, this effect again being antagonized by naloxone (Le Bars et al., 1976a, b; Woolf and Wall, 1986; Zieglgänsberger and Bayerl, 1976). Furthermore, in keeping with the relationship that System Theory specifies between apparent tolerance and dependence, naloxone, when given in these experiments after the intravenous morphine injection, increased firing to greater-than-spontaneous levels (Le Bars et al., 1976a), indicating hyperresponsiveness (i.e., enhanced δ'; see also Rohde et al., 1996). Similar depressions of both stimulus-evoked and spontaneous firing rate have been demonstrated with endogenous opiate peptides as well as with micropipette delivery of the compounds near the cell bodies of dorsal horn neurons (Duggan et al., 1977; Randic and Miletic, 1978; Satoh et al., 1979). Spinal dorsal horn neurons can also display opiate dependence as measured by their hyperresponsiveness after withdrawal, and, importantly, this dependence occurs while the neurons remain responsive to morphine's depressant action (Johnson and Duggan, 1984). The current evidence obtained from extracellular and intracellular recordings (Duggan and North, 1984) suggest these opiate effects to represent a direct action on the cell in which activity is being recorded. The inhibition by morphine both of the response to nociceptive stimulation and of spontaneous activity also occurs in the locus ceruleus (Aghajanian and Wang, 1986; Korf et al., 1974) as well as in other brain areas (Duggan and North, 1984; Haigler, 1987). System Theory further specifies that opiates initially decrease δ, but should induce hyperexcitability thereafter (figs. 2 and 10). Electrophysiological recordings do indeed indicate (Haigler, 1987) the typical response to morphine in different areas of the brain to consist of an initial decrease in spontaneous firing with a gradual recovery and hyperexcitability. The hyperexcitability occurs both with single neurons (Fry et al., 1980; Haigler, 1987) and with cell assemblies mediating polysynaptic reflexes (Goldfarb et al., 1978). Finally, System Theory specifies that when levels of adequate stimulation are high, opiates should generate apparent effects that are larger than they are otherwise (inverse apparent tolerance). As indicated above (section III.B.), the spontaneous firing of spinal dorsal horn neurons is enhanced in rats with adjuvant arthritis; morphine more powerfully depresses this firing when primary afferent fibers are left intact than after deafferentation (Lombard and Besson, 1989a).

Furthermore, System Theory defines several entities (i.e., φ_o, ι_τ and δ) that each respond both to adequate stimuli and to morphine, but that do so in different manners. It is legitimate to ask whether subcellular, molecular entities can be identified whose characteristics in responding to stimuli and opiates resemble those of these System Theory entities. It is a key characteristic of φ_o and δ, then, that their response to an opiate never changes[15]; in the transduction equation $\varphi_o = \varphi_\alpha - \mu$, the influence of μ on φ_o never fades because it is assumed that tolerance does not develop to opiates. Molecular entities thus may exist whose response to morphine never changes, regardless of whether the entity has or has not been exposed previously to morphine. Our analysis of the available evidence suggests adenylate cyclase may resemble φ_o or δ. Opiates inhibit adenylate cyclase, and decrease cyclic adenosine monophosphate levels, in homogenates of brain (Collier and Roy, 1974) and in cultured neuroblastoma × glioma hybrid cells (Collier, 1980; Sharma et al., 1975; Traber et al., 1975). In membranes prepared from rat locus ceruleus cells, acute morphine decreased the activity of adenylate cyclase to the same extent, regardless of whether the animals had been exposed or not to a previous, chronic, opiate treatment that produced dependence (Beitner et al., 1989; Duman et al., 1988); thus, previous treatment did not detract from the ability of morphine to inhibit adenylate cyclase activity. After previous chronic opiate treatment,

[15] This is true for δ if the opiate effect is expressed as e_s, not if it is expressed as e_r (table 1).

basal[16] adenylate cyclase activity was enhanced. System Theory does not specifically predict, nor explain, that φ_o should increase after chronic treatment, but it does specify such an increase for δ (see fig. 2).

The response characteristics of ι_τ are most peculiar. Like φ_o and δ, ι_τ can respond quickly to stimulation, but, depending on the sample period, its response cannot quickly disappear; with constant, prolonged stimulation, its response reaches asymptote well after the onset of the stimulation, and the response persists long after the adequate stimulus is discontinued (fig. 2). Also, morphine can prevent the occurrence of an ι_τ response to an adequate stimulus (fig. 3), but cannot acutely break the response down once it has been established. Second-messenger systems activate protein kinases that in turn phosphorylate neuronal proteins (e.g., Bronstein et al., 1993); the protein phosphorylation is short-lived, its lifespan being limited by neuronal phosphatases to no more than minutes (Cohen, 1992). Whereas, as discussed earlier in this section, these systems have response characteristics that may perhaps fit those of φ_o or δ, they possibly may not fully account for those of ι_τ that empirical evidence would suggest to operate with sample periods of hours, possibly months. Immediate-early genes may more likely mediate responses that reach their peak late after the onset of stimulation and last longer than minutes (for review, see Hughes and Dragunow, 1995). It is interesting, then, that c-Fos expression in spinal dorsal horn neurons possesses several of the characteristic response features of ι_τ. That is, dorsal horn c-Fos expression is enhanced by acute, peripheral, nociceptive stimulation, and this response can be prevented by morphine (Tolle et al., 1990). The rise in dorsal horn c-Fos expression that occurs in arthritic rats (Abbadie and Besson, 1992) parallels the chronic pain (Colpaert, 1987) and reaches its peak well after the onset of this pain; it then decays, and, as discussed above (section III.A.), this decay would appear to be delayed relative to that of the chronic pain. As in normal rats (Tolle et al., 1990), morphine in arthritic rats attenuates the acute rise in dorsal horn c-Fos expression that can be produced by a superimposed, acute, nociceptive stimulation (Abbadie and Besson, 1993); also, acutely administered morphine does not depress the enhanced dorsal horn c-Fos expression once it is established as the likely consequence of persistent nociceptive stimulation (Abbadie and Besson, 1993). For further research, it would be interesting to determine, with higher temporal resolution, the decay of enhanced dorsal horn c-Fos expression in arthritic rats and, also, whether chronic morphine can depress this expression in normal rats[17] and in animals in which arthritis is being established. Also, it would be very interesting to determine whether enhanced c-Fos expression can in some manner act to decrease basal adenylate cyclase activity.

In conclusion of this section, the characteristic features of apparent tolerance occur not only in whole organisms, but also with cell assemblies and single neurons; System Theory thus seems also to operate at these less-integrated, higher-resolution levels of analysis. One well documented instance to this effect is the actions of opiates on the firing rate of spinal dorsal horn neurons. At the subcellular level, it would seem that entities exist that may similarly reflect the operation of defined parameters of System Theory. The failure of previous opiate treatment to diminish morphine's ability to decrease adenylate cyclase activity in membranes prepared from locus ceruleus neurons makes adenylate cyclase resemble δ; also, remarkable similarities exist between the response characteristics of c-Fos expression in spinal dorsal horn neurons, and the peculiar, highly characteristic, response features of ι_τ. Therefore, although System Theory perhaps also may apply at the molecular level of analysis, further work is required to more specifically identify the corresponding molecular entities.

Inasmuch as spinal dorsal horn neurons may constitute the initial site of impact for opiates in producing spinal analgesia (Besson et al., 1978; Besson and Chaouch, 1987; Duggan and North, 1984; Le Bars et al., 1976a, 1976b), it is not certain that any subcellular entity will ever be identified at the spinal level that can account for durations of apparent tolerance to opiate analgesia that, even after a single morphine dose, can be of more than 1 year (Cochin and Kornetsky, 1964). This difficulty can be overcome, however, if System Theory would effectively operate, as the present section suggests it may, at different levels of the integration of information and by assuming that its operation at these different levels is arranged in a serial configuration. Thus, the outcome δ generated by a, first, System Theory system (STs) that operates at the level of primary afferent neurons and has a short sample period, would serve as the adequate stimulus φ_α to a second STs that operates at the level of a spinal dorsal horn cell assembly and has a longer sample period. This serial arrangement could exist in several layers until an n^{th} STs is reached that operates at the most integrated level of whole organisms and operates with the very long sample periods that are required to account for the 1 year or longer that apparent tolerance to opiate analgesia can last.

V. Further Issues

A. Opiate Addiction

Addiction to opiates has proven difficult to understand and even more difficult to treat effectively (Jaffe, 1980). System Theory sheds light on opiate addiction that may help one to grasp the immensity of the problem; specif-

[16] These studies use the wording "basal" for an adenylate cyclase activity that is measured in the absence of opiate compound, but is nonetheless stimulated (e.g., by forskolin).

[17] This possible depression may prove difficult to obtain experimentally because basal levels of spinal dorsal horn c-Fos expression are low.

ically, three notions may concur so as to make addiction virtually inaccessible to existing treatments.

The first is that, just as robustly and reliably as opiates produce one effect (i.e., decrease δ'' so that δ'' is smaller than δ'), they also produce the paradoxical effect (i.e., increase δ'; section IV.C.2.). In acting upon the physiological system of nociception, these opiate effects are empirically apparent as analgesia and hyperalgesia, respectively. Opiates are widely recognized to produce an analgesia that is said to be profound; however, the data in figure 10 (center panel) suggest the magnitude of the paradoxical effect can also be very large. Other than acting upon the physiological systems of nociception, opiates also act upon the physiological systems of reward and are thought to (in that manner) produce euphoria (for review, see Koob and Bloom, 1988). System Theory would hence indicate that opiates produce dysphoria just as reliably[18] as they produce euphoria, and that this dysphoria can be extremely large.

A second point to be made is that, although in different physiological systems the "first order" effect (i.e., decrease of δ'') of a given opiate dose occurs in the same instant and with the same amplitude (fig. 9), the time necessary to obtain the "second order," paradoxical, effect (i.e., increase of δ') may differ greatly among systems (fig. 11). This is because the sample period with which the different systems operate may differ. It follows that, while both analgesia and euphoria may occur early upon the administration of the opiate and be very marked, asymptotic dysphoria may require much more time to develop. Dysphoria might thus arise insidiously; its growth rate can be so small as to be barely noticeable, providing little opportunity for any early, warning signs to become apparent.

The third notion derives from the unique role that System Theory, through ι_τ, accords to time. The effects of any variable (e.g., φ_α, μ) that through φ_o can influence ι_τ, will always be unstable for a subsequent period of time, the duration of which is equal to ι_τ's sample period. Thus, no other known intervention can substitute for the mere passage of time; unlike any previous account of putative tolerance to and dependence on opiates (Cox, 1990; Johnson and Fleming, 1989) or of pain processing (Besson and Chaouch, 1987; Fields and Basbaum, 1994; Melzack and Wall, 1965), System Theory identifies time as an independent variable in its own right; also, this time, as indicated earlier in this section, can be long. Let us take system 2000 in figure 11 as a model for the physiological system mediating reward. The system's immediate response to an opiate will be euphoria, but to paradoxically build asymptotic dysphoria in this system would require much time. However, once built, only the passage of much time can act to make the dysphoria decay. Also, to suffer from dysphoria, even as it slowly decays, for such a long period of time might be just as difficult as it is to suffer, for example, from an oncological pain, the intensity of which can only be matched by the "profound" analgesia that high-efficacy opiates can also produce. Of course, the administration of an opiate at this stage, assuming as we do that tolerance does not develop to opiates, will act to decrease δ'' and thus offer a brief relief from the dysphoria. However it will also act to reset the timer that ticks off the decay of the dysphoria that persists.

System Theory thus portrays the addiction to opiates as a consequence of the dysphoria that opiates produce just as reliably as they produce euphoria. The dysphoria occurs within a time frame that is much unlike that with which such other opiate effects as analgesia and, also, euphoria are apparent. The dysphoria develops insidiously but can reach a very large magnitude. At that stage, only the mere passage of time, a long time during which the subject suffers from very severe distress (Wikler, 1973), can make the addiction decay. Time not being compressible, it is not surprising that the treatment of addiction to opiates remains essentially inaccessible to date. Note, however, that the inverse opiate agonists portrayed in section IV.C.5. would act to, in effect, compress time.

B. Opiate State

It is a characteristic feature of current accounts of putative tolerance to and dependence on opiates that they express the apparently firm belief that, in some way or other, the changes that are involved must serve some so-called adaptive or homeostatic purpose. This is especially the case with cellular and molecular accounts (e.g., Ammer and Schulz, 1996; Collin and Cesselin, 1991; Cox, 1990; Cox and Werling, 1991; Johnson and Fleming, 1989; Nestler, 1992; Takemori, 1975; Trujillo and Akil, 1991), although Koob and Bloom (1988) note that these adaptive changes and purposes remain poorly defined. Similarly, behavioral accounts (Goudie, 1990; Siegel, 1989, 1990) propose that adaptation and homeostasis are achieved by the organism's learning of so-called compensatory, or opponent, responses (e.g., hyperthermia) that presumably counterbalance the direct effects of opiates (e.g., hypothermia). In our account so far, there is no perspective of adaptation or homeostasis. Opiates are held to bind to opiate receptors and to exert an action, their primary action, to which tolerance does not develop. For the physiological system(s) that possess opiate receptors, the primary opiate action essentially acts to scramble the system's input; it both decreases δ'' and increases δ'. The effects and processes that follow this initial impact give rise to apparent tolerance and to genuine dependence; with the passage of time, and all other factors remaining equal, the system returns to its original position. From these operations of a single STs, there is little reason to ascribe any adaptive or homeostatic quality to System Theory. This might be all the more worrying, because endogenous ligands exist for

[18] For data to this effect in humans, see Bickel et al., 1988.

and act upon opiate receptors (Herz, 1993). However, the following points shed an interesting light on the downstream consequences of System Theory.

One is that within a single STs, an opiate acts, indirectly, to change the relationship between the adequate stimulus φ_α that serves as the input to the system, and the outcome δ that constitutes the system's output or response (i.e., the stimulus-response (S-R) relationship). Indeed, the sustained[19] administration of (a particular dose of) the opiate defines an S-R relationship that is different from the normal relationship and rather unique; there is, in fact, at this point no readily conceivable way whereby this particular S-R relationship can be reconstructed through the manipulation of independent variables other than opiates.

A second point is that, systemically administered, opiates interact with not just one STs, but with a large number of such systems that are coregulated by opiate receptors and govern such diverse physiological functions as nociception, respiration, gastrointestinal motility, vision, skeletal muscle tone, reward, and many others (Martin, 1984). Thus, opiates can act to redefine a new and particular S-R relationship with each of these many and important physiological functions; they do so with a particular set of functions, that is, with those systems that are coregulated by opiate receptors.

A third point is that, in interacting with their environment, whole organisms learn about and respond to this environment through the use of various sensory and motor systems; at least some and probably several of those physiological systems that are being mobilized in any condition are coregulated by opiate receptors. For example, when a food-deprived rat learns to press an operant lever to obtain food pellets, a coordinated assembly is to be constructed de novo between such opiate coregulated physiological systems as those that govern vision, reward and skeletal muscle tone. When carried out under conditions of opiate receptor activation, the assembly that is thus constructed is largely unique because it, for some, and possibly considerable part, uses a set of systems, the S-R relationships of which are peculiar and definitely different from their normal definition. Under opiate receptor activation, assemblies can thus be constructed that apply exclusively while opiate receptors are being activated. Once constructed, these assemblies might not even be available for recall in the absence of receptor activation, if only because the sensory systems involved can no longer generate the same output δ as that which prevailed during acquisition. The theoretical possibility thus arises that, after systemic opiate administration or mobilization of endogenous opiate systems, whole organisms construct acquired assemblies that are unique to this opiate state.

This latter possibility, in fact, is more than merely theoretical. Both physiological and behavioral studies have demonstrated the existence of a phenomenon that is currently referred to as state-dependence (e.g., Overton, 1974). That is, when an organism acquires some response (i.e., establishes de novo some S-R relationship at the whole organism level) while under the influence of some drug, it may appear that the recall of this response (specifically: the execution of this S-R relationship) is hampered, partially or completely, when the organism is in a different (e.g., the so-called normal) state. State-dependency can occur for different S-R relationships; it also can occur with different, exogenously administered, drugs and, also, with endogenous mediators. It also has been demonstrated with opiates (Belleville, 1964).

Therefore, it would seem that the (temporary) activation of opiate receptors can generate an opiate state that allows an organism to establish unique S-R relationships in interacting with its environment; the S-R relationships that are in this manner established apply only when opiate receptors are being activated again. It is in this notion of the opiate state that arguably can reside the "adaptiveness" of the primary action of opiates and of its downstream effects. That is, the occurrence and recurrence of opiate, and other, states throughout ontogeny allows the organism to learn about, and subsequently deploy, S-R relationships that are appropriate in particular conditions[20] only, the same S-R relationships being less appropriate under other conditions. In this rather astonishing, imaginative manner, state dependence would allow an organism to vastly multiply the capacity that it has available to learn and to deploy, but also to contain, the results of experience.

The above, highly speculative, reasoning meets with at least two concerns. One is that the opiate state can only operate as suggested if no tolerance develops to the ability of opiates to create, and recreate, the opiate state. Ongoing experiments (Bruins et al., unpublished) indicate that operant lever pressing for food in rats can be rendered dependent on the morphine state; using procedures used previously with benzodiazepines (Colpaert, 1990), the experiments also indicate that tolerance does not develop to morphine's ability to create, and recreate, the state upon which this acquired response was rendered dependent. These latter findings are, of course, consistent with our more general assumption that tolerance does not develop to opiates. A second concern is that, whereas learning and memory are recognized to interfere with pain perception (e.g., Waschulewski et al., 1994), it is unusual to invoke learning and memory with several other of the physiological systems that are coregulated by opiate receptors, respiration being a case in point. However, the effect that opiates exert on respiratory function is not simply to depress respiration; opi-

[19] By *sustained* is meant for a period of time long enough to cover the System's sample period.

