Biochemical Pharmacology, Vol. 32, No. 4, pp. 573–585, 1983.
Printed in Great Britain.

0006-2952/83/040573-13 $03.00/0

COMMENTARY

CARDIOVASCULAR CONSEQUENCES OF ENDOGENOUS OPIATE ANTAGONISM

JOHN W. HOLADAY

Neuropharmacology Branch, Department of Medical Neurosciences, Division of Neuropsychiatry, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, DC 20012, U.S.A.

An exciting new era of cardiovascular pharmacology has emerged as a consequence of the discovery of endogenous opiate systems. Prior to that time, alkaloid opiates had been shown to depress cardiovascular function by lowering heart rate, decreasing arterial pressure, and blunting baroreceptor reflexes. The combined autonomic actions of opiates in enhancing parasympathetic and inhibiting sympathetic outflow were shown to act synergistically to produce bradycardia and hypotension [1–4]. A secondary effect of opiate-induced histamine release contributed to the circulatory sequelae in certain species [5].

With the discovery of opiate receptors as well as the endogenous ligands with which they interact came a flurry of research directed at uncovering the possible physiological roles subserved by this system (see Ref. 6 for review). Important clues could be derived from the wealth of pharmacological history on the actions of alkaloid opiates. More uniquely important, however, was the availability of specific opiate antagonists such as naloxone. This substance is a critical tool with which to study endogenous opiate actions since alterations of behavioral or physiological endpoints following naloxone injection serve to implicate an endogenous opiate involvement [6–8].

An important contribution to studies of endogenous opiates (collectively referred to as "endorphins") was the demonstration that these systems are functionally quiescent until a real or perceived stress is imposed to disrupt normal homeostatic mechanisms. Guillemin and coworkers [9] reported that circulating concentrations of β-endorphin, an untriakontapeptide found in the anterior pituitary gland and the brain, were dramatically elevated in stressed rats. The antinociceptive effect of stress-induced endorphin activation was shown by Akil and colleagues [10]; electric foot shock in rats produced a naloxone-reversible increase in nociceptive latencies.

Although only a few years ago, these early days of endorphin pharmacology have yielded to a far more complex picture. At least ten different peptides, isolated and purified from biological tissues, have been shown to have naloxone-reversible opiate actions (Table 1). Moreover, endorphins have been shown to have widespread distribution in the central nervous system, sympathetic ganglia, and plexi of the gut, where they may subserve a role in neurotransmission. In the periphery, various endorphins are also found in the pituitary gland and adrenal medulla; stimulation of these neurohumoral tissues results in their release into the bloodstream to subserve a possible hormonal role.

Instead of a single population of opiate receptors, multiple opiate receptor subtypes have been characterized *in vitro* and *in vivo*. These include mu receptors, delta receptors, kappa receptors, and others [11–13]. Elucidation of the physiological importance of these opiate receptor subtypes awaits the development of selective antagonists. However, opiate agonist administration has suggested some fruitful areas for future research. Additionally, the relevance of high and low affinity binding sites to specific opiate receptor subtypes requires clarification.

What evidence has accrued to implicate endorphin involvement in cardiovascular function? First of all, endorphin-containing nerve cells [14–16] and opiate receptor populations [17–19] are densely distributed in neuroanatomical nuclei of the central nervous system which are known to subserve a role in autonomic regulation of the cardiovascular system. Using immunohistofluorescence and radioreceptor techniques, the pathways seem to provide an appropriate wiring network among parasympathetic nuclei in the brainstem and sympathetic nuclei in such areas as the hypothalamus and spinal cord (Fig. 1). The smaller enkephalin molecules are found widely distributed in neurons with short axons, suggesting an interneuronal function, whereas β-endorphin cell bodies are largely restricted to the arcuate nucleus of the hypothalamus with long axonal projections to the brainstem and other areas [20].

Although peripheral endogenous opiate pathways involving the vagus and its pulmonary and cardiovascular distribution have been suggested [18], specific demonstrations of opiate receptors at autonomic targets such as the heart, vasculature, or lungs have not, as yet, provided conclusive evidence of a direct endorphin action on these tissues.

Thus, the existence of anatomic pathways with endorphin-containing neurons and opiate receptors on cell surfaces is consistent with a neurotransmitter function for these systems. What about the hormonal action of endorphins? Can endorphins released from endocrine tissues act upon distant receptors in adequate concentrations to alter circulatory function?

Table 1. Listing of major endorphins and their amino acid structures

Name	Amino acid sequence	Molecular weight
1. Met-Enkephalin	Tyr-Gly-Gly-Phe-Met	573.8
2. Leu-Enkephalin	Tyr-Gly-Gly-Phe-Leu	555.7
3. α-Neo-Endorphin	Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Arg-Tyr-Pro-Lys	1228.6
4. Met-Enkephalin-Arg^6-Phe^7	Tyr-Gly-Gly-Phe-Met-Arg-Phe	877.1
5. Dynorphin	Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln	2147.8
6. α-Endorphin	Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr	1746.2
7. β-Endorphin (human)	Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ile-Ile-Lys-Asn-Ala-Tyr-Lys-Lys-Gly-Glu	3465.6
8. Kyotorphin	Tyr-Arg	337.4
9. β-Casomorphin	Tyr-Pro-Phe-Pro-Gly-Pro-Ile	790.0
10. Dermorphin	Tyr-*d*-Ala-Phe-Gly-Tyr-Pro-Ser	804.0

At present, the data available are inadequate to conclude directly that hormonally released endorphins play an important cardiovascular role. However, there are several reasons to believe that such actions are possible. Over the past few years, we have argued that several important autonomic areas in the brain could receive information from circulating hormones via circumventricular sites that lack a blood–brain barrier [8, 22]. Two specific regions include the area postrema (which is rich in opiate receptors [18] and in close anatomic proximity to brainstem autonomic nuclei) as well as the sub-fornical region (located in proximity to autonomic centers in the hypothalamus).