[20] Such as, perhaps, chronic pain (see Lombard and Besson, 1989b).

ates decrease the ventilatory response to the enhanced acidity of arterial blood, such as the response that can be brought about by increases in $PaCO_2$ (Mueller et al., 1982; see also Van den Hoogen and Colpaert, 1986). In most mammalian species, including humans (Chernick, 1978), the fetus before birth executes apparently chaotic breathing movements that are unrelated to its arterial $PaCO_2$; prepartum, it is the mother's respiratory function that responds to and regulates the acidity of the fetus' arterial blood. Immediately after birth, the breathing of the newborn remains erratic at first to only gradually, in the course of weeks, become regular and appropriately responsive to the $PaCO_2$ of the newborn's own arterial blood (for reviews, see Mortola, 1987; Rigatto, 1992). Because the notion of learning encompasses any change that occurs in the relationship between a stimulus and a response (Grossman, 1967), it follows that the coupling that comes about postpartum between breathing movements and arterial $PaCO_2$, is to be considered as an instance of learning (see also Mortola, 1987, p. 195). It also follows that the subsequent execution in adult life of this, so acquired, S-R relationship requires the organism to recall[21] this particular relationship. It would, in fact, be interesting to examine whether, in infants who have been exposed to an opiate pre- and postpartum, the then-normal responsiveness to CO_2 is or is not preserved on withdrawal of the opiate. The account offered above would suggest this withdrawal to paradoxically cause respiratory dysfunction[22]. Failing experimental data, it is interesting to note that infants born to opiate-addicted mothers present with neonatal abstinence syndrome (Desmond and Wilson, 1975), involving respiratory distress and, in some instances, so-called early death (Kandall et al., 1977). Specifically, these infants demonstrate tachypnea to alkalosis (Klain et al., 1972).

C. Tolerance With Nonopiate Drugs

Apparent tolerance and dependence also occur with such nonopiate agents as benzodiazepines, ethanol, barbiturates, nicotine, amphetamines, histamine-releasing agents and many other compounds (see Cox, 1990). Part of the tolerance that is observed with some agents (e.g., pentobarbital) is due to dispositional mechanisms (e.g., induction of metabolic enzymes), but these mechanisms fail to account (Cox, 1990; see also section IV.B.) for the general features that characterize tolerance across different agents and different mechanisms. Indeed, such features as dose-dependence, duration-dependence, and reversibility also apply with the putative tolerance, and dependence, that develop with many classes of nonopiate drugs (Cox, 1990). Although acknowledging that nonopiate drugs act through molecular mechanisms other than the activation of opiate receptors and affect sets of physiological systems that may not or only in part coincide with those that also possess opiate receptors, the question arises whether the fundamental mechanisms can be the same. That is, can the assumption that tolerance does not develop and can the operation of System Theory similarly account for the apparent tolerance and dependence that develop with nonopiate agents?

To exhaustively address this issue is beyond the scope of this article. Suffice it here to briefly consider two examples. The first concerns the dependence that develops to benzodiazepines (Martin et al., 1982; Ryan and Boisse, 1983) and, in particular, the state dependence that they produce. While under the influence of a benzodiazepine, food-deprived rats were trained to press an operant lever for food (Colpaert, 1990). Once established, the recall of the response was fully adequate when tests for recall were made after an additional benzodiazepine injection. Recall failed, however, when tests occurred after the injection of saline; the animals had thus been rendered dependent on benzodiazepines in that their ability to recall this response had effectively become dependent upon the presence of a benzodiazepine. This dependence appeared after approximately 10 sessions had expired during the acquisition of the response and, thus, after 10 benzodiazepine injections. Overtraining with benzodiazepine so that animals received no less than 50 injections of a large, 40-mg/kg, dose of chlordiazepoxide failed to destroy the state dependency. As indicated before (section IV.C.4.) with opiates, these data demonstrate that, at least for this particular case of (state) dependence, dependence cannot develop if tolerance occurs (Colpaert, 1990). This evidence of incompatibility constitutes further empirical support for our theories that tolerance does not develop (to opiates, to benzodiazepines), and that dependence can only develop if tolerance does not.

A second example concerns the so-called drug resistance that can occur with antibiotics and anticancer compounds. Specifically, previous exposure of whole organisms (i.e., patients: Georges et al., 1990; Pastan and Gottesman, 1991) or of cells in culture (Clynes, 1994; Skovsgaard et al., 1994) can reduce the therapeutic and cytotoxic activity, respectively, of chemotherapeutic agents. There is evidence that this resistance depends on the dose (in vivo: Goldie et al., 1972; or in vitro concentration: Hill, 1986; Schoenlein, 1993) and on the duration (Calabro-Jones et al., 1982; Goldie et al., 1972) of the drug exposure and that the resistance may be reversible (Dahllof et al., 1984; Lothstein and Horwitz, 1986). Dose-dose transposition occurs in that the resistance can be identified either as the same dose producing a smaller effect, as a shift to the right of the dose-

[21] Interestingly, in the French language, the apparent depression of respiration that opiates produce in adult organisms used to be referred to as "un oubli respiratoire," meaning the subject forgets to breathe.

[22] Such studies may also be relevant to sudden infant death, the causes of which remain poorly understood (Byard, 1991) but might involve a dysfunction of cardiorespiratory control (see Hunt, 1992).

response curve, or as a higher dose being required to produce the apparently same effect (Hosking et al., 1994; Kartner et al., 1983; Volm et al., 1988). The resistance can occur after prolonged drug administration (e.g., by infusion: Calabro-Jones et al., 1982; Goldie et al., 1972), but also after intermittent doses (Hosking et al., 1994; Whelan and Hill, 1993) or after a single exposure (Gupta, 1985; Rath et al., 1984). The rate at which resistance to one particular agent develops can differ, depending on the cell line or tumor type (Belvedere and Dolfini, 1993). The resistance established to one particular drug may be associated with a decreased apparent efficacy of other agents and is then referred to as multidrug resistance (Gerlach et al., 1986). Finally, and not unlike the enhanced analgesic effects of opiates in organisms exposed to nociceptive stimulation, the apparent inhibitory effect of chemotherapeutic agents on cell proliferation may be larger in cycling as opposed to quiescent cells (Hill, 1982). Drug resistance thus seems to also possess the key empirical features of apparent tolerance to opiates, suggesting that System Theory may apply to this resistance. The latter suggestion would have several interesting implications. One is that chemotherapeutic agents[23] may not, as is commonly believed, act by their killing cells (i.e., by a cytotoxic action) but by inhibiting some adequate stimulus for cell proliferation, and this according to the equation $\varphi_o = \varphi_\alpha - \mu$. Another is that the tumor growth that occurs after apparent resistance has been established may not be caused by the cells having in any way become resistant or tolerant to the drug. This at times virulent and fatal growth may instead be caused by dependence; much as opiates induce hyperalgesia, chemotherapeutic agents may increase δ', i.e., enhance the cell's response to adequate stimuli for cell proliferation. Analogous to apparent tolerance perhaps constituting the major problem in the treatment of pain (Kelemen, 1973), drug resistance arguably constitutes the major problem of cancer therapy (see Pastan and Gottesman, 1991). It would be of interest for future studies to examine whether the establishment of matches (section IV.A.3.) may help to resolve this problem.

D. Inadequacy of Tolerance

The notion of tolerance can, of course, explain that the analgesic effects of opiates diminish in certain conditions. However, and unlike System Theory, it fails to account for many other empirical findings that have been obtained with opiates (e.g., inverse apparent tolerance) and is incompatible with the phenomenon of opiate dependence. However, the inadequacy of the notion of tolerance goes beyond these observations.

Thus, it is now apparent (sections II. and IV.A.) that the changes in opiate effects that so far have been ascribed to putative tolerance to opiate receptor ligands reflect (at best; see later in this section) properties of physiological systems rather than of these ligands. Furthermore, the effects of adequate stimuli that also affect these systems will represent the mirror image (fig. 2) of those of opiates. It follows that tolerance would be as much a property of adequate stimuli as it would be of drugs; also, the same attribution would have to be made with regard to dependence. The notion of tolerance thus becomes uninformative; it adds nothing to the statement that opiates, like adequate stimuli, can produce effects. This uninformative attribute would have to be accorded to many classes of drugs other than opiates.

The notion of tolerance and, in particular, of it reflecting so-called cellular adaptive sensitivity changes (see Johnson and Fleming, 1989), also does not elucidate how whole organism effects of opiates can remain unchanged. Instances of such effects that now appear to have been well established are the discriminative (Colpaert, 1995) and the analgesic effects of opiates (provided the opiate matches the nociceptive input; section C.).

The notion of tolerance as one that reflects a loss of effect also disregards a phenomenon revealed in section IV.C.2. That is, just as much as there is a *loss of effect*, there inextricably also is a *gain in effect*; opiates do not have on initial administration, but acquire and then maintain with chronicity, the ability to prevent withdrawal. Specifically, the opiates first establish a dependence that causes a withdrawal to occur that the opiates are then able to prevent.

Yet another manner in which the notion of tolerance appears inadequate is with opiate analgesia. That is, for apparent tolerance to opiate analgesia to be obtained, it is necessary to *not* administer nociceptive stimulation; it is necessary to *not* let the opiate exert analgesic effects. If (matching) nociceptive stimulation is administered so that the opiate can display its analgesic effects, then no apparent tolerance develops (section III.). Also, even to state that tolerance to opiate analgesia develops in mismatching conditions is to disregard the paradoxical effect that also occurs; that is, a growing hyperalgesia then is equally well being induced by the opiate.

Finally, in our simulations, we have computed the opiate effect as the ratio e_r of δ' to δ'' and have found that, in so doing, System Theory can account for apparent tolerance. However, if we had chosen to compute this effect by subtraction (i.e., as e_s where $e_s = \delta' - \delta''$; see section II.), then we would not have found even *apparent* tolerance (see fig. 1). Note that, of course, the computation of e_s rather than of e_r would have made no difference[24] whatsoever to the System's (apparently adequate) operations.

Thus, tolerance is not a property of opiate drugs, and what we so far have referred to as apparent tolerance might not be even a property of the physiological sys-

[23] Those agents to which drug resistance develops.

[24] Note in particular that dependence persists; δ' in condition B of figure 1 is larger than δ' in condition A, regardless of the method by which the comparison is made.

tems that are coregulated by opiate receptors. Arguably, apparent tolerance is at best a property of an arbitrary method of computations applied to empirical data. Another, equally arbitrary, method renders even apparent tolerance nonexistent.

Thus, these observations demonstrate the inadequacy of the notion of tolerance; they do not, however, detract from System Theory, i.e., from a perhaps more accurate understanding of the modalities whereby physiological systems operate.

E. Limitations of System Theory

It should be noted that the results generated in the computer simulations described in section IV. do not claim to offer an exact numeral fit of any particular set of empirical data. The results that have been generated are to reflect, at best, ordinal measurement of a dependent variable (i.e., the response δ) as it varies as a function of the independent variable that is being manipulated (e.g., φ_α). Specifically, the results do not a priori possess the value of the interval and ratio measurements with which dependent variables are typically assayed in empirical experiments.

It should also be noted that the numerical model in some instances (not shown) produced meaningless results (e. g., negative values of e_τ). This occurred when large values were entered for the dimensions φ_α, μ, τ, and combinations thereof; thus, results were meaningful only within a limited, amorphous space defined by these dimensions. Interestingly, this space could be enlarged along several dimensions if it were assumed that the system was continuously fed by some modest magnitude[25] (e.g., 5 A.U.) of φ_α. The further assumption that μ did *not*, whereas activation of some other receptor could, detract from this φ_α endowed the System with response properties that may not be unlike those of cells on which several different receptors are colocalized. Greater mathematical sophistication of the otherwise most simple equations also enlarged the space within which the System generated meaningful results and endowed the System with somewhat different response properties. However, all of these maneuvers required additional or more complex assumptions; these were not made here because the model, in its most unassuming format, provided the adequate data described in section IV. It also is uncertain whether the validity of any such theoretical model needs to be limitless. For example, a cutaneously applied thermal stimulus generates a sensation of pain that is intensity-dependent within a particular range of temperatures. At excessive temperatures, the stimulus in fact destroys the sensor, and the initial relationship between stimulus and response effectively becomes meaningless.

Note also that it may prove difficult, perhaps impossible, for empirical data to verify all of the predictions that the System can make. We have, parsimoniously, assumed all the relationships between φ_α, φ_o, ι_τ and δ to be simply linear and, importantly, that the relationship between δ and the effector yielding the to-be-measured response is also linear. The latter assumption may readily prove oversimplistic, if only because "floor" and "ceiling" effects occur in empirical measurements (for discussion, see Vierck and Cooper, 1984). An elegant case in point is the inflammatory hyperalgesia that Gutstein et al. (1995; experiment 3) found when a low-intensity stimulus was used, but did not find with a higher-intensity stimulus (1995; experiment 1).

Finally, the output variable δ of the System permits responses to be graded, as is the case with the sensation of pain that varies quantitatively from small to larger intensities. However, some responses of single cells or of whole organisms (e.g., the action potential, the drug discriminative response), are quantal (i.e., of an all-or-none nature). Note, therefore, that the graded variable δ can be transformed into a quantal response by the application of some criterion value δ_c such as that represented by the dotted line in the bottom panel of figure 13. The optimal setting of such criterion values constitutes the object of other theories (i.e., Signal Detection and Decision Theories; Green and Swets, 1966; Swets, 1964; Vickers, 1979) that have been applied to studies of pain (e.g., Clark and Yang, 1983).

F. Opiates: Myth and Misnomers

To conclude, as we will, that tolerance does not develop to opiates raises the question as to how it has been possible that over the past 50 years, one of the most massive, sophisticated research efforts ever in neurobiological science has been misguided. While it is difficult to fully grasp the magnitude of what may well be this century's largest neurobiological myth[26], three points seem to merit consideration.

First, the earliest authoritative statements of putative opiate tolerance (Light et al., 1930; Rossbach, 1880) are derived from clinical, uncontrolled, observations in humans. However, even with respect to the therapeutically most valuable of opiate effects, this statement rarely has been followed up by rigourous, methodologically sound scientific studies. As recently as this decade, it has been noted that "There are remarkably few clinical studies that systematically address the issue of tolerance. . . " (Fields et al., 1991), that "In man, the development of analgesic tolerance. . . has not been measured with any precision. . . " (Foley, 1991), and that "The most glaring deficit in this field is the absence of research—of actual data. . . . " (Hammond, 1991). Nonetheless, ". . . it is generally agreed that tolerance does occur for opiate

[25] Rhythmic harmonic oscillations occur in the discharges of spinal dorsal horn neurons during background activity (Sandkühler and Eblen-Zajjur, 1994).

[26] The use of the term myth in regard to opiates has been introduced recently (Dubner, 1991; Zenz, 1991; see also Gourlay, 1994).

analgesia" (Fields et al., 1991), that "Chronic use of [opiates]. . . invariably leads to. . . tolerance" (Pasternak, 1993) and that "there is no limit to tolerance" (Foley, 1991; see also Foley, 1989; Rosow, 1987).

Second, this powerful impetus that clinical observations have given to the notion of opiate tolerance has been followed since the 1950s, by well-controlled laboratory studies in animals and other preparations that seemed to scientifically prove beyond any reasonable doubt that tolerance develops to opiates, and to opiate analgesia in particular (Kalant, 1987; Kornetsky, 1987; Smith et al., 1988). However, this research on opiate analgesia has invariably been conducted in animal preparations that did not suffer pain. Arguably, therefore, these studies were not about analgesia; they could observe only apparent tolerance *because* no pain was being implemented. This in turn may have followed from the limitation of Sherrington's legacy to acute pain (section III.B.) and from the other commonly held belief that chronic pain is simply a pain that lasts a long time. It has not been until our studies using chronic (Colpaert, 1979) or repeated (Colpaert et al., 1980a) nociceptive stimulation that opiates were studied experimentally for their effects on ongoing pain. As noted above (section I.), these studies were explicitly designed to test the hypothesis that tolerance does not develop to opiates and, very specifically, that no apparent tolerance to opiate analgesia should develop if the opiate matches the pain that is to be treated (Colpaert, 1978b; section II.). The studies provided sound empirical data to this latter effect, but their impact so far on opiate theory and practice has been limited. This may be because the tolerance myth has grown to all-encompassing dimensions.

Third, the account given in the present article of opiates and pain would indicate the subject is indeed complex. The complexity is not with the opiates, however; these simply act to diminish the impact of φ_α in the transduction equation $\varphi_o = \varphi_\alpha - \mu$. The complexity arises from the paradoxical responses (i.e., decreased δ'', increased δ') that physiological systems generate when an opiate is given. Adler (1987) may thus have been proven right in contending that "The lasting legacy of research on [opiate] tolerance and dependence may be in our. . . understanding of brain mechanisms."

The impact of the myth of opiate tolerance is difficult to overestimate. Scientifically, for decades, the myth has misguided opiate research toward identifying the elusive mechanisms whereby opiates supposedly lose their efficacy (Cox, 1990; Johnson and Fleming, 1989); thus, little physiological understanding has been achieved (Collin and Cesselin, 1991; Cox, 1990; Loh and Smith, 1990; Nestler, 1992; Rauhala et al., 1995). Effects of opiates have been considered as pharmacologically specific only if tolerance to them can be demonstrated (Shannon and Holtzman, 1976). Also, experimental pain models that failed to demonstrate tolerance to opiates have been considered misleading and have been abandoned (see Abbott et al., 1982). Therapeutically, the opiate myth for over a century has led (see Foley, 1991) to what has been referred to as a badgering mismanagement of chronic pain patients (Larue et al., 1995; McGivney and Crooks, 1984; Reuler et al., 1980; Walsh, 1984; Zenz, 1991). So-called opiophobia (Hill, 1994; Zenz and Willweber-Strumpf, 1993), doctrinaire pronouncements (Portenoy, 1994a), prejudices (Zenz and Sorge, 1991), biases (Portenoy, 1991) and misapprehensions (Warncke et al., 1994) continue to prevail and have spilled over to several other drug classes to which tolerance allegedly also develops (Cox, 1990). However, a glimmer of hope arises from recent clinical statements that opiates can lastingly relieve chronic pains (section III.C.), provided the opiate treatment constitutes an appropriate match (Foley, 1991; Melzack, 1992; Portenoy, 1994a) of the pain that is to be treated.

Several misnomers have also come about as a direct or indirect consequence of the tolerance myth to opiates. *Opiate tolerance* is a foremost misnomer; it misleadingly suggests that tolerance develops to opiates and we propose the wording *apparent tolerance to opiates* be used instead. Tolerance theory naturally failed to observe that the apparent effects of opiates can also be enhanced, so that *inverse apparent tolerance* is to be proposed de novo. *Dependence is real* and can exist only if tolerance does not develop. However, it is inappropriate to refer to whole organisms (as is often done) as being dependent on, or, for that matter, apparently tolerant to, opiate drugs. Opiates interfere with only some rather than all physiological systems. In addition, the dependence and apparent tolerance develop and decay at unequal rates with these different systems and may not occur at all with some of these. That is, adequate, matching stimulation of one or several systems will prevent these developments. For example, the chronic pain of cancer patients may prevent the nociceptive systems[27] from developing apparent tolerance and dependence, whereas these developments proceed normally with other opiate-sensitive systems mediating other opiate effects. As discussed elsewhere (section IV.C.3.), the term *opiate analgesia* is also inappropriate, a more adequate wording being *analgesic effects* of opiates; also, opiates equally well generate *hyperalgesic effects*. In a similar manner, opiates do not produce *respiratory depression* (section V.B.), although they can *decrease* or *increase respiratory responses* (to arterial $PaCO_2$ in particular). *Opiate addiction* is a particular and specific case of dependence; it perhaps evolves as an amplified

[27] Conceivably, the dysphoria of organisms suffering chronic pain might similarly prevent the development of apparent tolerance and dependence with the physiological systems mediating reward (see Lérida et al., 1987; Lyness et al., 1989). Some (Portenoy, 1994a), although not all (Maruta et al., 1979), clinical observations suggest opiate addiction to be only mild in chronic pain patients receiving chronic opiate treatment.

ability of opiates to produce dysphoria and remains a truly unresolved medical problem.

VI. Summary

Two decades ago, and of course in spite of the overwhelming evidence to the contrary, we (Colpaert, 1978b; Colpaert et al., 1976b) theorized that tolerance does not develop to opiates and does not, as is commonly believed, constitute a pharmacological property of these compounds. We also devised a theory that wholly attributes any changes in the apparent effects of opiates, to the physiological systems that mediate these effects and to the biometric methods by which the latter are analyzed in empirical studies. The theory is hence termed System Theory; it specifies in an abstract manner the mechanisms whereby the physiological systems controlling pain are able to detect nociceptive stimuli and permit opiates to exert analgesic effects (Colpaert, 1978b). This article constitutes the second of two in which we evaluate the theory that tolerance does not develop to opiates. The first review (Colpaert, 1995), which appeared in the December 1995 issue of *Pharmacological Reviews*, examined whether tolerance develops to the ability of opiates to act as discriminative stimuli; although studies of opiate drug discrimination have almost unanimously claimed to demonstrate the contrary (for review, see Young and Sannerud, 1989), this recent evaluation of the evidence confirms our earlier conclusion (Colpaert et al., 1976b) that tolerance does not develop to opiate drug discrimination (Colpaert, 1995). The present, second, review concerns the analgesic effects of opiates; it examines whether System Theory can account for findings that these effects can apparently change while assuming that tolerance does not develop to opiates.

System Theory of nociception generated specific predictions concerning pain sensitivity and the analgesic effects of opiates under conditions in which organisms are exposed to chronic nociceptive stimulation and chronic opiate treatment (Colpaert, 1978b; section II.). That is, the chronic administration of an opiate should induce hyperalgesia and apparent tolerance to the analgesic effects of opiates; chronic nociceptive stimulation should induce hypoalgesia and apparent inverse tolerance. Furthermore, chronic opiate treatment and chronic nociceptive stimulation should counteract each other in producing these effects; as a consequence, it should be possible to adequately control chronic pain with opiates without inducing apparent tolerance, provided the treatments match each other.

The available experimental evidence bearing on these predictions (section III.A.) confirms initial animal studies (Colpaert, 1979; Colpaert et al., 1980a) demonstrating these effects of chronic opiate treatment and of chronic nociceptive stimulation on pain sensitivity and on the apparent analgesic effects of opiates. As it applies to chronic pain, this experimental evidence relies critically, however, on the adjuvant polyarthritis that was introduced (Colpaert, 1978c) as a model of chronic pain to verify these hypotheses. Because of limitations in Sherrington's legacy on the identification of pain in laboratory animals, an extensive, imaginative effort has been required to generate methods allowing putative chronic pain to be identified, and measured, in animals. The evidence that is now available (section III.B.) supports the validity of adjuvant arthritis in the rat as an animal model of chronic pain; however, the inflammatory hyperalgesia that is also associated with adjuvant arthritis has complicated the interpretation of some data, and it remains desirable that at least one alternative model be developed.

For understandable reasons, clinical investigations have not offered entirely adequate, scientific evidence relating to all of the specific predictions that were made. However, such evidence as there is, and authoritative clinical opinion, appear to be consistent with these predictions (section III.C.); specifically, and provided the opiate matches the pain, it is now acknowledged (e.g., Portenoy and Foley, 1986) that chronic pains of malignant and nonmalignant etiologies can be treated adequately with opiates without any tolerance developing. Our review of the evidence thus is compatible with the theory that tolerance does not develop to the primary action of opiates that allows them to produce analgesic effects; it also suggests System Theory can account for the apparent tolerance, and apparent inverse tolerance, that opiates can generate under some circumstances.

Having reached this latter conclusion, section IV examines whether the reach of System Theory can be taken further. Empirical studies have shown, albeit never explained, the apparent tolerance to opiate analgesic effects to be characterized by a number of particular properties; we thus examined whether System Theory can accommodate, and account for, these empirical properties. To this end, a mathematical model of System Theory was devised (section IV.A.) allowing that numerical, computer-generated, simulations be made of its operation under various conditions. Data generated by these simulations indicate that System Theory can effectively accommodate and explain the major, empirically established, properties of apparent tolerance to opiate analgesia (i.e., dose-dependence, duration-dependence, reversibility, dose-dose transposition and the different modes whereby it can be induced; section IV.B.).

Furthermore, System Theory accommodates the apparent tolerance that can develop to opiate effects other than analgesic and elucidates the mechanism whereby apparent tolerance develops and decays at different rates with different opiate effects. System Theory also accommodates and explains dependence on opiates and elucidates the relationship that exists between apparent tolerance to and dependence on opiates. Beyond the highly integrated level of whole organisms, System Theory also appears to operate at such higher-resolution levels of analysis as cell assemblies and single neurons.

Thus, while System Theory was originally devised for the special case of the pain and analgesia that are assessed in whole organisms, evidence now suggests that its operation can be generalized to other opiate actions, as well as to less-integrated biological systems. Finally, System Theory coherently explains a multitude of findings on apparent tolerance and dependence that never have been accounted for; it thus satisfies the many and complex prerequisites that have been defined (Cox, 1990, p. 666) for a theory of the apparent tolerance to and dependence on opiates.

Empirical tests of the predictions that were initially derived from System Theory, were derived to pit two theories against each other. One is the common theory that tolerance develops to opiates and constitutes a pharmacological property of these agents (e.g., Cox, 1990). The other theory holds that tolerance does not develop to opiates, and that whatever changes, decreases or enhancements that may (but do not necessarily) occur in the apparent effects of opiates do not result from any change in the opiates' primary action (Colpaert, 1978b). That is, these changes result from the particular manner, specified by System Theory, in which physiological systems operate and are found if a particular, arbitrarily chosen method is used to evaluate the systems' output. It appears, then, that System Theory can account for all of the empirical evidence and data from computer simulations that we have considered here. The classical theory that tolerance develops to opiates, can also account for some of the results (in particular, for the development of apparent tolerance to the analgesic effects of opiates). The classical theory, however, provides no explanation for further findings (such as inverse apparent tolerance) and is incompatible with others (e.g., dependence). Having thus compared the two theories, we now conclude that tolerance does not develop to the pharmacological action that allows opiates to exert analgesic effects. Having concluded elsewhere (Colpaert, 1995; Colpaert et al., 1976b) that tolerance also does not develop to opiate drug discrimination, we now conclude further that tolerance does not develop to opiates. *The Basis of Pharmacology* (Cox, 1990, p. 639) specifies that "Drug tolerance is a. . . decreased responsiveness to the pharmacological effect of a drug as a result of prior exposure. . . "; we suggest that the pharmacology of opiates can no longer rest on this basis.

System Theory is a highly abstract theory that attempts to explain the relationships that exist in physiological systems between their adequate stimulation φ_α and the action μ of opiates on the one hand, and the System's response δ (in particular; δ' and δ'') on the other. It invokes the existence of a relevant physiological activity φ_o and of the temporal integration ι_τ of this activity. Most remarkably, it appears that a set of three utterly simple equations (section IV.A.) relating φ_α, μ, φ_o, ι_τ, δ and, also, time, can account for the many and often highly complex empirical findings that are available. System Theory is uniquely parsimonious and coherent in providing this account; no other theory or sets of theories have been offered to date that would explain these findings while making fewer assumptions. It is for further work to more adequately identify the biological substrates of System Theory, to refine its operations through more sophisticated mathematical models, or to possibly challenge its validity.

The evidence and analyses discussed in this review elucidate the actions of opiates but also those of the neurobiological systems governing pain. Moving beyond Sherrington's legacy, methods have been devised de novo to identify and measure chronic pain in animals, and adjuvant arthritis in the rat has been introduced and uniquely validated as a laboratory animal model of chronic pain. The mechanisms and response characteristics whereby nociceptive systems operate have been specified in an abstract manner, thus providing a framework in which to interpret the wealth of behavioral, electrophysiological, biochemical, and molecular evidence that is available from empirical studies. These abstract mechanisms identify the mere passage of time as an indispensable, independent variable in its own right. Thus, a novel notion to the physiology of pain is introduced: that of some entity, represented here by ι_τ, that is capable of making an integration over time of relevant physiological activity.

Should endogenous opiate systems operate in accordance with System Theory, then this would shed an astonishing light on the role of such opiate systems throughout the organism's ontogeny. State dependence, controlled by endogenous opiates, would allow the organism to vastly multiply its capacity to acquire and to deploy, but also appropriately to contain, the results of previous experience (section V.B.). These mechanisms could conceivably govern the host of physiological systems in which endogenous opiates are involved, including digestion, respiration, motor movement, secretion of anterior pituitary hormones and, also, the perception of pain.

The System Theory proposed here challenges the pervasive theory of opiate tolerance that, over the past 50 years, has guided one of the most massive, sophisticated research efforts ever in neurobiological science. It identifies a singular process that appears to operate with different physiological systems and at different levels of integration. In so doing, System Theory suggests new avenues for future research in such areas as pain and endogenous opiate systems. The theory also offers scientific support to the efforts of clinicians to adequately match with opiates the chronic pains that are so much in want of treatment.

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REFERENCES

ABBADIE, C., AND BESSON, J.-M.: C-fos expression in rat lumbar spinal cord during the development of adjuvant-induced arthritis. Neuroscience **48:** 965–993, 1992.

ABBADIE, C., AND BESSON, J.-M.: Effects of morphine and naloxone on basal and evoked Fos-like immunoreactivity in lumbar spinal cord neurons of arthritic rats. Pain **52:** 29–39, 1993.

ABBADIE, C., BESSON, J.-M., AND CALVINO, B.: C-fos expression in the spinal cord and pain-related symptoms induced by chronic arthritis in the rat are prevented by pretreatment with Freund adjuvant. J. Neurosci. **14:** 5865–5871, 1994.

ABBOTT, F. V., FRANKLIN, K. B. J., LUDWICK, R. J., AND MELZACK, R.: Apparent lack of tolerance in the formalin test suggests different mechanisms for morphine analgesia in different types of pain. Pharmacol. Biochem. Behav. **15:** 637–640, 1981.

ABBOTT, F. V., MELZACK, R., AND LEBER, B. F.: Morphine analgesia and tolerance in the tail-flick and formalin tests: dose-response relationships. Pharmacol. Biochem. Behav. **17:** 1213–1219, 1982.

ADLER, M. W.: Mechanisms of opioid tolerance and dependence: symposium summary. *In* Problems of Drug Dependence, Proceedings of the 48th Annual Scientific Meeting, ed. by L. S. Harris, The Committee on Problems of Drug Dependence, Inc., NIDA Res. Monogr., US Government Printing Office, Washington, DC, vol. 76, pp. 63–68, 1987.

AGHAJANIAN, G. K., AND WANG, Y. Y.: Pertussis toxin blocks the outward currents evoked by opiate and alpha two agonists in locus coeruleus neurons. Brain Res. **371:** 390–394, 1986.

ALARCON, G., AND CERVERO, F.: The effects of electrical stimulation of A and C visceral afferent fibres on the excitability of viscerosomatic neurones in the thoracic spinal cord of the cat. Brain Res. **509:** 24–30, 1990.

AMMER, H., AND SCHULZ, R.: Morphine dependence in human neuroblastoma SH-SY5Y cells is associated with adaptive changes in both the quantity and functional interaction of PGE_1 receptors and stimulatory G proteins. Brain Res. **707:** 235–244, 1996.

ANDREWS, H. L.: The effect of opiates on the pain threshold in post-addicts. J. Clin. Invest. **22:** 511–516, 1943.

ANDREWS, H. L., AND HIMMELSBACH, C. K.: Relation of the intensity of the morphine abstinence syndrome to dosage. J. Pharmacol. Exp. Ther. **81:** 288–293, 1944.

ARIËNS, E. J.: The mode of action of biologically active compounds. *In* Molecular Pharmacology, vol. 1, Academic Press, New York, 1964.

ARNER, S., AND ARNER, B.: Differential effects of epidural morphine in the treatment of cancer-related pain. Acta Anaesthesiol. Scand. **29:** 32–36, 1985.

ARNER, S., RAWAL, N., AND GUSTAFSSON, L. L.: Clinical experience of long-term treatment with epidural and intrathecal opioids: a nationwide survey. Acta Anaesthesiol. Scand. **32:** 253–259, 1988.

AWOUTERS, F., NIEMEGEERS, C. J. E., LENAERTS, F. M., AND JANSSEN, P. A. J.: The effects of suprofen in rats with *Mycobacterium butyricum*-induced arthritis. Arzneim. Forsch. **25:** 1526–1537, 1975.

BABBINI, M., AND DAVIS, W. M.: Time dose relationship for locomotor activity effects of morphine after acute or repeated treatment. Br. J. Pharmacol. **46:** 213–224, 1972.

BALDESSARINI, R. J.: Drugs and the treatment of psychiatric disorders. *In* Goodman and Gilman's The Pharmacological Basis of Therapeutics, ed. by A. Goodman Gilman, T. W. Rall, A. S. Nies, and P. Taylor, 3rd ed., pp. 383–435, Pergamon Press, New York, 1990.

BASBAUM, A. I., AND FIELDS, H. L.: Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. Annu. Rev. Neurosci. **7:** 309–338, 1984.

BASBAUM, A. I., MENÉTREY, D., PRESLEY, R. W., AND LEVINE, J. D.: The contribution of the nervous system to experimental arthritis in the rat. *In* The Arthritic Rat as a Model of Clinical Pain, ed. by J.-M. Besson and G. Guilbaud, pp. 41–54, Elsevier, Amsterdam, 1988.

BEECHER, H. K.: The measurement of pain. Pharmacol. Rev. **9:** 59–209, 1957.

BEECHER, H. K.: Measurement of Subjective Responses: Quantitative Effects of Drugs. Oxford University Press, New York, 1959.

BEITNER, D. B., DUMAN, R. S., AND NESTLER, E. J.: A novel action of morphine in the rat locus coeruleus: persistent decrease in adenylate cyclase. Mol. Pharmacol. **35:** 559–564, 1989.

BELLEVILLE, R. E.: Control of behavior by drug-produced internal stimuli. Psychopharmacologia **5:** 95–105, 1964.

BELVEDERE, G., AND DOLFINI, E.: Studies on low-level MDR cells. Cytotechnology **12:** 257–264, 1993.

BERVOETS, K., AND COLPAERT, F. C.: Respiratory effects of intrathecal capsaicin in arthritic and non-arthritic rats. Life Sci. **34:** 2477–2483, 1984.

BESSON, J.-M., AND CHAOUCH, A.: Peripheral and spinal mechanisms of nociception. Physiol. Rev. **67:** 67–186, 1987.

BESSON, J.-M., DICKINSON, A. H., LE BARS, D., AND OLIVERAS, J.-L.: Opiate analgesia: the physiology and pharmacology of spinal pain systems. *In* Neuropsychopharmacology, Proceedings of the 7th International Congress of Pharmacology, ed. by J.-M. Besson and A. H. Dickinson, pp. 61–81, Pergamon Press: Oxford, 1978.

BHARGAVA, H. A., MATWYSHYN, G. A., GERK, P. M., BOZEK, P. S., BAILEY, M. D., KO, K. H., SIMKO, R. J., AND THORAT, S. N.: Effects of naltrexone pellet implantation on morphine tolerance and physical dependence in the rat. Gen. Pharmacol. **25:** 149–155, 1994.

BICKEL, W. K., STITZER, M. L., LIEBSON, I. A., AND BIGELOW, G. D.: Acute physical dependence in man: effects of naloxone after brief morphine exposure. J. Pharmacol. Exp. Ther. **244:** 126–132,1988.

BLÄSIG, J., HERZ, A., REINHOLD, K., AND ZIEGLGANSBERGER, S.: Development of physical dependence on morphine in respect to time and dosage and quantification of the precipitated withdrawal syndrome in rats. Psychopharmacology **33:** 19–38, 1973.