Recently, Sapru and colleagues [23] have suggested that pulmonary "J" receptors, located in the alveoli of the lung adjacent to pulmonary capillaries, may be targets for circulating endorphins. In addition to pulmonary effects, these chemoreceptors upon stimulation transmit information via vagal afferents to the nucleus tractus solitarius and nucleus ambiguus which results in bradycardia and hypotension in anesthetized animals. It is tempting to speculate that the appropriate circulatory anatomy between the adrenal gland and the lungs would be direct enough to prevent hemodilution or enzymatic degradation of adrenal medullary enkephalins and thus ensure adequate concentrations at pulmonary "J" chemoreceptors [24]. Specifically, the adrenal venous effluent goes almost directly into the right heart via the vena cava and then enters the pulmonary capillary bed. Blood from the adrenal vein is at least ten times more enriched with enkephalin relative to blood from the femoral vein [25]. Since the lung is a rich source of peptidase activity, the actions of blood enriched with enkephalins could be limited to that organ by rapid enkephalin metabolism [24].

Evidence for adrenal enkephalin function as a hormonal modulator of circulatory variables can be gleaned from the recent work of Hanbauer *et al.* [26]. Those studies demonstrated that, in the anesthetized dog depleted of adrenal catecholamines by reserpine pretreatment, stimulation of the splanchnic nerve resulted in a naloxone-reversible depression of heart rate and arterial pressure. More recently, studies by Eiden and Ruth [27] using isolated rat atria have shown that, although various opiate peptides had no direct effect at concentrations up to 10^{-5} M, as little as 10^{-7} M enkephalin significantly antagonized the chronotropic effects of norepinephrine.

To conclude, the first line of evidence to implicate endorphins in cardiovascular function is the demonstration of neuronal networks and hormonal localizations which are consistent with autonomic pathways involved in regulation of the heart and vasculature. A second reason to suggest that endorphin systems are functionally involved is the wealth of pharmacological studies which have shown potent cardiovascular effects of endorphin peptides when administered centrally or peripherally.

Since the work of Flórez and Mediavilla [28], numerous investigators have injected endorphins into different brain ventricles, autonomic nuclei, or peripheral veins in an attempt to define their pharmacologic effects [24, 29]. What has resulted is a