BORGBJERG, F. M., NIELSEN, K., AND FRANKS, J.: Experimental pain stimulates respiration and attenuates morphine-induced respiratory depression: a controlled study in human volunteers. Pain **64:** 123–128, 1996.

BOUHASSIRA, D., GALL, O., CHITOUR, D., AND LE BARS, D.: Dorsal horn convergent neurones: negative feedback triggered by spatial summation of nociceptive afferents. Pain **62:** 195–200, 1995.

BOUHASSIRA, D., LE BARS, D., AND VILLANUEVA, L.: Heterotopic activation of Aδ- and C-fibres triggers inhibition of trigeminal and spinal convergent neurones in the rat. J. Physiol. (Lond.) **389:** 301–317, 1987.

BRONSTEIN, J. M., FARBER, D. B., AND WASTERLAIN, C. G.: Regulation of type-II calmodulin kinase: functional implications. Brain Res. Rev. **18:** 135–147, 1993.

BRUERA, E., MACMILLAN, D., HANSON, J., AND MACDONALD, R. N.: The Edmonton staging system for cancer pain: preliminary report. Pain **37:** 203–210, 1989.

BRUERA, E., MACMILLAN, K., KUEHN, N., AND MILLER, M. J.: Circadian distribution of extra doses of narcotic analgesics in patients with cancer pain: a preliminary report. Pain **49:** 311–314, 1992.

BUCKLEY, P. F.: Somatic nerve block for post operative analgesia. *In* Acute Pain, ed. by G. Smith and B. G. Covino, pp. 205–227, Butterworth & Co., London, 1985.

BUCSICS, A., AND LEMBECK, F.: In vitro release of substance P from spinal cord slices by capsaicin congeners. Eur. J. Pharmacol. **71:** 71–77, 1981.

BUDAI, D., AND LARSON, A. A.: Role of substance P in the modulation of C-fiber-evoked responses of spinal dorsal horn neurones. Brain Res. **710:** 197–203, 1996.

BURITOVA, J., HONORÉ, P., CHAPMAN, V., AND BESSON, J.-M.: Concurrent reduction of inflammation and spinal Fos-LI neurons by systemic diclofenac in the rat. Neurosci. Lett. **188:** 175–178, 1995.

BUTLER, S. H., WEIL-FUGAZZA, J., GODEFROY, F., AND BESSON, J.-M.: Reduction of arthritis and pain behaviour following chronic administration of amitryptiline or imipramine in rats with adjuvant-induced arthritis. Pain **23:** 159–175, 1985.

BYARD, R. W.: Possible mechanisms responsible for the sudden infant death syndrome. J. Paediatr. Child Health **27:** 147–157, 1991.

CALABRO-JONES, P. M., BYFIELD, J. E., WARD, J. F., AND SHARP, T. R.: Time dose relationship for 5-fluorouracil toxicity against human epithelial cancer cells in vivo. Cancer Res. **42:** 4413–4419, 1982.

CALVINO, B., COURAND, J. Y., AND BESSON, J.-M.: Prevaccination with diluted Freund adjuvant prevents the development of chronic pain and transient release of cerebrospinal fluid substance P in adjuvant-induced arthritis in rats. Pain **58:** 211–217, 1994.

CALVINO, B., CREPON-BERNARD, M.-O., AND LE BARS, D.: Parallel clinical and behavioural studies of adjuvant-induced arthritis in the rat: possible relationship with "chronic pain." Behav. Brain Res. **24:** 11–29, 1987a.

CALVINO, B., VILLANUEVA, L., AND LEBARS, D.: Dorsal horn (convergent) neurones in the intact anesthetized arthritic rat: I. segmental excitatory influences. Pain **28:** 81–98, 1987b.

CANNON, W. B.: Bodily Changes in Pain, Hunger, Fear and Rage, 2nd ed. Appleton, New York, 1929.

CAPETOLA, R. J., SHRIVER, D. A., AND ROSENTHALE, M. E.: Suprofen, a new peripheral analgesic. J. Pharmacol. Exp. Ther. **214:** 16–23, 1980.

CAPPELL, H., LE BLANC, A. E., AND ENDRENYI, L.: Aversive conditioning by psychoactive drugs: effects of morphine, alcohol and chlordiazepoxide. Psychopharmacology **29:** 239–246, 1973.

CAPUTI, C. A., BUSCA, G., FOGLIARDI, A., AND GIUGLIANO, F.: Evaluation of tolerance in long-term treatment of cancer pain with epidural morphine. Int. J. Clin. Pharmacol. Ther. Toxicol. **21:** 587–590, 1983.

CARMON, A., MOR, J., AND GOLDBERG, J.: Application of laser to psychophysiological study of pain in man. *In* Advances in Pain Research and Therapy, ed. by J. J. Bonica and D. Albe-Fessard, vol. 1, pp. 375–380, Raven Press, New York, 1976.

CESSELIN, F., BOURGOIN, S., ARTAUD, F., AND HAMON, L.: Basic and regulatory mechanisms of in vitro release of met-enkephalin form the dorsal zone of the rat spinal cord. J. Neurochem. **43:** 763–773, 1984.

CESSELIN, F., MONTASTRUC, J. L., GROS, C., BOURGOIN, S., AND HAMON, M.: Met-enkephalin levels and opiate receptors in the spinal cord of chronic suffering rats. Brain Res. **191:** 289–293, 1980.

CHAPMAN, C. R., CASEY, K. L., DUBNER, R., FOLEY, K. M., GRACELY, R. H., AND READING, A. E.: Pain measurement: an overview. Pain **22:** 1–31, 1985.

CHENEY, D. L., AND GOLDSTEIN, A.: Tolerance to opioid narcotics: time and

reversibility of physical dependence in mice. Nature (Lond.) **232:** 477–478, 1971.
CHERNICK, V.: Fetal breathing movements and the onset of breathing at birth. Clin. Perinatol. **5:** 257–268, 1978.
CHERY-CROZE, S., KOCHER, L., BERNARD, C., AND CHAYVIALLE, J. A.: Substance P-, somatostatin-, vasoactive intestinal peptide- and cholecystokinine-like levels in the spinal cord of polyarthritic rats. Brain Res. **339:** 183–185, 1985.
CLARK, W. C., AND YANG, J. C.: Application of sensory decision theory to problems in laboratory and clinical pain. *In* Pain Measurement and Assessment, ed. by R. Melzack, pp. 3–25, Raven Press, New York, 1983.
CLOUET, D. H., AND IWATSUBO, K.: Mechanisms of tolerance to and dependence on narcotic analgesic drugs. Annu. Rev. Pharmacol. **15:** 49–71, 1975.
CLUTTON-BROCK, J.: The cerebral effects of overventilation. Br. J. Anaesth. **29:** 111–113, 1957.
CLYNES, M., ED.: Multiple Drug Resistance in Cancer: Cellular, Molecular and Clinical Approaches. Kluwer Academic Publishers, Dordrecht, The Netherlands, 1994.
COCHIN, J., AND KORNETSKY, C.: Development and loss of tolerance to morphine in the rat after single and multiple injections. J. Pharmacol. Exp. Ther. **145:** 1–10, 1964.
COGGESHALL, R. E., HONG, K. A. P., LANGFORD, L. A., SCHAIBLE, H. G., AND SCHMIDT, R. F.: Discharge characteristics of fine medial articular afferents at rest, during passive movements of inflamed knee joints. Brain Res. **272:** 185–188, 1983.
COHEN, P.: Signal integration at the level of protein kinases, protein phosphatases and their substrates. Trends Biochem. Sci. **17:** 408–413, 1992.
COLLIER, H. O. J.: Cellular site of opiate dependence. Nature (Lond.) **283:** 625–629, 1980.
COLLIER, H. O. J., AND ROY, A. C.: Morphine like drugs inhibit the stimulation by E prostaglandins of cyclic AMP formation by rat brain homogenate. Nature (Lond.) **248:** 24–27, 1974.
COLLIN, E., POULAIN, P., GAUVAIN-PIQUARD, A., PETIT, G., AND PICHARD-LEANDRI, E.: Is disease progression the major factor in morphine "tolerance" in cancer pain treatment? Pain **55:** 319–326, 1993.
COLLIN, E., AND CESSELIN, F.: Neurobiological mechanisms of opioid tolerance and dependence. Clin. Neuropharmacol. **14:** 465–488, 1991.
COLPAERT, F. C.: Narcotic cue and narcotic state. Life Sci. **20:** 1097–1108, 1977.
COLPAERT, F. C.: Discriminative stimulus properties of narcotic analgesic drugs. Pharmacol. Biochem. Behav. **9:** 863–887, 1978a.
COLPAERT, F. C.: Narcotic cue, narcotic analgesia, and the tolerance problem: the regulation of sensitivity to drug cues and to pain by an internal cue processing model. *In* Stimulus Properties of Drugs: Ten Years of Progress, ed. by F. L. Colpaert and J. Rosecrans, pp. 301–321, Elsevier Biomedical Press, Amsterdam, 1978b.
COLPAERT, F. C.: Long term suppression of pain by narcotic drugs in the absence of tolerance development. Arch. Int. Pharmacodyn. Ther. **236:** 293–295, 1978c.
COLPAERT, F. C.: Can chronic pain be suppressed despite purported tolerance to narcotic analgesia. Life Sci. **24:** 1201–1210, 1979.
COLPAERT, F. C.: The pharmacological specificity of opiate drug discrimination. *In* Drug Discrimination: Applications in CNS Pharmacology, ed. by F. L. Colpaert and J. Slangen, pp. 3–16, Elsevier Biomedical Press, Amsterdam, 1982.
COLPAERT, F. C.: Evidence that adjuvant arthritis in the rat is associated with chronic pain. Pain **28:** 201–202, 1987.
COLPAERT, F. C.: A mnesic trace locked into the benzodiazepine state of memory. Psychopharmacology **102:** 28–36, 1990.
COLPAERT, F. C.: Drug discrimination: no evidence for tolerance to opiates. Pharmacol. Rev. **47:** 605–629, 1995.
COLPAERT, F. C., BERVOETS, K. J. W., AND VAN DEN HOOGEN, R. H. W. M.: Pharmacological analysis of hyperventilation in arthritic rats. Pain **33:** 243–258, 1987.
COLPAERT, F. C., DE WITTE, P., MAROLI, A. N., AWOUTERS, F., NIEMEGEERS, C. J. E., AND JANSSEN, P. A. J.: Self administration of the analgesic suprofen in arthritic rats: evidence of mycobacterium butyricum-induced arthritis as an experimental model of chronic pain. Life Sci. **27:** 921–928, 1980b.
COLPAERT, F. C., DONNERER, J., AND LEMBECK, P.: Effects of capsaicin on inflammation and on the substance P content of nervous tissues in rats with adjuvant arthritis. Life Sci. **32:** 1827–1834, 1983.
COLPAERT, F. C., AND JANSSEN, P. A. J.: Agonist and antagonist effects of prototype opiate drugs in rats discrimination fentanyl from saline: characteristics of partial generalization. J. Pharmacol. Exp. Ther. **230:** 193–199, 1984.
COLPAERT, F. C., AND JANSSEN, P. A. J.: Agonist and antagonist effects of prototype opiate drugs in fentanyl dose-dose discrimination. Psychopharmacology **90:** 222–228, 1986.
COLPAERT, F. C., KUYPS, J. J. M. D., NIEMEGEERS, C. J. E., AND JANSSEN, P. A. J.: Discriminative stimulus properties of fentanyl and morphine: tolerance and dependence. Pharmacol. Biochem. Behav. **5:** 401–408, 1976b.
COLPAERT, F. C., MEERT, T. H., DE WITTE, P. H., AND SCHMITT, P.: Further evidence validating adjuvant arthritis as an experimental model of chronic pain in the rat. Life Sci. **31:** 67–75, 1982.
COLPAERT, F. C., NIEMEGEERS, C. J. E., AND JANSSEN, P. A. J.: The narcotic discriminative stimulus complex: relation to analgesic activity. J. Pharm. Pharmacol. **28:** 183–187, 1976c.
COLPAERT, F. C., NIEMEGEERS, C. J. E., AND JANSSEN, P. A. J.: Theoretical and methodological considerations on drug discrimination learning. Psychopharmacologia **46:** 169–177, 1976a.
COLPAERT, F. C., NIEMEGEERS, C. J. E., AND JANSSEN, P. A. J.: On the ability of narcotic antagonists to produce the narcotic cue. J. Pharmacol. Exp. Ther. **197:** 180–187, 1976d.
COLPAERT, F. C., NIEMEGEERS, C. J. E., AND JANSSEN, P. A. J.: Studies on the regulation of sensitivity to the narcotic cue. Neuropharmacology **17:** 705–713, 1978a.
COLPAERT, F. C., NIEMEGEERS, C. J. E., AND JANSSEN, P. A. J.: Narcotic cuing and analgesic activity of narcotic analgesics: associative and dissociative characteristics. Psychopharmacology **57:** 21–26, 1978b.
COLPAERT, F. C., NIEMEGEERS, C. J. E., AND JANSSEN, P. A. J.: Nociceptive stimulation prevents development of tolerance to narcotic analgesia. Eur. J. Pharmacol. **49:** 335–336, 1978c.
COLPAERT, F. C., NIEMEGEERS, C. J. E., JANSSEN, P. A. J., AND MAROLI, A. N.: The effects of prior fentanyl administration and of pain on fentanyl analgesia: tolerance to and enhancement of narcotic analgesia. J. Pharmacol. Exp. Ther. **213:** 418–424, 1980a.
COLPAERT, F. C., AND SHEARMAN, G. T.: Tolerance, endorphins and other aspects of opiate drug discrimination. *In* Endorphins, Opiates and Behavioural Processes, ed. by R. L. Rodgers and S. J. Cooper, pp. 77–105, J. Wiley and Sons, Ltd., London, 1988.
COLPAERT, F. C., AND SLANGEN, J., EDS.: Drug Discrimination: Applications in CNS Pharmacology. Elsevier Biomedical Press, Amsterdam, 1982.
COLPAERT, F. C., AND VAN DEN HOOGEN, R. H. W. M.: Ventilatory response to adjuvant arthritis in the rat. Life Sci. **32:** 957–963, 1983a.
COLPAERT, F. C., AND VAN DEN HOOGEN, R. H. W. M.: Time course of the ventilatory response to adjuvant arthritis in the rat. Life Sci. **33:** 1065–1073, 1983b.
COMROE, J. H., FORSTER, R. E., DUBOIS, A. B., BRISCOE, W. A., AND CARLSEN, E.: The Lung, 2nd ed. Year Book Medical Publishers, Chicago, 1962.
COSTA, T., AND HERZ, A.: Antagonists with negative intrinsic activity at δ opioid receptors coupled to GTP-binding proteins. Proc. Natl. Acad. Sci. USA **86:** 7321–7325, 1989.
COSTA, T., OGINO, Y., MUNSON, P. J., ONORAN, H. O., AND RODBARD, D.: Drug efficacy at guanine nucleotide-binding regulatory protein-linked receptors: thermodynamic interpretation of negative antagonism and of receptor activity in the absence of ligand. Mol. Pharmacol. **41:** 549–560, 1990.
COX, B. M.: Drug tolerance and physical dependence. *In* Principles of Drug Action. The Basis of Pharmacology, ed. by W. L. Pratt and P. Taylor, pp. 639–690, Churchill Livingstone, New York, 1990.
COX, B. M., GINSBURG, M., AND OSMAN, O. H.: Acute tolerance to narcotic analgesic drugs in rats. Br. J. Pharmac. Chemother. **33:** 245–256, 1968.
COX, B. M., AND WERLING, L. L.: Opioid tolerance and dependence. *In* The Biological Bases of Drug Tolerance and Dependence, ed. by J. A. Pratt, pp. 199–229, Academic Press, New York, 1991.
CRUWYS, S. C., GARRETT, N. E., AND KIDD, B. L.: Sensory denervation with capsaicin attenuates inflammation and nociception in arthritic rats. Neurosci. Lett. **193:** 205–207, 1995.
DAHLLOF, B., MARTINSSON, T., AND LEVAN, G.: Resistance to actinomycin D and to vincristine induced in a SEWA mouse tumor cell line with concomitant appearance of double minutes and a low-molecular-weight protein. Exp. Cell Res. **152:** 415–426, 1984.
DARDICK, S. J., BASBAUM, A. I., AND LEVINE, J. D.: The contribution of pain to disability in experimentally induced arthritis. Arthritis Rheum **29:** 1017–1022, 1986.
DE CASTRO-COSTA, M., DE SUTTER, P., GYBELS, J., AND VAN HEES, J.: Adjuvant induced arthritis in rats: a possible animal model of chronic pain. Pain **10:** 173–185, 1981.
DE CASTRO-COSTA, M., GYBELS, J., KUPERS, R., AND VAN HEES, J.: Scratching behaviour in arthritic rats: a sign of chronic pain or itch? Pain **29:** 123–131, 1987.
DE LEON-CASASOLA, O. A., AND LEMA, M. J.: Epidural bupivacaine/sufentanil therapy for postoperative pain control in patients tolerant to opioid and unresponsive to epidural bupivacaine/morphine. Anesthesiology **80:** 303–309, 1994.
DENEAU, G. A., AND SEEVERS, M. H.: Pharmacological aspects of drug dependence. Adv. Pharmacol. Chemother. **3:** 267–283, 1964.
DENNIS, S. G., AND MELZACK, R.: Comparison of phasic and tonic pain in animals. Adv. Pain Res. Ther. **3:** 747–760, 1979.
DESMOND, M. M., AND WILSON, G. S.: Neonatal Abstinence Syndrome: recognition and diagnosis. Addict. Dis. **2:** 113–121, 1975.
DICKINSON, A. H.: Mechanisms of the analgesic action of opiates and opioids. Br. Med. Bull. **47:** 690–702, 1991.
DICKINSON, A. H., AND LE BARS, D.: Diffuse noxious inhibitory controls (DNIC) involve trigeminothalamic and spinothalamic neurones in the rat. Exp. Brain Res. **49:** 174–180, 1983.
DING, Y.-Q., NOMURA, S., KANETO, T., AND MIZUNO, N.: Co-localization of μ-opioid receptor-like and substance P-like immunoreactivities in axon terminals within the superficial layers of the medullary and spinal dorsal horns of the rat. Neurosci. Lett. **198:** 45–48, 1995.
DRIESSEN, J. J., DE MULDER, P. H. M., CLAESSEN, J. J. L., VAN DIEJEN, D., AND WOBBES, T.: Epidural administration of morphine for control of cancer pain: long-term efficacy and complications. Clin. J. Pain **5:** 217–222, 1989.