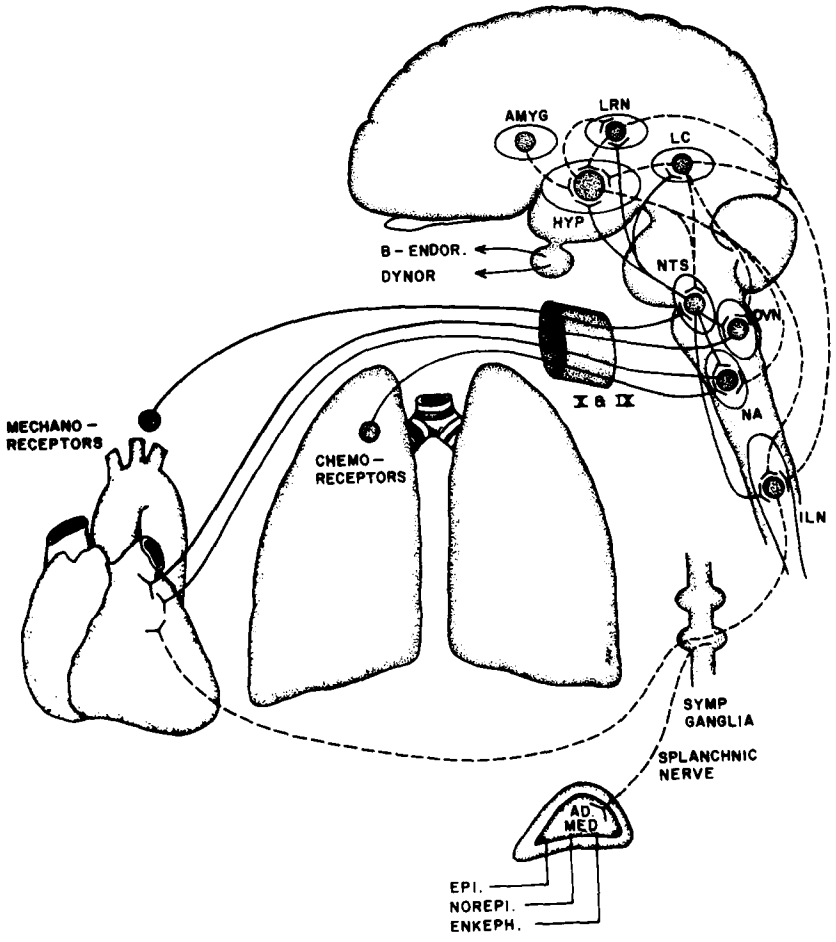

Fig. 1. Simplified schematic of central autonomic pathways which provide afferent and efferent information in regulation of cardiovascular responses. Solid lines generally represent parasympathetic innervations, whereas dashed lines indicate pathways with greater direct relevance to sympathetic integration. The simplification of this illustration of central pathways is realized by the fact that the hypothalamus alone contains at least nine different nuclei with different anatomical and functional relationships among each other and with other autonomic nuclei. For a complete reference, see Ref. 21. Abbreviations: AMYG, amygdala; LRN, lateral reticular nucleus; LC, locus coeruleus; HYP, hypothalamus (many nuclei); ILN, intermediolateral nucleus; NTS, nucleus tractus solitarius; DVN, dorsal vagal nucleus; NA, nucleus ambiguus; X, vagus nerve; IX, ninth cranial nerve; B-ENDOR, beta-endorphin; EPI, epinephrine; ENKEPH, enkephalin; DYNOR, dynorphin; NOREPI, norepinephrine; and AD MED, adrenal medulla.

series of observations which demonstrate that opiate peptides can produce hypertension or hypotension and tachycardia or bradycardia, depending upon the ligand chosen, doses used, site of injection, species studied, or the presence or absence of anesthetics. Given the complex neuronal and hormonal networks involved (Fig. 1; [24]), it is not surprising that different sites bathed by different opiates acting at different receptors would produce a confusion of effects. Although the direct effect of opiate agonists upon a secondary system is usually inhibitory [6], the inhibition of a second inhibitory neuron could result in excitation of the subsequent nerve cell. Such networks within and among autonomic nuclei which can depress (parasympathetic) or stimulate (sympathetic) circulatory function further add to the confusion.

What is apparent from these studies is that endogenous opiate systems may be involved in many aspects of cardiovascular homeostasis or dyshomeostasis. Pharmacological data provide little or no directly useful information on specifics of endorphin involvement in cardiovascular function following discrete physiological release at central or peripheral targets in response to appropriate stimuli. No doubt, the imposition of stress or disruption of normal homeostatic processes results in a well defined orchestration of endorphin effects upon specific systems involved in regulating circulatory function. Therefore, in defining the possible physiological actions of endorphins, one must consider their potential role in hypotension, hypertension, and baroreceptor (orthostatic) reflexes.

The third reason to believe that endorphins play

a regulatory role in cardiovascular function is perhaps the most compelling. As previously mentioned, naloxone is a strategic tool with which to implicate a physiological endorphin involvement. The focus of the remainder of this commentary will deal with the use of opiate antagonists which act at the receptor level [e.g. naloxone and related substances] or endorphin antagonists which reverse selected opiate actions through their own receptors and effector systems [e.g. thyrotropin releasing hormone (TRH)]. These tools have provided evidence that endorphins are involved in the pathophysiology of shock, spinal injury, orthostatic hypotension, anesthetic hypotension, and possibly in essential hypertension and stroke as well. Moreover, evidence accrued in these areas suggests novel applications of these substances in the clinical domain.

ENDORPHINS IN CIRCULATORY SHOCK AND TRAUMA

Many of the signs and symptoms of opiate overdose resemble those which occur in circulatory shock. In addition to compromised cardiovascular function, there is often a lack of responsiveness to nociceptive stimuli and a disruption of body temperature. Moreover, since stress activates endorphin systems [9, 10], it was proposed that endorphins may act like morphine to depress cardiovascular variables [30]. These observations were reinforced by the finding that intravenous β-endorphin injections had apparently fatal circulatory actions in adrenalectomized mice [31]. Dr. Alan Faden and I initiated a series of studies to address the possibility that the stress of shock would functionally activate endorphin systems and thereby contribute to the hypotension and decreased tissue perfusion which characterize the shock syndrome. We assumed that, if endorphins contribute to the pathophysiology of shock, then administration of the opiate antagonist naloxone should reverse the endorphin components of shock and improve survival [30].

Endotoxic shock. The administration of Gram-negative bacterial lipopolysaccharide endotoxin in animals has been widely used as an experimental model of human septic shock [32]. Following the intravenous injection of an LD_{50} dose of *Escherichia coli* lipopolysaccharide endotoxin into conscious, unrestrained rats, mean arterial pressure (MAP) fell precipitously within minutes to a value 25–30 mm Hg below control arterial pressure. Within seconds after the intravenous injection of naloxone (10 mg/kg), an immediate improvement in MAP and pulse pressure (PP) was observed [30].

Subsequent studies revealed that as little as 0.1 mg/kg of naloxone improved circulatory variables in endotoxemic rats [33]. However, to evaluate the possible stereospecific involvement of opiate receptors as opposed to non-specific effects of naloxone, we performed studies comparing the active (−)-isomer of naloxone with the inactive (+)-isomer [the chemically identical mirror image of (−)-naloxone]. Only the active (−)-naloxone isomer improved cardiovascular function in hypotensive, endotoxemic rats; the (+)-isomer, which does not bind to opiate receptors *in vitro* or *in vivo*, was without therapeutic effect. These data provide evidence for a stereospecific action of naloxone at opiate receptors, probably by competitively displacing endorphins and thus reversing their hypotensive effects [33].

Further studies, conducted in collaboration with Reynolds, Gurll, Vargish, and Lechner [34], demonstrated that in endotoxemic dogs, as in rats, naloxone had significant therapeutic effects upon circulatory variables. Experiments with anesthetized dogs yielded additional important information about the specific cardiovascular actions of naloxone. Naloxone was shown to attenuate the drop in left ventricular contractility and MAP; the decline in cardiac output and stroke volume was also reversed. By contrast, naloxone had no effect upon heart rate, pulmonary arterial wedge pressure, or total peripheral vascular resistance. Collectively, these findings provide evidence that naloxone may exert its therapeutic effects in shock by improving ionotropic function. The net result of these correlated actions of naloxone was to significantly improve survival in endotoxemic dogs [34].

These initial studies as well as others (see below) provided an important additional result which verified that endogenous opiate systems are normally quiescent until homeostatic processes are disrupted. At least with regard to circulatory function, naloxone injections into unanesthetized or anesthetized control animals which were not subjected to shock produced little or no alterations of cardiovascular variables. Thus, naloxone has no significant pressor effects of its own. Instead, naloxone appears to exert a selective action in reversing an endorphin-mediated cardiovascular depression.

Recently, work in other laboratories has corroborated these observations on the therapeutic effects of naloxone in endotoxic shock across a number of species. Wright and Weller [35] observed that naloxone prevented the fall in temperature as well as the decreases in circulating white blood cells and platelets in endotoxemic mice. Data presented by Raymond *et al.* [36] demonstrated that naloxone attenuated the hypotension, hemoconcentration, acidosis, and hypoglycemia and also improved survival in dogs subjected to endotoxic shock. Gahhos and associates [37] recently reported that naloxone exerts therapeutic effects in pigs subjected to live *E. coli* sepsis. Horses subjected to endotoxic shock also responded to the therapeutic effects of naloxone [38]. Most recently, monkeys have been shown by Gurll and associates [39] to experience improvement in cardiovascular variables and survival when naloxone is administered following the induction of endotoxic shock.

Factors limiting the therapeutic effects of naloxone in endotoxemia. It has been our observation that the earlier stages of cardiovascular decompensation in endotoxic shock are more completely reversed by naloxone than the later stages [33]. Perhaps this relates to a lesser role of endorphins in the terminal stages of shock. Alternatively, a decrease in the efficacy of naloxone owing to a change in the physiologic milieu may be considered.

Blood pH is a critical factor in endotoxemia. Indeed, Raymond *et al.* [36] demonstrated that naloxone prevents the progressive acidosis in endotoxemic dogs. Recently, Rees and colleagues [40],

using a live organism model of *E. coli* sepsis in dogs, found that naloxone reversed gastric epithelial hypoxia as well as prevented the development of systemic acidosis at doses that did not affect cardiovascular variables. However, naloxone treatment was initiated early following the onset of endotoxic shock in those studies. These results indicate that naloxone may have a direct peripheral effect at the tissue level.

Since acidosis is known to severely blunt the effects of opiate agonists and antagonists [41], naloxone administration to an acidotic subject would be expected to produce a diminished response. Indeed, Gurll and colleagues [39] have recently shown in endotoxemic monkeys that the greater the acidosis, the less the pressor response to naloxone. It is critical that normal blood pH be restored if naloxone is to elicit its maximal therapeutic effects in the later stages of shock characterized in part by systemic acidosis.

Another factor which may modify the therapeutic effects of naloxone is ambient temperature. Janssen *et al.* [42] have demonstrated that the pressor response to naloxone in endotoxic hypotension is blunted by a cold ambient temperature. This may relate to the potentiation of endorphin systems by heat [8] as well as the generally poor prognosis for recovery in endotoxic patients who become hypothermic.

Site(s) and mechanism(s) of naloxone effects in endotoxemia. Evidence cited above indicates that naloxone exerts its actions by displacing endorphins from opiate receptors. The precise site(s) and mechanism(s) by which these therapeutic effects are mediated have been the subject of research in a number of laboratories. Janssen and Lutherer [43] reported that the ventriculo-cisternal administration of naloxone protected against severe hypotension in dogs subjected to endotoxic shock. These data, indicating that naloxone improves circulatory function at sites within the brain, are in close agreement with our studies demonstrating central nervous system actions of naloxone in various shock models (see Ref. 44). Moreover, Rios and Jacob [45] found that the iodomethylate of naloxone, which does not cross the blood–brain barrier, failed to reverse endotoxic hypotension in rats upon peripheral injection, whereas central injection of this molecule improved blood pressure in this model. Taken together, evidence indicates an important central nervous system component in the therapeutic effects of naloxone in endotoxic shock.

In recent studies designed to evaluate the peripheral mechanisms involved in mediating the central autonomic responses to naloxone in endotoxemic rats, experiments were conducted with adrenalectomized and adrenal demedullated rats to evaluate the specific importance of sympatho-medullary function [46]. It was found that both total adrenalectomy and selective adrenal demedullation dramatically enhanced endotoxic shock susceptibility (>15-fold). Moreover, both procedures completely blocked the pressor response to centrally or intravenously administered naloxone [46].