DRORBAUGH, J. E., AND FENN, W. O.: A barometric method for measuring ventilation in newborn infants. Pediatrics 16: 81–87, 1955.
DUBNER, R.: Editorial comment. Pain 47: 1–2, 1991.
DUBUISSON, D., AND DENNIS, S. G.: The formalin test: a quantitative study of the analgesic effects of morphine, meperidine, and brain stem stimulation in rats and cats. Pain 4: 161–174, 1977.
DUGGAN, A. W., HALL, J. G., AND HEADLEY, P. M.: Enkephalins and dorsal horn neurones of the cat: effects on responses to noxious and innocuous skin stimuli. Br. J. Pharmacol. 61: 399–408, 1977.
DUGGAN, A. W., AND NORTH, R. A.: Electrophysiology of opioids. Pharmacol. Rev. 35: 219–281, 1984.
DUMAN, R. S., TALLMAN, J. F., AND NESTLER, E. J.: Acute and chronic opiate-regulation of adenylate cyclase in brain: specific effects in locus coeruleus. J. Pharmacol. Exp. Ther. 246: 1033–1039, 1988.
DUTTAROY, A., AND YOBURN, B. C.: The effect of intrinsic efficacy on opioid tolerance. Anesthesiology 82: 1226–1236, 1995.
EDDY, N. B., HALBACH, H., AND BRAENDON, O. J.: Synthetic substances with morphine-like effect. Bull. W. H. O. 17: 569–863, 1957.
EGER, E. I., DOLAN, W. M., STEVENS, W. C., MILLER, R. D., AND WAY, W. L.: Surgical stimulation antagonizes the respiratory depression produced by forane. Anesthesiology 36: 544–549, 1972.
ESPOSITO, R. V., AND KORNETSKY, C.: Opioids and rewarding brain stimulation. Neurosci. Biobehav. Rev. 2: 115–122, 1978.
FACCINI, E., UZUMAKI, M., GOVONI, S., MISSALE, C., SPANO, P. F., COVELLI, V., AND TRABUCCHI, M.: Afferent fibres mediate the increase of met-enkephalin elicited in rat spinal cord by localized pain. Pain 18: 25–31, 1984.
FERNANDES, M., KLUWE, S., AND COPER, H.: Development of tolerance to morphine in the rat. Psychopharmacology 54: 197–201, 1977a.
FERNANDES, M., KLUWE, S., AND COPER, H.: Quantitative assessment of tolerance to and dependence on morphine in mice. Naunyn-Schmiedebergs Arch. Pharmakol. 297: 53–60, 1977b.
FIELDS, H. L., AND BASBAUM, A. I.: Central nervous system mechanisms of pain modulation. *In* Textbook of Pain, ed. by P. L. Wall and R. Melzack, pp. 243–257, Churchill Livingstone, Edinburgh, 1994.
FIELDS, H. L., COX, B. M., FOLEY, K. M., HAASE, A. F., HERZ, A., HUMMEL, T., IADORALA, M. J., JAGE, J., LADUBON, P., STEIN, C., STEWART, J., VAUGHT, J. L., AND YAKSH, T. L.: Strategies for improving the pharmacological approaches to the maintenance of analgesia in chronic pain. *In* Towards a New Pharmacotherapy of Pain, ed. by A. L. Basbaum and J.-M. Besson, pp. 205–226, John Wiley & Sons, Ltd., New York, 1991.
FITZGERALD, M.: c-Fos and the changing face of pain. Trends Neurosci. 13: 439–440, 1990.
FITZGIBBON, D. R., AND GALER, B. S.: The efficacy of opioids in cancer pain syndromes. Pain 58: 429–431, 1994.
FLECKNELL, P. A., KIRK, A. J. B., LILES, J. H., HAYES, P. H., AND DARK, J. H.: Post-operative analgesia following thoracotomy in the dog: an evaluation of the effects of bupivacaine intercostal nerve block and nalbuphine on respiratory function. Lab. Anim. 25: 319–324, 1991.
FLEISCHMANN, A., AND URCA, G.: Clip induced analgesia: noxious neck pinch suppresses spinal and mesencephalic neural responses to noxious peripheral stimulation. Physiol. Behav. 46: 151–157, 1989.
FOLEY, K. M.: Controversies in cancer pain: medical perspectives. Cancer 63: 2257–2265, 1989.
FOLEY, K. M.: Clinical tolerance to opioids. *In* Towards a New Pharmacotherapy of Pain, ed. by A. I. Basbaum and J.-M. Besson, pp. 181–203, John Wiley & Sons, Ltd., New York, 1991.
FOLKARD, S., GLYNN, C. J., AND LLOYD, J. W.: Diurnal variation and individual differences in the perception of intractable pain. J. Psychosom. Res. 20: 289–301, 1976.
FRASER, H. F., ISBELL, H., AND VAN HORN, G. D.: Effects of morphine as compared with a mixture of morphine and diaminophenylthiazole (daptazole). Anesthesiology 18: 531–535, 1957.
FREDERICKSON, R. C. A., BURGIS, V., HARRELL, C. E., AND EDWARDS, J. D.: Dual actions of substance P on nociception: possible role of endogenous opioids. Science (Wash. DC) 199: 1359–1362, 1978.
FRY, J. P., ZIEGLGÄNSBERGER, W., AND HERZ, A.: Development of acute opioid tolerance and dependence in rat striatal neurones. Naunyn-Schmiedebergs Arch. Pharmakol. 313: 145–149, 1980.
FU, Q.-G., SANDKÜHLER, J., AND ZIMMERMANN, M.: B-vitamins enhance afferent inhibitory controls of nociceptive neurons in the rat spinal cord. Klin. Wochenschr. 68: 125–128, 1990.
GAMSE, R., HOLZER, P., AND LEMBECK, F.: Decrease of substance P in primary afferent neurones and impairment of neurogenic plasma extravasation by capsaicin. Br. J. Pharmacol. 68: 207–213, 1980.
GARCIA, J., KIMMELDORF, D. J., AND KOELING, R. A.: Conditioned aversion to saccharin resulting from exposure to gamma radiation. Science (Wash. DC) 122: 157–158, 1955.
GAUTRON, M., AND GUILBAUD, G.: Somatic responses of ventrobasal thalamic neurons in polyarthritic rats. Brain Res. 237: 459–471, 1982.
GEAR, R. W., AND LEVINE, J. D.: Antinociception produced by an ascending spino-supraspinal pathway. J. Neurosci. 15: 3154–3161, 1995.
GEDDES, I. C., AND GRAY, T. C.: Hyperventilation for the maintenance of anaesthesia. Lancet, ii: 4–6, 1959.
GELLERT, V. F., AND HOLTZMAN, S. G.: Development and maintenance of morphine tolerance and dependence in the rat by scheduled access to morphine drinking solutions. J. Pharmacol. Exp. Ther. 205: 536–549, 1978.
GELLERT, V. F., AND SPARBER, S. B.: A comparison of the effects of naloxone upon body weight loss and suppression of fixed-ratio operant behavior in morphine dependent rats. J. Pharmacol. Exp. Ther. 201: 44–54, 1977.
GEORGES, E., SHAROM, F. F., AND LING, V.: Multidrug resistance and chemosensitization: therapeutic implications for cancer chemotherapy. Adv. Pharmacol. Chemother. 21: 185–220, 1990.
GERLACH, J. H., KARTNER, N., BELL, D. R., AND LING, V.: Multidrug resistance. Cancer Surv. 5: 25–46, 1986.
GLAVINA, M. J., AND ROBERTSHAW, R.: Myoclonic spasms following intrathecal morphine. Anaesthesia 43: 389–390, 1988.
GLYNN, C. J., LLOYD, J. W., AND FOLKHARD, S.: Ventilatory response to intractable pain. Pain 11: 201–211, 1981.
GODEFROY, F., WEIL-FUGAZZA, J., AND BESSON, J.-M.: Complex temporal changes in 5-hydroxytryptamine synthesis in the central nervous system induced by experimental polyarthritis in the rat. Pain 28: 223–238, 1987.
GOLD, L. H., STINUS, L., INTURISSI, C. E., AND KOOB, G. F.: Prolonged tolerance, dependence and abstinence following subcutaneous morphine pellet implantation in the rat. Eur. J. Pharmacol. 253: 45–51, 1994.
GOLDFARB, J., KAPLAN, E. I., AND JENKINS, H. R.: Interaction of morphine and naloxone in acute spinal cats. Neuropharmacology 17: 569–575, 1978.
GOLDIE, J. H., PRICE, L. A., AND HARRAP, K. R.: Methotrexate toxicity: correlation with duration of administration, plasma levels, dose and excretion. Eur. J. Cancer 8: 409–414, 1972.
GOLDSTEIN, A., AND SHEEHAN, P.: Tolerance to opioid narcotics. I. Tolerance to the "running fit" caused by levorphanol in the mouse. J. Pharmacol. Exp. Ther. 169: 175–184, 1969.
GOUDIE, A. J.: Conditioned opponent processes in the development of tolerance to psychoactive drugs. Prog. Neuropsychopharmacol. Biol. Psychiatr. 14: 675–688, 1990.
GOUDIE, A. J., AND EMMETT-OGLESBY, M. W., EDS. Tolerance and Sensitization, Humana Press, Clifton, New York, 1989.
GOUDIE, A. J., THORNTON, E. W., AND WHEALLER, T. J.: Drug pretreatment effects in drug-induced taste aversions: effects of dose and duration of pretreatment. Pharmacol. Biochem. Behav. 4: 629–633, 1976.
GOURLAY, G. K.: Long term use of opioids in chronic pain patients with non terminal disease states. Pain Rev. 1: 62–76, 1994.
GRAY, T. C., AND REES, G. J.: The role of apnoea in anesthesia for major surgery. Br. Med. J. 47: 891–893, 1952.
GREEN, D. M., AND SWETS, J. A.: Signal Detection Theory and Psychophysics, Wiley, New York, 1966.
GROSSMAN, S. P.: A Textbook of Physiological Psychology, John Wiley & Sons, Inc., New York, 1967.
GUILBAUD, G., BENOIST, J. M., GAUTRON, M., AND KAYSER, V.: Aspirin clearly depresses responses of ventrobasal thalamus neurons to joint stimuli in arthritic rats. Pain 13: 153–163, 1982.
GUILBAUD, G., IGGO, A., AND TEGNER, R.: Sensory receptors in ankle joint capsules of normal and arthritic rats. Exp. Brain Res. 58: 29–40, 1985a.
GUILBAUD, G., IGGO, A., AND TEGNER, R.: Sensory changes in joint-capsule receptors of arthritic rats: effect of aspirin. *In* Advances in Pain Research and Therapy, ed. by H. L. Fields, vol. 9, pp. 81–89, Raven Press, New York, 1985b.
GUPTA, R. S.: Cross resistance of vinblastine- and taxol-resistant mutants of Chinese hamster ovary cells to other anticancer drugs. Cancer Treat. Rep. 69: 515–521, 1985.
GUTSTEIN, H. B., TRUJILLO, K. A., AND AKIL, H.: Does chronic nociceptive stimulation alter the development of morphine tolerance? Brain Res. 680: 173–179, 1995.
GYBELS, J., DOM, R., AND COSYNS, P.: Electrical stimulation of the central gray for pain relief in human: autopsy data. Acta Neurochir. 30(suppl.): S259–S268, 1980.
HAIGLER, H. J.: Neurophysiological effects of opiates in the CNS. Monogr. Neural Sci. 13: 132–160, 1987.
HAMMOND, D. L.: Do opiates relieve central pain? *In* Pain and Central Nervous System Disease: The Central Pain Syndromes, ed. by K. L. Casey, pp. 233–241, Raven Press, New York, 1991.
HANKS, G. W., TWYCROSS, R. G., AND LLOYD, J. W.: Unexpected complications of successful nerve block. Morphine-induced respiratory depression precipitated by removal of severe pain. Anaesthesia 36: 37–39, 1981.
HENRY, J. L.: Effects of substance P on functionally identified units in cat spinal cord. Brain Res. 114: 439–451, 1976.
HERLING, S., AND WOODS, J. H.: Discriminative stimulus effects of narcotics: evidence for multiple receptor-mediated actions. Life Sci. 28: 1571–1584, 1981.
HERZ, A., ED.: Opioids I., Springer-Verlag, New York, 1993.
HILL, B. T.: Biochemical and cell kinetic aspects of drug resistance. *In* Drug and Hormone Resistance in Neoplasia: Basic Concepts, ed. by L. Bruchovsky and J. H. Goldie, vol. 1, pp. 21–53, CRC Press, Boca Raton, FL, 1982.
HILL, B. T.: In vitro human tumour model systems for investigating drug resistance. Cancer Surv. 5: 129–149, 1986.
HILL, R. G.: Pharmacological considerations in the use of opioids in the management of pain associated with nonterminal disease states. Pain Rev. 1: 47–61, 1994.
HIROSE, K., AND JYOYAMA, H.: Measurement of arthritic pain and effects of

analgesics in the adjuvant-treated rat. Jpn. J. Pharmacol. **21:** 717–720, 1971.

HÖKFELT, T., KELLERTH, J. D., NILSSON, G., AND PERNOW, B.: Experimental immunohistochemical studies on the localization and distribution of substance P in cat primary sensory neurons. Brain Res. **100:** 235–252, 1975.

HOLTZMAN, S. G.: Stimulus properties of opioids with mixed agonist and antagonist activity. Fed. Proc. **41:** 2328–2332, 1982.

HOSKING, L. K., WHELAN, R. D. H., SHELLARD, S. A., DAVIES, S. L., HICKSON, M. K., AND HILL, B. T.: Multiple mechanisms of resistance in a series of human testicular teratoma cell lines selected for increasing resistance to etoposide. Int. J. Cancer **57:** 259–267, 1994.

HOUDE, R. W.: Nathan B. Eddy Memorial Lecture: the analgesic connection. *In* Problems of Drug Dependence 1984, Proceedings of the 46th Annual Scientific Meeting, ed. by L. S. Harris, The Committee on Problems of Drug Dependence, Inc., NIDA Res. Monogr., **55:** 4–13, 1985.

HOUDE, R. W., WALLENSTEIN, S. L., AND BEAVER, W. T.: Evaluation of analgesics in patients with cancer pain. *In* Clinical Pharmacology, International Encyclopedia of Pharmacology and Therapeutics, ed. by L. Lasagna, vol. 1, pp. 59–98, Pergamon, Oxford, 1966.

HUGHES, P., AND DRAGUNOW, M.: Induction of immediate-early genes and the control of neurotransmitter-regulated gene expression within the nervous system. Pharmacol. Rev. **47:** 133–178, 1995.

HUNT, C. E.: The cardiorespiratory control hypothesis for sudden infant death syndrome. Clin. Perinatol. **19:** 757–771, 1992.

HUNT, S. P., PINI, A., AND EVAN, Y.: Induction of C-fos-like protein in spinal cord neurons following sensory stimulation. Nature (Lond.) **328:** 632–634, 1987.

HYLDEN, J. L. K., THOMAS, D. A., IARDOLA, M. J., NAHIR, R. L., AND DUBNER, R.: Spinal opioid analgesic effects are enhanced in a model of unilateral inflammation/hyperalgesia: possible involvement of noradrenergic mechanisms. Eur. J. Pharmacol. **194:** 135–143, 1991.

INOKI, R., OHNISHI, T., SAITO, K., MAEDA, S., MATSUMOTO, K., AND SAKUDA, M.: Chronic morphine administration and in vivo pertussis toxin treatment induce hyperalgesia and enhance ^{3}H-nitrendipine binding. Prog. Clin. Biol. Res. **328:** 469–472, 1990.

JACQUET, Y. F.: β-Endorphin and ACTH-opiate peptides with coordinated roles in the regulation of behavior. TINS **2:** 140–143, 1979.

JADAD, A. R., CARROLL, D., GLYNN, C. J., MOORE, R. A., AND MCQUAY, H. J.: Morphine responsiveness of chronic pain: double-blind randomized crossover study with patient-controlled analgesia. Lancet **339:** 1367–1371, 1992.

JAFFE, J. H.: Drug addiction and drug abuse. *In* Goodman and Gilman's The Pharmacological Basis of Therapeutics, ed. by A. G. Goodman, L. S. Goodman, and A. Gilman, pp. 534–584, MacMillan, New York, 1980.

JAFFE, J. H., AND MARTIN, W. R.: Opioid agonists and antagonists. *In* Goodman and Gillman's The Pharmacological Basis of Therapeutics, ed. by A. G. Gillman, T. W. Rall, A. L. Nies, and P. Taylor, P., vol. 9, pp. 485–593, MacMillan, New York, 1990.

JANSSEN, P. A. J., NIEMEGEERS, C. J. E., AND DONY, J. G. H.: The inhibitory effect of fentanyl (R 4263) and other morphine-like analgesics on the warm water induced tail withdrawal reflex in rats. Arzneim. Forsch. **13:** 502–507, 1963.

JANSSEN, P. A. J., NIEMEGEERS, C. J. E., SCHELLEKENS, K. H. L., MARSBOOM, R. H. M. HERIN, V. V., AMERY, W. K. P., ADMIRAAL, P. V., BOSKER, J. T., CRUL, J. F., PEARCE C., AND ZEGVELD, C.: Bezitramide (R4845), a new potent and orally long-acting analgesic compound. Arzneim. Forsch. **21:** 862–867, 1971.