Several important conclusions can be drawn from these studies. First, adrenal enkephalins do not appear to be primarily involved in the depression of circulatory function in endotoxemia since surgical elimination of adrenal enkephalins enhances (as opposed to protects) shock susceptibility. Second, the beneficial cardiovascular effects of naloxone appear to involve central nervous system actions which are peripherally mediated by sympatho-medullary discharge. Third, since adrenal-demedullated rats were shown to have normal adrenocortical hormonal function, the importance of endogenous corticosteroids in endotoxic shock susceptibility appears secondary to adrenal medullary actions. These findings, supporting a central sympatho-inhibitory effect of endorphins and their reversal by naloxone, are consistent with the observations of Dashwood and Feldberg [47] who demonstrated that the pressor response to naloxone following extensive surgical stress in cats was blocked by adrenalectomy and attenuated by cutting splanchnic nerves. Manugian and colleagues [48] have also found that intravenous or intracisternal naloxone injections resulted in an increase in preganglionic splanchnic nerve activity accompanied by elevated arterial pressure in anesthetized cats.

Since endogenous opiates appear to play an important role in the cardiovascular sequelae of endotoxic shock, are they also involved in the behavioral depression associated with that syndrome? Recently, it was demonstrated in rats that endotoxic shock produced an increase in analgesic latencies which was attentuated by naloxone injection [49]. These findings implicate an even more global involvement of endorphins beyond autonomic circulatory effects in endotoxic shock. However, they also raise the possibility that blockade of pain-relieving effects of endorphins by naloxone could complicate the clinical utilization of naloxone in shock (see below).

A final observation linking opiate systems with endotoxic shock was also obtained in our laboratories. Since the opiate antagonist naloxone improves cardiovascular variables in endotoxic shock, does the opiate agonist morphine exacerbate shock hypotension? Indeed, it has been shown that analgesic doses of morphine in the rat, when injected after endotoxin, act additively to result in an even more severe depression of circulatory function [50].

Endotoxemia: conclusions and speculation. To summarize, the pathophysiology of endotoxic shock appears to involve an important endorphin component which is reversed by the opiate antagonist naloxone. These studies have been experimentally confirmed in mice, rats, cats, dogs, sheep, pigs, horses, and monkeys. Naloxone has been shown to improve hemodynamic variables, particularly cardiac contractility, which was also associated with increased tissue perfusion and survival. In addition to cardiovascular effects, naloxone also affected body temperature, improved white blood cell and platelet counts, attenuated hypoglycemia, prevented acidosis, and improved survival. These therapeutic effects of naloxone appear to be largely mediated at opiate receptors within the brain, and intact sympatho-medullary function is essential for their expression. Acidosis and hypothermia significantly blunt the responses to naloxone in experimental

endotoxemia. The effects of acidosis may be to limit blood–brain barrier penetration of intravenously administered naloxone; however, this requires experimental confirmation.

Since naloxone was also shown to reverse increases in experimental analgesic latencies observed during endotoxic shock, it appears possible that naloxone would have the adverse effect of enhancing pain perception while exerting beneficial cardiovascular effects. Two different approaches to this problem of reversing shock without enhancing pain will be discussed later.

Still at issue is the important matter as to which endorphins are involved in the pathophysiology of endotoxic shock. Adrenal enkephalins appear to play a lesser role since their surgical removal enhances shock susceptibility. Logically, the converse should occur (i.e. protection from shock) if adrenal enkephalins were the endogenous opiates primarily responsible for endotoxic shock. Since adrenalectomy also elevates β-endorphin levels due to a loss of corticosteroid feedback inhibition [9], it appears that pituitary endorphins could be involved. Indeed, our laboratories, in collaboration with Gurll, Reynolds, Vargish, and Gaines, have observed 5- to 10-fold increases in circulating β-endorphin levels during endotoxic shock in monkeys [51]. However, demonstrations of elevations in circulating endorphins along with naloxone reversibility do not necessarily link these observations at a cause-and-effect level. In fact, endotoxemic, adrenalectomized animals fail to respond to naloxone even though β-endorphin levels are elevated [46].

Regarding specific endorphin involvement, the hypothesis that is most difficult to disprove supports a functional role for central enkephalins or β-endorphin at sympathetic centers (perhaps at the hypothalamus) which decrease sympatho-medullary outflow to result in the cardiovascular pathophysiology of endotoxic shock. This tentative conclusion requires further experimental verification through manipulations of central and peripheral β-endorphin or enkephalin neuronal pathways.

Hemorrhagic shock. The involvement of endorphins in endotoxic shock pathophysiology seemed apparent from our early work. However, the possibility existed that these hemodynamic effects of naloxone were unique to an interaction with endotoxins and not generalizable to other forms of shock. To test the hypothesis that endorphins are fundamentally involved in the etiology of a variety of shock states, we studied the effects of naloxone injections in conscious rats subjected to hemorrhagic shock by rapid removal of 50% of estimated total blood volume [52]. This model was shown to be 50% lethal in untreated rats.

Naloxone, at a dose of 1.0 mg/kg, significantly improved MAP and PP in hypovolemic rats. Moreover, survival in the naloxone-treated group was also significantly improved [52]. Subsequent studies with Vargish and colleagues [53] were even more dramatic. As with endotoxemic dogs, naloxone (2 mg/kg bolus + 2 mg/kg/hr) improved inotropic function, which was reflected in elevations in cardiac output and MAP; however, heart rate, total peripheral resistance, and portal venous pressure were unaffected. Moreover, all saline-treated dogs died, whereas all naloxone-treated dogs survived this severe, acute hemorrhagic shock protocol.

More recently, Gurll and colleagues [54, 55] have demonstrated that the therapeutic effects of naloxone in canine hemorrhagic shock are dose related. Even without blood reinfusion, naloxone prolonged survival in a dose-dependent manner [55]. Furthermore, studies in their laboratory [56] have demonstrated that the putatively longer-acting opiate antagonist naltrexone also improved cardiovascular function and survival in canine hemorrhagic shock.

Hemorrhagic shock has also been shown to be reversed by naloxone in other species as well. Feuerstein *et al.* [57] demonstrated that 0.1 mg/kg/min naloxone infusions promoted a sustained improvement in arterial pressure in intact as well as anephric cats. Curtis and Lefer [58] reported that a similar dose of naloxone had beneficial effects upon hemodynamic and metabolic variables in hemorrhaged cats. Naloxone reduced lysosomal enzyme release and depressed circulating concentrations of myocardial depressant factor (MDF), a toxic pancreatic peptide which is released in shock. MDF is not an endorphin, however, since they have shown MDF to be without opiate-like activity *in vitro* [58].

Schadt and York [59] have also found therapeutic effects of naloxone in conscious rabbits subjected to hemorrhagic shock. A dose-related increase in MAP was accompanied by a decrease in heart rate in their studies. Recently, we have observed elevated plasma β-endorphin concentrations in hemorrhagic monkeys.* Moreover, naloxone has been shown by Gurll and colleagues* to significantly improve circulatory function and survival in these animals.

In studies designed to assess the site(s) of the action of naloxone as well as the origin of endorphins involved in hemorrhagic shock, experiments were conducted with hypophysectomized and sham-operated rats [60]. Following induction of hemorrhagic shock, naloxone was initially injected intraventricularly, followed by a later intravenous dose. As before, low doses of naloxone injected into brain ventricles significantly improved MAP in animals with intact pituitary glands, thus indicating a central site of action.

If pituitary endorphins were important contributors to hemorrhagic shock hypotension, naloxone would be expected to have no effect in hypovolemic animals which lacked pituitary endorphin due to hypophysectomy. Indeed, this was the case; hypophysectomy blocked the beneficial responses to naloxone. However, this simplistic interpretation must be re-evaluated in light of the atrophic effects of hypophysectomy on secondary endocrine systems. For example, both adrenal cortical and medullary function are severely compromised by pituitary extirpation. Indeed, Patton *et al.* [61] have shown that adrenalectomy abolishes the effect of naloxone in canine hemorrhagic shock just as we observed in endotoxic shock [46].

In all likelihood, intact sympatho-medullary function will also be shown to be crucial to the beneficial

* N. J. Gurll, D. G. Reynolds, T. Vargish, E. Ganes, E. Mougey and J. W. Holaday, unpublished data.

hemodynamic effects of naloxone in hemorrhagic shock as was demonstrated in endotoxic shock. Although Feuerstein *et al.* [62] failed to observe significant plasma catecholamine elevations accompanying pressor responses to naloxone injections in hemorrhagic shock, Schadt and York [63] obtained evidence that the pressor effects of naloxone in hemorrhaged rabbits are alpha-adrenergically mediated. The bradycardia they observed in this model following naloxone treatment was due to a loss of beta-adrenergic tone and an increase in vagal-cholinergic activity.

Hemorrhagic shock: conclusions and speculation. A great number of similarities between endotoxic and hemorrhagic shock have emerged regarding the putative involvement of endorphin systems. Both forms of circulatory shock are reversed at sites within the central nervous system. The improvement in cardiovascular function is inotropically mediated and accompanied by an improvement of metabolic variables as well as survival. As with endotoxic shock, hypothermia and acidosis significantly attenuate the pressor response to naloxone in monkeys subjected to hemorrhagic shock [64]. Both naloxone and naltrexone have beneficial effects, and autonomic pathways are involved. Adrenalectomy blocks the effects of naloxone; however, hydrocortisone replacement restored the effects of naloxone in hemorrhaged dogs [61]. Since hydrocortisone functions to delay catecholamine metabolism through inhibition of catechol-*O*-methyl transferase activity, this could be related to a potentiation of vascular actions of sympathetically released norepinephrine.

Once again, however, the issue as to which endorphin systems are etiologically involved remains to be determined. Although plasma endorphins* or adrenally derived enkephalins [25] are elevated in hemorrhagic shock, cause and effect cannot be directly related to these observations for the reasons mentioned previously.

An important caveat must be remembered: the actual loss of blood due to hemorrhage or its functional loss by sequestration during shock (e.g. endotoxemia) results in a lower absolute volume in which to distribute any endogenously released substance or pharmacologically administered material. If a gland secretes a hormone at a constant rate, and if functional blood volume decreases by half, an apparent doubling of concentration will occur. Likewise, any drug administered intravenously on a basis of mg/kg total body weight will be dissolved in a lesser volume of blood in an organism subjected to shock. Effective concentrations of blood-borne hormones or drugs will thus be higher than in the normovolemic animal.

Neurogenic shock. Although naloxone reversal of endotoxic and hemorrhagic shock may indicate a generalized involvement of endorphins in the etiology of circulatory shock as a whole, we sought to further reinforce this generalization by developing a neurogenic model of shock [62]. Although it has long been known that rapid transection of the cervical spinal cord produces an alteration of somatic reflex states referred to as "spinal shock", the cardiovascular aspects of spinal shock have been poorly studied.