JASINSKI, D. R.: Assessment of the abuse potentiality of morphine-like drugs (methods used in man). *In* Drug Addiction I., ed. by W. R. Martin, pp. 197–258, Springer-Verlag, New York, 1977.

JOHNSON, S. M., AND DUGGAN, A. W.: Dependence in the absence of tolerance to morphine. Eur. J. Pharmacol. **97:** 305–308, 1984.

JOHNSON, S. M., AND FLEMING, W. W.: Mechanisms of cellular adaptive sensitivity changes: applications to opioid tolerance and dependence. Pharmacol. Rev. **41:** 435–488, 1989.

JONES, R. S., AND WARD, J. R.: Studies on adjuvant-induced polyarthritis in rats. II. Histogenesis of joint and visceral lesions. Arthritis Rheum. **6:** 23–35, 1963.

JONES, R. S., AND WARD, J. R.: Adjuvant induced polyarthritis in rats. Methods Achiev. Exp. Pathol. **1:** 607–638, 1966.

JORIS, J., COSTELLO, A., DUBNER, R., AND HARGREAVES, K. M.: Opiates suppress carrageenan-induced edema and hyperthermia at doses that inhibit hyperalgesia. Pain **43:** 95–103, 1990.

KAIKO, R. F., WALLENSTEIN, S. L., ROGERS, A. G., GRABINSKI, P. Y., AND HOUDE, R. W.: Analgesic and mood effects of heroin and morphine in cancer patients with postoperative pain. N. Engl. J. Med. **304:** 1501–1505, 1981.

KALANT, H.: Nathan B. Eddy Memorial Award Lecture: tolerance and its significance for drug and alcohol dependence. *In* Problems of Drug Dependence 1986, Proceedings of the 48th Annual Scientific Meeting, ed. by L. S. Harris, The Committee on Problems of Drug Dependence, Inc., NIDA Res. Monogr., **76:** 9–19, 1987.

KANDALL, S. R., ALBIN, R. S., GARTNER, L. M., LEE, K. S., EIDELMAN, A., AND LOWINSON, J.: The narcotic dependent mother: fetal and neonatal consequences. Early Human Dev. **1:** 159–169, 1977.

KANETO, H., KOIDA, M., NAKANISHI, H., AND SASANO, H.: A scoring system for abstinence syndrome in morphine dependent mice and application to evaluate morphine type dependence liability of drugs. Jpn. J. Pharmacol. **23:** 701–707, 1973.

KANETO, H., YAMAZAKI, A., AND KIHARA, T.: Evidence for dissociation of morphine analgesia, tolerance and dependence. J. Pharmacol. **37:** 507–508, 1985.

KANTOR, T. G., CANTOR, R., AND TOM, E.: A study of hospitalized surgical patients on methadone maintenance. Drug Alcohol Depend. **6:** 163–173, 1980.

KARTNER, N., SHALES, M., RIORDAN, J. R., AND LING, V.: Daunorubicin resistant Chinese hamster ovary cells expressing multidrug resistance and a cell-surface P-glycoprotein. Cancer Res. **43:** 4413–4419, 1983.

KAYAN, S., AND MITCHELL, C. L.: The effects of chronic morphine administration on tooth pulp threshold in dogs and cats. Proc. Soc. Exp. Biol. (NY) **128:** 755–790, 1968.

KAYAN, S., FERGUSON, R. K., AND MITCHELL, C. L.: An investigation of pharmacologic and behavioral tolerance to morphine in rats. J. Pharmacol. Exp. Ther. **185:** 300–306, 1973.

KAYAN, S., WOODS, L. A., AND MITCHELL, C. L.: Morphine induced hyperalgesia in rats tested on the hot plate. J. Pharmacol. Exp. Ther. **177:** 509–513, 1971.

KAYSER, V., BENOIST, J. M., AND GUILBAUD, G.: Further evidence for a strong depressive effect of low doses of morphine on VB thalamic neuronal responses (a study on arthritic rats). Brain Res. **267:** 187–191, 1983.

KAYSER, V., BESSON, J.-M., AND GUILBAUD, G.: Paradoxical hyperalgesic effect of exceedingly low doses of systemic morphine in an animal model of persistent pain (Freund's adjuvant-induced arthritic rats). Brain Res. **414:** 155–157, 1987.

KAYSER, V., BESSON, J.-M., AND GUILBAUD, G.: Effects of the analgesic agent tramadol in normal and arthritic rats: comparison with the effects of different opioids, including tolerance and cross-tolerance to morphine. Eur. J. Pharmacol. **195:** 37–45, 1991.

KAYSER, V., FOURNIÉ-ZALUSKI, M. C., GUILBAUD, G., AND ROQUES, B. P.: Potent antinociceptive effects of kelatorphan (a highly efficient inhibitor of multiple enkephalin-degrading enzymes) systemically administered in normal and arthritic rats. Brain Res. **497:** 94–101, 1989.

KAYSER, V., AND GUILBAUD, G.: Dose dependent analgesic and hyperalgesic effects of systemic naloxone in arthritic rats. Brain Res. **226:** 344–348, 1981.

KAYSER, V., AND GUILBAUD, G.: The analgesic effects of various doses of morphine, but not those of the enkephalinase inhibitor thiorphan, are enhanced in arthritic rats. Brain Res. **267:** 131–138, 1983.

KAYSER, V., AND GUILBAUD, G.: Further evidence for changes in the responsiveness of somatosensory neurons in arthritic rats: a study of the posterior intralaminar region of the thalamus. Brain Res. **323:** 144–147, 1984.

KAYSER, V., AND GUILBAUD, G.: Can tolerance to morphine be induced in arthritic rats? Brain Res. **334:** 335–338, 1985.

KAYSER, V., AND GUILBAUD, G.: Differential effects of various doses of morphine and naloxone on two nociceptive test thresholds in arthritic and normal rats. Pain **41:** 353–363, 1990.

KAYSER, V., NEIL, A., AND GUILBAUD, G.: Repeated low doses of morphine induce a rapid tolerance in arthritic rats but a potentiation of opiate analgesia in normal animals. Brain Res. **383:** 392–396, 1986.

KELEMEN, K.: Analgesia, tolerance and drug dependence. *In* Hormones and Brain Function, ed. by K. Lissak, pp. 273–283, Plenum Press, New York, 1973.

KIM, D. H., FIELDS, H. L., AND BARBARO, N. M.: Morphine analgesia and acute physical dependence: rapid onset of two opposing, dose-related processes. Brain Res. **516:** 37–40, 1990.

KITAHATA, L. M., KOSAKA, Y., TAUB, A., BONIKOS, K., AND HOFFERT, M.: Lamina specific suppression of dorsal horn unit activity by morphine sulfate. Anesthesiology **41:** 39–48, 1974.

KJAERSGAARD-ANDERSEN, P., NAFEI, A., SKOV, O., MODSEN, F., ANDERSEN, H. M., KRONER, K., HVASS, I., GJODERUM, O., PEDERSEN, L., AND BRANEBJERG, P. E.: Codeine plus paracetamol versus paracetamol in longer-term treatment of chronic pain due to osteoarthritis of the hip: a randomised double-blind, multi-centre study. Pain **43:** 309–318, 1990.

KLAIN, D. B., KRAUSS, A. N., AND AULD, P. A. M.: Tachypnea and alkalosis in infants of narcotic-addicted mothers. N.Y. State J. Med. **1:** 367–368, 1972.

KOLB, L., AND HIMMELSBACH, C. K.: Clinical studies of drug addiction. Am. J. Psychiatry **94:** 759–799, 1938.

KOOB, G. F., AND BLOOM, F. E.: Cellular and molecular mechanisms of drug dependence. Science (Wash. DC) **242:** 715–723, 1988.

KORF, J., BUNNEY, B. S., AND AGHAJANIAN, G. K.: Noradrenergic neurons: morphine inhibition of spontaneous activity. Eur. J. Pharmacol. **25:** 165–169, 1974.

KORNETSKY, C.: Early studies of tolerance to morphine. *In* Problems of Drug Dependence, Proceeding of the 48th Annual Scientific Meeting, ed. by L. S. Harris, The Committee on Problems of Drug Dependence, Inc., NIDA Res. Monogr., **76:** 20–28, 1987.

KOSERSKY, D. S., HARRIS, R. A., AND HARRIS, L. S.: Naloxone jumping activity in mice following the acute administration of morphine. Eur. J. Pharmacol. **21:** 122–126, 1974.

KREEK, M. J.: Tolerance and dependence: implications for the pharmacological treatment of addiction. *In* Problems of Drug Dependence, Proceedings of the 48th Annual Scientific Meeting, ed. by L. S. Harris, The Committee on Problems of Drug Dependence, Inc., NIDA Res. Monogr., **76:** 53–62, 1987.

KUPERS, R. C., AND GYBELS, J.: The consumption of fentanyl is increased in rats

with nociceptive but not with neuropathic pain. Pain 60: 137–141, 1995.
KUPERS, R. C., KONINGS, H., ADRIAENSEN, H., AND GYBELS, J. M.: Morphine differentially affects the sensory and affective pain ratings in neurogenic and idiopathic forms of pain. Pain 47: 5–12, 1991.
KUPERS, R. C., VOS, B. P. J., AND GYBELS, J.: Stimulation of the nucleus paraventricularis thalami suppresses scratching and biting behaviour of arthritic rats and exerts a powerful effect on tests for acute pain. Pain 32: 115–125, 1988.
KURAISHI, Y., NAGASAWA, T., HAYASHI, K., AND SATOH, M.: Scratching behavior induced by pruritogenic but not algesiogenic agents in mice. Eur. J. Pharmacol. 275: 229–233, 1995.
LAIRD, J. M. A., AND CERVERO, F.: A comparative study of the changes in receptive-field properties of multireceptive and nociceptive rat dorsal horn neurons following noxious mechanical stimulation. J. Neurophysiol. 62: 854–863, 1989.
LAMOUR, Y., GUILBAUD, G., AND WILLER, J. C.: Altered properties and laminar distribution of neuronal responses to peripheral stimulation in the SMI cortex of the arthritic rat. Brain Res. 273: 183–187, 1983.
LARUE, F., COLLEAU, S. M., BRASSEUR, L., AND CLEELAND, C. S.: Multicentre study of cancer pain and its treatment in France. Br. Med. J. 310: 1034–1037, 1995.
LE BARS, D., CHITOUR, D., AND CLOT, A. M.: The encoding of thermal stimuli by diffuse noxious inhibitory controls (DNIC). Brain Res. 230: 394–399, 1981.
LE BARS, D., DICKENSON, A. H., AND BESSON, J.-M.: Diffuse noxious inhibitory controls (DNIC). I. Effects on dorsal horn convergent neurones in the rat. Pain 6: 283–304, 1979.
LE BARS, D., GUILBAUD, G., JURNA, I., AND BESSON, J.-M.: Differential effects of morphine on responses of dorsal horn lamina V type cells elicited by A and C fibre stimulation in the spinal cat. Brain Res. 115: 518–524, 1976b.
LE BARS, D., MENETREY, D., BESSON, J.-M.: Effects of morphine upon the lamina V type cells activities in the dorsal horn of the decerebrate cat. Brain Res. 113: 293–310, 1976a.
LE BARS, D., VILLANUEVA, L., BOUHASSIRA, D., AND WILLER, J.-C.: Diffuse noxious inhibitory controls (DNIC) in animals and in man. Pathol. Physiol. Exp. Ther. 4: 55–65, 1992.
LEHMANN, K. A., AND ZECH, D.: Transdermal fentanyl: clinical pharmacology. J. Pain Sympt. Manag. 7(suppl.): S8–S16, 1992.
LEMBECK, F., DONNERER, J., AND COLPAERT, F. C.: Increase of substance P in primary afferent nerves during chronic pain. Neuropeptides 1: 175–180, 1981.
LEMBECK, F., AND ZETLER, G.: Substance P: a polypeptide of possible physiological significance, especially within the nervous system. Int. Rev. Neurobiol. 4: 159–215, 1962.
LÉRIDA, M., SANCHEZ-BLAZQUEZ, P., AND GARZON, J.: Incidence of morphine withdrawal and quasi-abstinence syndrome in a model of chronic pain in the rat. Neurosci. Lett. 81: 155–158, 1987.
LEVINE, J. D., FIELDS, H. L., AND BASBAUM, A. I.: Peptides and the primary afferent nociceptor. J. Neurosci. 13: 2273–2286, 1993.
LIGHT, A. B., TORRANCE, E. G., KARR, W. G., FEY, E. G., AND WOLFF, W. A.: Opium Addiction (reprinted from Arch. Intern. Med. 43-44: 1929–1930), American Medical Association, Chicago, 1930.
LING, G. S. F., PAUL, D., SIMANTOV, R., AND PASTERNAK, G. W.: Differential development of acute tolerance to analgesia, respiratory depression, gastrointestinal transit and hormone release in a morphine infusion model. Life Sci. 45: 1627–1636, 1989.
LIPMAN, J. J., BLUMENKOPF, B., AND PARRIS, W. C.: Chronic pain assessment using heat beam dolometry. Pain 30: 59–67, 1987.
LIU, X.-G., AND SANDKÜHLER, J.: The effects of extrasynaptic substance P on nociceptive neurons in laminae I and II in rat lumbar spinal dorsal horn. Neuroscience 68: 1207–1218, 1995.
LOCKE, K. W., AND HOLTZMAN, S. G.: Behavioral effects of opioid peptides selective for mu or delta receptors. J. Pharmacol. Exp. Ther. 238: 997–1003, 1986.
LOH, K. H., AND SMITH, A. P.: Molecular characterization of opioid receptors. Annu. Rev. Pharmacol. Toxicol. 30: 123–147, 1990.
LOMBARD, M.-C., AND BESSON, J.-M.: Attempts to gauge the relative importance of pre- and postsynaptic effects of morphine on the transmission of noxious messages in the dorsal horn of the rat spinal cord. Pain 37: 335–345, 1989a.
LOMBARD, M.-C., AND BESSON, J.-M.: Electrophysiological evidence for a tonic activity of the spinal cord intrinsic opioid systems in a chronic pain model. Brain Res. 477: 48–56, 1989b.
LOTHSTEIN, L., AND HORWITZ, S. B.: Expression of phenotypic traits following modulation of colchicine resistance in J774.2 cells. J. Cell Physiol. 127: 253–260, 1986.
LYNESS, W. H., SMITH, F. L., HEAVNER, J. E., IACONO, C. U., AND GARVIN, R. D.: Morphine self-administration in the rat during adjuvant-induced arthritis. Life Sci. 45: 2217–2224, 1989.
MAN IN'T VELD, A. J., VAN DEN MEIRACKER, A. H., AND SCHALEKAMP, M. A.: Do beta-blockers really increase peripheral vascular resistance? Review of the literature and new obeervations under basal conditions. Am. J. Hypertens. 1: 91–96, 1988.
MAO, J., PRICE, D. D., AND MAYER, D. J.: Mechanisms of hyperalgesia and morphine tolerance: a current view of their possible interactions. Pain 62: 259–274, 1995.
MARKLEY, H. G.: Chronic headache: appropriate use of opiate analgesics. Neurology 44(suppl. 3): S18–S24, 1994.
MARTIN, W. R.: Drug Addiction I. & II., Springer, New York, 1977.
MARTIN, W. R.: Pharmacology of opioids. Pharmacol. Rev. 35: 283–323, 1984.
MARTIN, W. R., AND EADES, C. G.: A comparison between acute and chronic physical dependence in the chronic spinal dog. J. Pharmacol. Exp. Ther. 146: 385–394, 1964.
MARTIN, W. R., GILBERT, P. E., JASINSKI, P. E., AND MARTIN, C. D.: An analysis of naltrexone precipitated abstinence in morphine-dependent chronic spinal dogs. J. Pharmacol. Exp. Ther. 240: 565–570, 1987.
MARTIN, W. R., AND JASINSKI, D. R.: Physiological parameters of morphine dependence in man-tolerance, early abstinence, protracted abstinence. J. Psychiatr. Res. 7: 9–17, 1969.
MARTIN, W. R., MCNICHOLAS, L. F., AND CHERIAN, S.: Diazepam and pentobarbital dependence in the rat. Life Sci. 31: 721–730, 1982.
MARUTA, T., SWANSON, D. W., AND FINLAYSON, R. E.: Drug abuse and dependency in patients with chronic pain. Mayo Clin. Proc. 54: 241–244, 1979.
MCGIVNEY, W. T., AND CROOKS, G. M.: The care of patients with severe chronic pain in terminal illness. JAMA 251: 1182–1188, 1984.
MCLAUGHLIN, C. R., AND DEWEY, W. L.: A comparison of the antinociceptive effects of opioid agonists in neonatal and adult rats in phasic and tonic nociceptive tests. Pharmacol. Biochem. Behav. 49: 1017–1023, 1994.
MELZACK, R.: Humans versus pain: the dilemma of morphine. Adv. Pain Res. Ther. 20: 149–159, 1992.
MELZACK, R., AND WALL, P. D.: Pain mechanisms: a new theory. Science (Wash. DC) 150: 971–979, 1965.
MÉNARD, D. P., VAN ROSSUM, D., KAR, S., JOLICOEUR, F. B., JHAMANDAS, K., AND QUIRION, R.: Tolerance to the antinociceptive properties of morphine in the rat spinal cord: alteration of calcitocin gene-related peptide-like immuno-staining and receptor binding sites. J. Pharmacol. Exp. Ther. 273: 887–894, 1995.
MENETREY, D., AND BESSON, J. M.: Electrophysiological characteristics of dorsal horn cells in rats with cutaneous inflammation resulting from chronic arthritis. Pain 13: 343–364, 1982.
MERCADANTE, S., MADDALONI, S., ROCELLA, S., AND SALVAGGIO, L.: Predictive factors in advanced cancer pain treated only by analgesics. Pain 50: 151–155, 1992.
MERSKEY, H.: The status of pain. *In* Modern Trends in Psychosomatic Medicine, ed. by O. W. Hill, vol. 3, pp. 166–186, Butterworth, London, 1976.
MERSKEY, H., AND BOGDUK, N., EDS.: Classification of Chronic Pain. IASP Press, Seattle, 1994.
MEYERSON, B. A.: Electrostimulation procedures: effects, presumed rationale, and possible mechanisms. *In* Advances in Pain Research and Therapy, ed. by J. J. Bonica, U. Lindblom, and A. Iggo, vol. 5, pp. 395–542, Raven Press, New York, 1983.
MILLAN, M. J., MILLAN, M. H., COLPAERT, F. C., AND HERZ, A.: Chronic arthritis in the rat: differential changes in discrete brain pools of vasopressin as compared to oxytocin. Neurosci. Lett. 54: 33–37, 1985a.
MILLAN, M. J., MILLAN, M. H., CZLONKOWSKI, A., HÖLLT, V., PILCHER, C. W. T., HERZ, A., AND COLPAERT, F. C.: A model of chronic pain in the rat: responses of multiple opioid systems to adjuvant-induced arthritis. Neuroscience 6: 899–906, 1986a.
MILLAN, M. J., MILLAN, M. H., CZLONKOWSKI, A., PILCHER, C. W. T., HÖLLT, V., COLPAERT, F. C., AND HERZ, A.: Functional response of multiple opioid systems to chronic arthritic pain in the rat. N.Y. Acad. Sci. 467: 182–193, 1986b.
MILLAN, M. J., MILLAN, M. H., PILCHER, C. W. T., COLPAERT, F. C., AND HERZ, A.: Chronic pain in the rat: selective alterations in CNS and pituitary pools of dynorphin as compared to vasopressin. Neuropeptides 5: 423–424, 1985b.
MILLAN, M. J., MILLAN, M. H., PILCHER, C. W. T., CZLONKOWSKI, A., HERZ, A., AND COLPAERT, F. C.: Spinal cord dynorphin may modulate nociception via a κ-opioid receptor in chronic arthritis rats. Brain Res. 340: 156–159, 1985c.
MILLIGAN, G., BOND, R. A., AND LEE, M.: Inverse agonism: pharmacological curiosity or potential therapeutic strategy? TIPS 16: 10–13, 1995.
MOHIBUR-RAHMAN, A. F. M., TAKAHASHI, M., AND KANETO, H.: Development of tolerance to morphine antinociception in mice treated with nociceptive stimulants. Jpn. J. Pharmacol. 63: 59–64, 1993.
MOHRLAND, J. S., AND JOHNSON, E. E.: Use of the adjuvant-induced arthritic rat model to evaluate non-steroidal anti-inflammatory analgesics. J. Pharm. Pharmacol. 35: 401, 1983.
MORGAN, J. I., AND CURRAN, T.: Stimulus transcription coupling in the nervous system: involvement of the inducible proto-oncogenes fos and jun. Annu. Rev. Neurosci. 14: 421–451, 1991.
MORGAN, M. M., GOGAS, K. R., AND BASBAUM, A. I.: Diffuse noxious inhibitory controls reduce the expression of noxious stimulus-evoked Fos-like immunoreactivity in the superficial and deep laminae of the rat spinal cord. Pain 56: 347–352, 1994.
MORLEY, J. S., MILES, J. B., WELLS, J. C., AND BOWSHER, D.: Paradoxical pain. Lancet 340: 1045, 1992.
MORTOLA, J. P.: Dynamics of breathing in newborn mammals. Physiol. Rev. 67: 187–243, 1987.
MORTON, C. R., MAISCH, B., AND ZIMMERMANN, M.: Diffuse noxious inhibitory controls of lumbar spinal neurons involve a supraspinal loop in the cat. Brain Res. 410: 347–352, 1987.
MOUNT, B. M., AJEMIAN, I., AND SCOTT, J. F.: Use of the Brompton mixture in