Using anesthetized rats, we monitored the cardiovascular responses to rapid cervical cord transection and noted that subsequent to the acute hypertensive surge was a secondary hypotension (a drop of 20–30 mm Hg) which occurred several minutes later. Intravenous naloxone (10 mg/kg) or intraventricular (−)-naloxone (48 μg) rapidly restored MAP and PP to pretransection levels. As with studies of endotoxemia in the rat, the (+)-stereoisomer of naloxone (48 μg intraventricularly) was also inactive in this model of shock. Since peripherally ineffective doses of naloxone resulted in a stereospecific reversal of spinal shock hypotension upon intraventricular injection, it was concluded that the therapeutic effects of naloxone in spinal shock were mediated by opiate receptors within the central nervous system [65].

In addition to cardiovascular effects, spinal shock also results in hypothermia and a decrease in respiratory rates. These autonomic effects were also shown to be specifically reversed by naloxone, thus providing further evidence for the involvement of endorphins in thermoregulation as well as respiratory depression [6, 65]. Moreover, opiate antagonists improve survival since naloxone injection following acute spinal transection was shown to block the lethal effects of this procedure in rats.†

This model of neurogenic shock provided a unique opportunity to address the specific autonomic systems involved in these pressor responses following naloxone injection. Supraspinal (brain) control of sympathetic outflow is lost when the cervical spinal cord is severed; only parasympathetic circuits remain intact. Since naloxone nonetheless produced an improvement in MAP upon cerebroventricular injection, parasympathetic vagal pathways had to be involved.

In studies with both rats and cats [66], bilateral cervical vagotomy by itself was shown to improve blood pressure following spinal shock. This observation, along with the beneficial effects produced by the muscarinic antagonists methylatropine and atropine following spinal shock hypotension in animals with intact vagi, confirmed that spinal shock hypotension involved cholinergic activation due to increased parasympathetic-vagal outflow [66]. Presumably, endorphin receptors at central autonomic sites were indirectly mediating this elevation in vagal tone. Thus, naloxone exerted therapeutic effects by blocking this adverse endorphin action.

Consistent with other shock models (*vide supra*), in none of these studies of spinal shock was naloxone shown to alter heart rate. Naloxone specifically improved the left ventricular pressure-time variable in cats following acute cervical spinal cord transection [66]. These data indicate that naloxone was ultimately producing an increase in left ventricular contractility, a finding consonant with the positive inotropic effects of naloxone in other forms of circulatory shock. Although the textbook version of cardiovascular physiology emphasizes the negative chronotropic effects of parasympathetic-vagal out-

* N. J. Gurll, E. D. Reynolds, T. Vargish, E. Ganes, E. Mougey and J. W. Holaday, unpublished data.

† G. Nilaver, personal communication.

flow, DeGeest and colleagues [67] have provided convincing evidence that negative inotropism can occur without bradycardia when certain parasympathetic pathways are activated. Such a system would be compatible with our observations.

Spinal (neurogenic) shock: conclusions and perspectives. From the above data, it appears that spinal shock hypotension is mediated via endorphin effects upon opiate receptors at central parasympathetic centers; the result is an increase in vagal tone and a decrease in cardiac contractility. Sympathetic outflow is not directly involved in the therapeutic response to naloxone since the preganglionic pathways are severed by cervical transection. By contrast, endotoxic (and perhaps hemorrhagic) shock appears to primarily involve an endorphin action at central sympathetic nuclei which produces a decrease in sympatho-medullary function. Thus, endorphin effects upon different autonomic pathways may be involved in the etiology of various forms of circulatory shock. This is not surprising since opiates are known to cause cardiovascular depression through increased parasympathetic tone and decreased sympathetic tone (*vide supra*). Both effects are naloxone reversible, and endorphin involvement is inferred since opiate antagonists effectively reverse these autonomic sequelae in endotoxic, hemorrhagic, and spinal shock.

The source of endorphin involvement in spinal shock is also poorly known. Central enkephalin or β-endorphin actions are implicated since intraventricular naloxone reverses the hypotension of spinal shock. However, I will speculate that adrenal enkephalins may also play an important role in the genesis of this form of neurogenic shock. The intense sympathetic discharge produced by electrical currents of injury following cervical spinal cord transection results in a very large increase in blood pressure. Sympatho-medullary outflow may be an important contributor, due to pressor effects of catecholamines. Adrenal enkephalins, co-released with catecholamines [68], may subsequently act upon pulmonary "J" chemoreceptors [24] and, in the anesthetized animal, produce an enkephalin-mediated depressor response. Since the effects of naloxone in spinal shock were completely reversed by central injections of this opiate antagonist, central endorphin systems could also modulate the information from peripheral chemoreceptors, perhaps at the parasympathetic nuclei of the brainstem, and thereby block the adverse effects of this chemo- or baroreflex arc. Thus, naloxone may act both upon peripheral afferent or central efferent pathways in this model by reversing cardiodepressant endorphin effects at either site.

Endorphin involvement in other forms of induced hypotension. Other forms of circulatory shock and hypotension have been less well studied than those mentioned above. An activation of endorphin-mediated hypotension by surgical stress was inferred by Dashwood and Feldberg [47, 69]. Those investigators found that the more extensive the surgical procedures the greater the pressor response following naloxone injection. Vagotomy failed to block this effect of naloxone. Huidobro-Toro and Musacchio [70] have reported that insulin-induced hypotension is reversed by naloxone in rats pretreated with reserpine. They concluded that hypoglycemia caused a release of opiate-like material that mediated a hypotensive response; the adrenal gland did not appear to be involved, however.