treating the chronic pain of malignant disease. CMAJ **115:** 122–124, 1976.
MUELLER, R. A., LUNDBERG, D. B. A., BREESE, G. R., HEDNER, J., HEDNER, T., AND JONASON, J.: The neuropharmacology of respiratory control. Pharmacol. Rev. **34:** 255–285, 1982.
MULÉ, S. J., CLEMENTS, T. H., LAYSON, R. C., AND HAERTZEN, C. A.: Analgesia in guinea pigs: a measure of tolerance development. Arch. Int. Pharmacodyn. **173:** 201–212, 1968.
MULLER, H., STOYANOV, M, BORNER, U., AND HEMPELMANN, G.: Epidural opiates for relief of cancer pain. *In* Spinal Opiate Analgesia, ed. by T. L. Yaksh, H. Muller, and A. Engquist, pp. 125–137, Springer, Berlin, 1982.
NEIL, A. V., KAYSER, G., GACEL, G., BESSON, J.-M., AND GUILBAUD, G.: Opioid receptor types and antinociceptive activity in chronic inflammation: both κ- and μ-opiate agonistic effects are enhanced in arthritic rats. Eur. J. Pharmacol. **130:** 203–208, 1986.
NESS, T. J., AND GEBHART, G. F.: Interactions between visceral and cutaneous nociception in the rat. I. Noxious cutaneous stimuli inhibit visceral nociceptive neurons and reflexes. J. Neurophysiol. **66:** 20–28, 1991a.
NESS, T. J., AND GEBHART, G. F.: Interactions between visceral and cutaneous nociception in the rat. II. Noxious visceral stimuli inhibit cutaneous nociceptive neurons and reflexes. J. Neurophysiol. **66:** 29–39, 1991b.
NESTLER, E. J.: Molecular mechanisms of drug addiction. J. Neurosci. **12:** 2439–2450, 1992.
NIES, A. S.: Principles of therapeutics. *In* The Pharmacological Basis of Therapeutics, ed. by A. G. Gilman, T. W. Rall, A. S. Nies, and P. Taylor, pp. 62–83, Pergamon Press, New York, 1990.
OHNISHI, T., SAITO, K., MAEDA, S., MATSUMOTO, K., SAKUDA, M., AND INOKI, R.: Intracerebroventricular treatment of mice with pertussis toxin induces hyperalgesia and enhances ^{3}H-nitrendipine binding to synaptic membranes: similarity with morphine tolerance. Naunyn-Schmiedebergs Arch. Pharmakol. **341:** 123–127, 1990.
OKUYAMA, S., AND AIHARA, H.: Inhibition of electrically-induced vocalization in adjuvant-arthritic rats as a novel method for evaluating analgesic drugs. Jpn. J. Pharmacol. **34:** 67–77, 1984a.
OKUYAMA, S., AND AIHARA, H.: Effects of morphine and indomethacin on evoked neuronal reponses of ventrobasal thalamic neurones: site of action of analgesic drugs in adjuvant arthritic rats. Jpn. J. Pharmacol. **36:** 177–186, 1984b.
ONOFRIO, B. M., AND YAKSH, T. L.: Long term pain relief produced by intrathecal morphine infusion in 53 patients. J. Neurosurg. **72:** 200–209, 1990.
OVERTON, D. A.: Experimental methods for the study of state-dependent learning. Fed. Proc. **33:** 1800–1813, 1974.
OWEN, H., AND WHITE, P. F.: Patient controlled analgesia: an overview. *In* Acute Pain Mechanisms and Management, ed. by R. S. Sinatra, A. H. Hord, B. Ginsberg, and L. M. Preble, pp. 151–164, Mosby, Boston, 1992.
PAPPAGALLO, M., AND CAMPBELL, J. N.: Chronic opioid therapy as alternative treatment for post-herpetic neuralgia. Ann. Neurol. **35:** S54–S56, 1994.
PARSONS, C. M., AND GOETZL, F. R.: Effects of induced pain on pain threshold. Proc. Soc. Exp. Biol. **60:** 327–329, 1945.
PASTAN, I., AND GOTTESMAN, M. M.: Multidrug resistance. Annu. Rev. Med. **42:** 277–286, 1991.
PASTERNAK, G. W.: Multiple morphine and enkephalin receptors and the relief of pain. JAMA **259:** 1362–1367, 1988.
PASTERNAK, G. W.: Pharmacological mechanisms of opioid analgesics. Clin. Neuropharmacol. **16:** 1–18, 1993.
PEARSON, C. M.: Development of arthritis, periarthritis and periostitis in rats given adjuvant. Proc. Soc. Exp. Biol. Med. (NY) **91:** 95–101, 1956.
PEARSON, C. M.: Experimental joint disease: observations on adjuvant-induced arthritis. J. Chronic Dis. **16:** 863–874, 1963.
PERNOW, B.: Substance P. Pharmacol. Rev.: **35:** 85–141, 1983.
PICKER, M. J., AND YARBROUGH, J.: Cross tolerance and enhanced sensitivity to the response rate-decreasing effects of opioids with varying degress of efficacy at the mu receptor. Psychopharmacology **105:** 459–466, 1991.
PIRCIO, A. W., FEDELE, C. T., AND BIERWAGEN, M. E.: A new method for the evaluation of analgesic activity using adjuvant-induced arthritis in the rat. Eur. J. Pharmacol. **31:** 207–215, 1975.
POLLEN, J. J., AND SCHMIDT, J. D.: Bone pain in metastatic cancer of prostate. Urology **13:** 129–134, 1979.
PORTENOY, R. K.: Chronic opioid therapy for persistent noncancer pain: can we get past the bias? Am. Pain Soc. Bull. **1:** 1–5, 1991.
PORTENOY, R. K.: Opioid therapy for chronic nonmalignant pain: current status. *In* Progress in Pain Research and Management, ed. by H. L. Fields and J. C. Liebeskind, vol. 1, pp. 247–287, IASP Press, Seattle, 1994a.
PORTENOY, R. K.: Tolerance to opioid analgesics: clinical aspects. Cancer Surv. **21:** 49–65, 1994b.
PORTENOY, R. K., AND FOLEY, K. M.: Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. Pain **25:** 171–186, 1986.
PORTENOY, R. K., FOLEY, K. M., AND INTURISSI, C. E.: The nature of opioid responsiveness and its implications for neuropathic pain: new hypotheses derived from studies of opioid infusions. Pain **43:** 273–286, 1990.
POTTER, J. M., REID, D. B., SHAW, R. J., HACKETT, P., AND HICKMANN, P. E.: Myoclonus associated with treatment with high doses of morphine: the role of supplemental drugs. Br. Med. J. **299:** 150–153, 1989.
PROCACCI, P., ZOPPI, M., AND MARESCA, M.: Experimental pain in man. Pain **6:** 123–140, 1979.
RAINSFORD, K. D.: Adjuvant polyarthritis in rats: is this a satisfactory model for screening anti-arthritic drugs? Agents Actions **12:** 452–458, 1982.
RALPHS, J. A., WILLIAMS, A. C. C., RICHARDSON, P. H., PITHER, C. E., AND NICHOLAS, M. K.: Opiate reduction in chronic pain patients: a comparison of patient-controlled reduction and staff controlled cocktail methods. Pain **56:** 279–288, 1994.
RANDIC, M., AND MILETIC, V.: Depressant actions of methionine-enkephalin and somatostatin in cat dorsal horn neurones activated by noxious stimuli. Brain Res. **152:** 196–202, 1978.
RATH, H., TISTY, T., AND SCHIMKE, R. T.: Rapid emergence of methotrexate resistance in cultured mouse cells. Cancer Res. **44:** 3303–3306, 1984.
RAUHALA, P., IDÄNPÄÄN-HEIKKILÄ, J. J., TUOMINEN, R. K., AND MÄNNISTÖ, P. T.: Differential disappearance of tolerance to thermal, hormonal and locomotor effects of morphine in the male rat. Eur. J. Pharmacol. **285:** 69–77, 1995.
REDMOND, D. E., AND KRYSTAL, J. H.: Multiple mechanisms of withdrawal from opioid drugs. Annu. Rev. Neurosci. **7:** 443–478, 1984.
REISINE, T.: Opiate receptors. Neuropharmacology **34:** 463–472, 1995.
REULER, J. B., GIRARD, D. E., AND NARDONE, D. A.: The chronic pain syndrome: misconceptions and management. Ann. Intern. Med. **93:** 588–596, 1980.
RIGATTO, H.: Maturation of breathing. Clin. Perinatol. **19:** 739–756, 1992.
RITZMANN, R. F.: Opiate dependence following acute injections of morphine and naloxone: the assessment of various withdrawal signs. Pharmacol. Biochem. Behav. **14:** 575–577, 1981.
ROBY-BRAMI, A., BUSSEL, B., WILLER, J. C., AND LE BARS, D.: An electrophysiological investigation into the pain-relieving effects of heterotopic nociceptive stimuli. Brain **110:** 1497–1508, 1987.
RODGERS, R. J., AND RANDALL, J. I.: Environmentally induced analgesia: situational factors, mechanisms and significance. *In* Endorphins, Opiates and Behavioural Processes, ed. by R. J. Rodgers and S. J. Cooper, pp. 107–142, John Wiley, New York, 1988.
ROHDE, D. S., DETWEILER, D. J., AND BASBAUM, A. I.: Spinal cord mechanisms of opioid tolerance and dependence: fos-like immunoreactivity expression increases in subpopulations of spinal cord neurons during withdrawal. Neuroscience **72:** 233–242, 1996.
ROSENTHALE, M. E., AND CAPETOLA, R. J.: Adjuvant arthritis: immunopathological and hyperalgesic features. Fed. Proc. **41:** 2577–2582, 1982.
ROSOW, C.: Acute and chronic tolerance relevance for clinical practice. *In* Problems of Drug Dependence, Proceedings of the 48th Annual Scientific Meeting, ed. by L. S. Harris, L. S., The Committee on Problems of Drug Dependence, Inc., NIDA Res. Monogr., **76:** 29–34, 1987.
ROSSBACH, M. J.: Ueber die Gewöhnung an Gifte. Arch. Gesmante Physiol. Mens. Tiere **21:** 213–225, 1880.
RUBINSTEIN, R. B., SPIRA, I., AND WOLFF, W. I.: Management of surgical problems in patients on methadone maintenance. Am. J. Surg. **131:** 566–569, 1976.
RUOFF, G. E.: Treatment of the chronic pain of osteoarthritis: zomepirac versus aspirin. Curr. Ther. Res. **32:** 638–645, 1982.
RYAN, G. P., AND BOISSE N. R.: Experimental induction of benzodiazepine tolerance and physical dependence. J. Pharmacol. Exp. Ther. **226:** 100–107, 1983.
SAGEN, J., AND WANG, H.: Adrenal medullary grafts suppress c-fos induction in spinal neurons of arthritic rats. Neurosci. Lett. **192:** 181–184, 1995.
SALTER, M. W., AND HENRY, J. L.: Differential responses of nociceptive vs. non-nociceptive spinal dorsal horn neurones to cutaneously applied vibration in the cat. Pain **40:** 311–322, 1990a.
SALTER, M. W., AND HENRY, J. L.: Physiological characteristics of responses of wide dynamic range spinal neurones to cutaneously applied vibration in the cat. Brain Res. **507:** 69–84, 1990b.
SANDKÜHLER, J., AND EBLEN-ZAJJUR, A. A.: Identification and characterization of rhythmic nociceptive and non-nociceptive spinal dorsal horn neurons in the rat. Neuroscience **61:** 991–1006, 1994.
SATOH, M., KAWAJIRI, S. I., UKAI, Y., AND YAMAMOTO, M.: Selective and non-selective inhibition by enkephalins and noradrenaline of nociceptive responses of lamina V type neurons in the spinal dorsal horn of the rabbit. Brain Res. **177:** 384–387, 1979.
SAUNDERS, D. C.: Principles of symptom control in terminal care. Med. Clin. North Am. **66:** 1169–1183, 1982.
SCHEPELMAN, K., MESSLINGER, K., SCHAIBLE, H.-G., AND SCHMIDT, R. F.: The opioid antagonist naloxone does not alter discharges of nociceptive afferents from the acutely inflamed knee joint of the cat. Neurosci. Lett. **187:** 212–214, 1995.
SCHOENEN, J., VAN HEES, J., GYBELS, J., DE CASTRO-COSTA, C. M., AND VANDERHAEGHEN, J. J.: Histochemical changes of substance P, serotonin and succinic dehydrogenase in the spinal cord of rats with adjuvant arthritis. Life Sci. **36:** 1247–1254, 1985.
SCHOENLEIN, P. V.: Molecular cytogenetics of multiple drug resistance. Cytotechnology **122:** 63–89, 1993.
SHANNON, H. E., AND HOLTZMAN, S. G.: Evaluation of the discriminative effects of morphine in the rat. J. Pharmacol. Exp. Ther. **198:** 54–65, 1976.
SHARMA, S. K., NIRENBERG, M., AND KLEE, W. A.: Morphine receptors as regulators of adenylate cyclase activity. Proc. Natl. Acad. Sci. USA **72:** 590–594, 1975.
SHERMAN, J. E., PROCTOR, C., AND STRUB, H.: Prior hot plate exposure enhances morphine analgesia in tolerant and drug-naive rats. Pharmacol. Biochem. Behav. **17:** 229–232, 1982.

SHERRINGTON, C. S.: The Integrative Action of the Central Nervous System, Constable, London, 1906.
SHIPPENBERG, T. S., STEIN, C., HUBER, C., MILLAN, M. J., AND HERZ, A.: Motivational effects of opioids in an animal model of prolonged inflammatory pain: alteration in the effects of kappa—-but not of mu—receptor agonists. Pain **35:** 179–186, 1988.
SIEGEL, S.: Pharmacological conditioning and drug effects. *In* Psychoactive Drugs: Tolerance and Sensitization, ed. by A. J. Goudie and M. W. Emmett-Oglesby, pp. 115–180, Humana Press, Clifton, NY, 1989.
SIEGEL, S.: Classical conditioning and opiate tolerance and withdrawal. *In* Psychotropic Drugs of Abuse, ed. by D. K. J. Balfour, pp. 59–85, Pergamon, New York, 1990.
SIGURDSSON, A., AND MAIXNER, W.: Effects of experimental and clinical noxious irritants on pain perception. Pain **57:** 265–275, 1994.
SJOGREN, P., AND ERIKSEN, J.: Opioid toxicity. Curr. Opin. Anaesthesiol. **7:** 465–469, 1994.
SJOGREN, P., JONSSON, T., JENSEN, N.-H., DRENCK, N.-E., AND JENSEN, T. S.: Hyperalgesia and myoclonus in terminal cancer patients treated with continuous intravenous morphine. Pain **55:** 93–97, 1993.
SKINNER, B. F.: The Behavior of Organisms, Appleton-Century-Crofts, Inc., New York, 1938.
SKOVSGAARD, T., NIELSEN, D., MAARE, A., AND WASSERMANN, K.: Cellular resistance to cancer chemotherapy. Int. Rev. Cytol. **156:** 77–157, 1994.
SMITH, A. P., LAW, P.-Y., AND LOH, H. H.: Role of opioid receptors in narcotic tolerance/dependence. *In* The Opiate Receptors, ed. by G. W. Pasternak, pp. 441–489, Humana Press, Totowa, NY, 1988.
SOFIA, R. D., AND VASSAR, H. B.: Changes in serotonin (5-HT) concentrations in brain tissue of rats with adjuvant-induced polyarthritis. Arch. Int. Pharmacodyn. **211:** 74–79, 1974.
STANFA, L., DICKINSON, A., XU, X.-J., AND WIESENFELD-HALLIN, Z.: Cholecystokinin and morphine analgesia. TIPS **15:** 65–66, 1994.
STEIN, C.: Peripheral mechanisms of opioid analgesia. Anesth. Analg. **76:** 182–191, 1993.
STEIN, C., MILLAN, M. J., YASSOURDIS, A., AND HERZ, A.: Antinociceptive effects of μ- and κ-agonists in inflammation are enhanced by a peripheral opioid receptor-specific mechanism. Eur. J. Pharmacol. **155:** 255–264, 1988a.
STEIN, C., MILLAN, M. J., SHIPPENBERG, T. S., AND HERZ, A.: Peripheral effects of fentanyl upon nociception in inflamed tissue of the rat. Neurosci. Lett. **84:** 225–228, 1988b.
STERNBACH, R. A.: Pain: a psychophysiological analysis. Academic Press, New York, 1968.
STERNBACH, R. A.: Acute versus chronic pain. *In* Textbook of Pain, ed. by P. D. Wall and R. Melzack, pp. 173–177, Churchill Livingstone, New York, 1984.
STEVENS, C. W., AND YAKSH, T. L.: Potency of infused spinal antinociceptive agents is inversely related to magnitude of tolerance after continuous infusion. J. Pharmacol. Exp. Ther. **250:** 1–8, 1989.
STRIAN, F., LAUTENBACHER, S., GALFE, G., AND HÖLZL, R.: Diurnal variations in pain perception and thermal sensitivity. Pain **36:** 125–131, 1989.
SUFKA, K.: Conditioned place preference paradigm: a novel approach for analgesic drug assessment against chronic pain. Pain **58:** 355–366, 1994.
SWETS, J. A.: Signal Detection and Recognition by Human Observers, Wiley, New York, 1964.
SWINGLE, K. F.: Evaluation of antiinflammatory activity. *In* Antiinflammatory Agents, ed. by R. A. Scherrer and M. W. Whitchouse, vol. 2, pp. 33–122, Academic Press, New York, 1974.
TAKEMORI, A. E.: Neurochemical basis for narcotic tolerance and dependence. Biochem. Pharmacol. **24:** 2121–2126, 1975.
TALBOT, J. D., DUNCAN, G. H., AND BUSHNELL, M. C.: Effects of diffuse noxious inhibitory controls (DNICs) on the sensory-discriminative dimension of pain perception. Pain **36:** 231–238, 1989.
TAUB, A.: Opioid analgesics in the treatment of chronic intractable pain of non-neoplastic origin. *In* Narcotic Analgesics in Anesthesiology, ed. by L. M. Kitahata and D. Collins, pp. 199–208, Williams & Wilkins, Baltimore, 1982.
TESKEY, G. C., AND KAVALIERS, M.: Modifications of social conflict-induced analgesic and activity responses in male mice receiving chronic opioid agonist and antagonist treatments. Pharmacol. Biochem. Behav. **38:** 485–493, 1991.
THALER, H. T., FRIEDLANDER-KLAR, H., CIRRINCIONE, C.: A statistical approach to measuring analgesic response, *In* Proceedings of the VIth World Congress on Pain, ed. by M. R. Bond, J. E. Charlton, and C. J. Woolf, pp. 543–546, Elsevier, Amsterdam, 1991.
THERIAULT, E., OTSUKA, M., AND JESSEL, T.: Capsaisin evoked release of substance P from primary sensory neurons. Brain Res. **170:** 209–213, 1979.
THUREL, C., BARDIN, T., AND BOCCARD, E.: Analgesic efficacy of an association of 500 mg paracetamol plus 30 mg codeine versus 400 mg paracetamol plus 30 mg dextropropoxyphene in repeated doses for chronic lower back pain. Curr. Ther. Res. **50:** 463–473, 1991.
TILSON, H. A., RECH, R. H., AND STOLMAN, S.: Hyperalgesia during withdrawal as a means of measuring the degree of dependence in morphine dependent rats. Psychopharmacologia **28:** 287–300, 1973.
TOLLE, T. R., CASRO-LOPES, J. M., COIMBRA, A., AND ZIEGLGÄNSBERGER, W.: Opiates modify induction of c-fos proto-oncogene in the spinal cord of the rat following noxious stimulation. Neurosci. Lett. **111:** 46–51, 1990.
TOYOOKA, H., HANOAKA, K, OHTANI, M., YAMASHITA, M., TAUB, A., AND KITAHATA, L. M.: Suppressive effect of morphine on single-unit activity of cells in Rexed lamina VII. Anesthesiology **47:** 513–517, 1977.
TRABER, J., GULLIS, R., AND HAMPRECHT, B.: Influence of opiates on the levels of adenosine 3′: 5′-cyclic monophosphate in neuroblastoma X glioma hybrid cells. Life Sci. **16:** 1863–1868, 1975.
TRUJILLO, K. A., AND AKIL, H.: Opiate tolerance and dependence: recent findings and synthesis. New Biologist **3:** 915–923, 1991.
TWYCROSS, R. G.: Clinical experience with diamorphine in advanced malignant disease. Int. J. Clin. Pharmacol. Ther. Toxicol. **9:** 184–198, 1974.
TWYCROSS, R. G.: Relief of pain. *In* The Management of Terminal Disease, ed. by C. M. Saunders, pp. 65–98, Edward Arnold, Ltd., London, 1978.
TWYCROSS, R. G., AND MCQUAY, H. J.: Opioids. *In* The Textbook of Pain, ed. by P. D. Wall and R. Melzack, pp. 686–701, Churchill Livingstone, London, 1989.
TWYCROSS, R. G., AND WALD, S. J.: Longterm use of diamorphine in advanced cancer. *In* Advances in Pain Research and Therapy, ed. by J. J. Bonica and D. G. Albe-Fessard, vol. 1, pp. 653–661, Raven Press, New York, 1976.
VACCARINO, A. L., MAREK, P., KEST, B., BEN-ELIYAHU, S., COURET, L. C., KAO, B., AND LIEBESKIND, J. C.: Morphine fails to produce tolerance when administered in the presence of formalin pain in rats. Brain Res. **627:** 287–290, 1993.
VAN BEVER, W., AND LAL, H. (EDS.) Synthetic Antidiarrheal Drugs, Marcel Dekker, Inc., New York, 1976.
VAN DEN HOOGEN, R. H. W. M., BERVOETS, K. J. W., AND COLPAERT, F. C.: Respiratory effects of epidural morphine and sufentanil in the absence and presence of chlordiazepoxide. Pain **37:** 103–110, 1989.
VAN DEN HOOGEN, R. H. W. M., AND COLPAERT, F. C.: Respiratory effects of morphine in awake unrestrained rats. J. Pharmacol. Exp. Ther. **237:** 252–259, 1986.
VICKERS, D.: Decision processes in visual perception. Academic Press, New York, 1979.
VIERCK, C. J., AND COOPER, B. Y.: Guidelines for assessing pain reactions and pain modulation in laboratory animal subjects. *In* Advances in Pain Research and Therapy, ed. by L. Kruger and J. C. Liebeskind, vol. 6, pp. 305–322, Raven Press, New York, 1984.
VLOK, G. J., AND VAN VUREN, J. P.: Comparison off a standard ibuprofen treatment regimen with a new ibuprofen/paracetamol/codeine combination in chronic osteoarthritis. S. Afr. Med. J. **1(suppl.):** 4–6, 1987.
VOLM, M., BAK, M., JR., EFFERTH, T., AND MATTERN, J.: Induced multidrug-resistance in murine sarcoma 180 cells grown in vitro and in vivo and associated changes in expression of multidrug-resistance DNA-sequences and membrane glycoproteins. Anticancer Res. **8:** 1169–1178, 1988.
WALLENSTEIN, S. L., HOUDE, R. W., PORTENOY, R. K., LAPIN, J., ROGERS, A., AND FOLEY, K. M.: Clinical analgesic assay of repeated and single doses of heroin and hydromorphone. Pain **41:** 5–13, 1990.
WALSH, T. O.: Oral morphine in chronic cancer pain. Pain **18:** 1–11, 1984.
WAND-TETLEY, J. I.: Historical methods of counter-irritation. Ann. Phys. Med. **3:** 90–98, 1956.
WANG, H., AND SAGEN, J.: Attenuation of pain-related hyperventilation in adjuvant arthritic rats with adrenal medullary transplants in the spinal subarachnoid space. Pain **63:** 313–320, 1995.
WARD, J. R., AND JONES, R. S.: Studies on adjuvant-induced polyarthritis in rats. I. Adjuvant composition, route of injection and removal of depot site. Arthritis Rheum. **5:** 557–571, 1962.
WARNCKE, T., BREIVIK, H., AND VAINIO, A.: Treatment of cancer pain in Norway: a questionnaire study. Pain **57:** 109–116, 1994.
WASCHULEWSKI, F. H., MILTNER, W., BRODY, S., AND BRAUN, C.: Classical conditioning in pain responses. Int. J. Neurosci. **78:** 21–32, 1994.
WAY, E. L., LOH, H. H., AND SHEN, F.-H.: Simultaneous quantitative assessment of morphine tolerance and physical dependence. J. Pharmacol. Exp. Ther. **167:** 1–8, 1969.
WEI, E., LOH, H. H., AND WAY, E. L.: Quantitative aspects of precipitated abstinence in morphine-dependent rats. J. Pharmacol. Exp. Ther. **184:** 398–403, 1973.
WEIHE, E., IADORALA, M. J., NOHR, D., MÜLLER, S., MILLAN, M. J., YANAIHARA, N., STEIN, C., AND HERZ, A.: Sustained expression and colocalization of proenkephalin and prodynorphin opioids and C-fos protein in dorsal horn neurones revealed in arthritic rats. *In* New Leads in Opioid Research, ed. by J. van Ree, A. H. Mulder, V. M. Wiegant, and T. B. van Wimersma Greidanus, pp. 92–94, Elsevier, Amsterdam, 1990.
WEIL-FUGAZZA, J., GODEFROY, F., AND BESSON, J.-M.: Changes in brain and spinal tryptophan and 5-hydroxyindoleacetic acid levels following acute morphine administration in normal and arthritic rats. Brain Res. **175:** 291–301, 1979.
WEIL-FUGAZZA, J., GODEFROY, F., BINEAU-THUROTTE, M., AND BESSON, J. M.: Plasma tryptophan levels and 5-hydroxytryptamine synthesis in the brain and the spinal cord in arthritic rats. *In* Progress in Tryptophan and Serotonin Research, ed. by H. G. Schlossberger, W. Kochen, B. Linzen, and H. Steinhart, pp. 405–408, Walter de Gruyter, Berlin, 1984.
WEIL-FUGAZZA, J., GODEFROY, F., COUDERT, D., AND BESSON, J.-M.: Total and free serum tryptophan levels and brain 5-hydroxytryptamine metabolism in arthritic rats. Pain **9:** 319–325, 1980.
WEIL-FUGAZZA, J., GODEFROY, F., MANCEAU, V., AND BESSON, J.-M.: Increased norepinephrine and uric acid levels in the spinal cord of arthritic rats. Brain Res. **374:** 190–194, 1986.

WHELAN, R. D. H., AND HILL, B. T.: Differential expression of steroid receptors, hsp27 and pS2 in a series of drug resistant human breast tumor cell lines derived following exposure to antitumor drugs or to fractionated X-irradiation. Breast Cancer Res. Treat. **26:** 23–39, 1993.

WIKLER, A.: Dynamics of drug dependence. Arch. Gen. Psychiatry **28:** 611–616, 1973.

WILCOX, R. E., MIKULA, J. A., AND LEVITT, R. A.: Periaqueductal gray naloxone microinjections in morphine-dependent rats: hyperalgesia without "classical" withdrawal. Neuropharmacology **18:** 639–641, 1979.

WILLER, J. C., ROBY, A., AND LE BARS, D.: Psychophysical and electrophysiological approaches to the pain relieving effects of heterotopic nociceptive stimuli. Brain **107:** 1095–1112, 1984.

WINTER, C. A., AND FLATAKER, L.: Reaction thresholds to pressure in edematous hindpaws of rats and responses to analgesic drugs. J. Pharmacol. Exp. Ther. **150:** 65–171, 1965.

WINTER, C. A., KLING, P. J., TOCCO, D. J., AND TANABE, K.: Analgesic activity of difunisal in rats with hyperalgesia induced by Freund's adjuvant. J. Pharmacol. Exp. Ther. **211:** 678–725, 1979.

WOLFF, H. G., HARDY, J. D., AND GOODELL, H.: Studies on pain. Measurement of the effect of morphine, codeine, and other opiates on the pain threshold and an analysis of their relationship to the pain experience. J. Clin. Invest. **19:** 659–680, 1940.

WOOLF, C. J., AND WALL, P. D.: Morphine sensitive and morphine-insensitive actions of C-fibre input on the rat spinal cord. Neurosci. Lett. **64:** 221–225, 1986.

WÜSTER, M., SCHULZ, R., AND HERZ, A.: The development of opiate tolerance may dissociate from dependence. Life Sci. **31:** 1695–1698, 1982.

YAKSH, T. L., AND NOUEIHED, R.: The physiology and pharmacology of spinal opiates. Annu. Rev. Pharmacol. Toxicol. **25:** 433–462, 1985.

YAKSH, T. L., AND RUDY, T. A.: Studies on the direct spinal action of narcotics in the production of analgesia in the rat. J. Pharmacol. Exp. Ther. **202:** 411–418, 1977.

YASHPAL, K., PITCHER, G. M., AND HENRY, J. L.: Noxious peripheral stimulation produces antinociception mediated via substance P and opioid mechanisms in the rat tail-flick test. Brain Res. **674:** 97–103, 1995.

YOBURN, B. C., CHEN, J., HUANG, T., AND INTURRISI, C. E.: Pharmacokinetics and pharmacodynamics of subcutaneous morphine pellets in the rat. J. Pharmacol. Exp. Ther. **235:** 282–286, 1985.

YONEHARA, N., KUDO, T., IWATSUBO, K., MAEDA, S., SAITO, K., AND INOKI, R.: A possible involvement of the central endorphin system in autoanalgesia induced by chronic administration of Freund's Adjuvant solution in rats. Pain **17:** 91–98, 1983.

YOUNG, A. M.: Tolerance to drug stimulus control. Drug Dev. Res. **20:** 205–215, 1990.

YOUNG, A. M.: Tolerance to drugs acting as discriminative stimuli. *In* Drug Discrimination: Applications to Drug Abuse Research, ed. by R. A. Glennon, T. U. C. Järbe, and J. Frankenheim, NIDA Res. Monogr. 116, pp. 197–212, U.S. Government Printing Office, Washington, D.C., 1991.

YOUNG, A. M., AND SANNERUD, C. A.: Tolerance to drug discriminative stimuli. *In* Tolerance and Sensitization, ed. by A. J. Goudie and M. W. Emmett-Oglesby, pp. 221–278, Humana Press, Clifton, NY, 1989.

ZENZ, M.: Morphine myths: sedation, tolerance, addiction. Postgrad. Med. J. **67**(suppl.)**:** S100–S102, 1991.

ZENZ, M., SCHAPPLER-SCHEELE, B., NEUHAUS, R., PIEPENBROCK, S., AND HILFRICH, J.: Long term peridural analgesia in cancer pain [letter]. Lancet **1:** 91, 1981.

ZENZ, M., AND SORGE, J.: Is the therapeutic use of opioids adversely affected by prejudice and law? Recent Results Cancer Res. **121:** 43–50, 1991.

ZENZ, M., STRUMPF, M., AND TRYBA, M.: Long-term opioid therapy in patients with chronic nonmalignant pain. J. Pain Symptom Manage. **7:** 69–77, 1992.

ZENZ, M., STRUMPF, M., TRYBA, M., RÖHRS, E., AND STEFFMAN, B.: Retardiertes Morphin zur Langzeittherapie schwerer Tumorschmerzen. Dtsch. Med. Wochenschr. **114:** 43–47, 1989.

ZENZ, M., AND WILLWEBER-STRUMPF, A.: Opiophobia and cancer pain in Europe. Lancet **341:** 1075–1076, 1993.

ZIEGLGÄNSBERGER, W., AND BAYERL, H.: The mechanism of inhibition of neuronal activity by opiates in the spinal cord of the cat. Brain Res. **115:** 111–128, 1976.

ZYLICZ, Z., AND TWYCROSS, R. G.: Oral opioids in the treatment of cancer pain. Neth. J. Med. **39:** 108–114, 1991.