Recent work by Vargish and associates* has shown that the hypotension following burn shock in guinea pigs is also reversed by naloxone. Endorphin action in various visceral arterial occlusion shock models has also been demonstrated [71–73]. Eddy and colleagues demonstrated that naloxone treatment increased plasma dopamine concentrations in canine splanchnic arterial occlusion shock [73], a finding which parallels our evidence that indicated a possible dopamine involvement in the cardiovascular responses to naloxone following spinal shock [74].

Goldstein *et al.* [75] have evidence that naloxone attenuates the hypotension induced by Hageman factor, but not hypotension resulting from kallikrein, bradykinin, or nitroglycerine injections. They surmised that Hageman factor could generate vasoactive-opioid peptides from circulating precursors. Recent work by Rubin and associates [76] has shown that the fall in blood pressure during non-rapid eye movement sleep in humans is prevented by naloxone.

Hypotension following certain anesthetics, such as pentobarbital, is not reversed by naloxone treatment. However, Arndt and Freye [77] have shown that the hypotensive effects of halothane are stereospecifically reversed by naloxone perfusion of brainstem parasympathetic centers. This work was confirmed by Artru and colleagues [78].

Alpha-adrenergic agonists such as clonidine and α-methyldopa have hypotensive actions which prompt their use in treating hypertension. Studies in animals by Farsang and Kunos [79] as well as in humans by Resnick *et al.* [80] have demonstrated that the hypotensive actions of clonidine are reversed by naloxone. Farsang *et al.* [81] also found that a α-methyldopa-induced hypotension was naloxone sensitive. It is interesting to note that Pettibone and Mueller [82] have shown recently that clonidine acts at the pituitary gland to increase the release of β-endorphin into the bloodstream. Perhaps it is the depressor response following clonidine-induced β-endorphin release which is reversed by subsequent naloxone treatment.

ARE ENDORPHINS INVOLVED IN CHRONIC HYPERTENSION?

Since the hypotensive actions of clonidine are reversed by naloxone, does this indicate a role of endorphins in essential hypertension? Indeed, in unanesthetized animals, injection of enkephalins results in a potent increase in arterial pressure [83–87]. However, this effect is resistant to naloxone reversal [88], and naloxone is without effect upon elevated blood pressures in spontaneously hypertensive rats, in rats rendered hypertensive by unilateral renal arterial occlusion, or in hypertension produced by deoxycorticosterone acetate administration [89, 90].

* T. Vargish, personal communication.

Perhaps this lack of naloxone reversibility of physiologic or pharmacologic hypertension only reflects the relative inability of naloxone to bind to specific opiate receptor subtypes (e.g. delta) which may be more primarily involved. This seems doubtful since adequately high doses of naloxone were used (10 mg/kg [90]) to overcome its lower affinity for delta receptors. However, Yukimura *et al.* [91] have shown recently that the opiate receptor antagonist diprenorphine produces a greater hypotension in spontaneously hypertensive rats than in normotensive control animals.

To conclude from the above [91] that endogenous opiates are involved in maintenance of chronic hypertension may be premature for the following reasons. Martucci and Hahn [92] have reported that, coincidental with the onset of hypertension in developing hypertensive rats, a doubling of the number of opiate binding sites was observed. The demonstration of Schaz and colleagues [93] that the hypertensive effects of Leu-enkephalin were magnified in spontaneously hypertensive rats may relate to the increased number of opiate receptors. Importantly, however, diprenorphine has agonist properties since it is not a pure opiate antagonist.* Thus, the magnification of depressor responses to diprenorphine in spontaneously hypertensive rats may reflect an exaggerated hypotensive response to the agonist actions of diprenorphine.

The possible role of endorphins in hypertension and in the maintenance of chronically elevated arterial pressures seems in doubt. Since a positive finding would have important therapeutic relevance, more specific and selective opiate receptor antagonists are required to resolve this issue in the future. However, this does not preclude the possible involvement of endorphin systems in the generation (as opposed to maintenance) of chronic hypertension. From experimental results, Dworkin *et al.* [94] have suggested that some hypertension may begin as an instrumentally learned blood pressure response for which the reward is a baroreceptor-mediated reduction in the aversiveness of ambient noxious stimuli. Indeed, endorphins may be involved in this "reward" system since Zamir and colleagues [89, 90] have demonstrated a naloxone-reversible increase in analgesic latencies following experimental hypertension.

BARORECEPTOR REFLEXES AND ENDORPHIN FUNCTION

One of the most widely accepted cardiovascular actions of opiate alkaloids is the depression of compensatory changes in heart rate and arterial pressure produced by activation of baroreflex arcs. To address the possible physiologic role of endogenously activated endorphins in baroreceptor responses, we administered transauricular electroconvulsive shock (ECS) to rats [95]. This procedure resulted in an immediate 200% increase in arterial pressure, followed by a return to baseline pressures by 20 sec following ECS in control animals; the post-ECS bradycardia lasted 35 sec. Naloxone pretreatment, at doses of 1.0 and 10.0 mg/kg, resulted in an exaggerated hypotensive swing accompanied by enhancement of the reflex bradycardia. These data suggested to us that baroreflex activation by non-pharmacological, non-invasive means involves endogenous opiate systems [95]. Moreover, since naloxone exaggerated reflex cardiovascular responses, this indicated that endorphins may provide a physiological "buffering" of usual reflex swings in heart rate and arterial pressure which was blocked by naloxone. Our more recent work with spinal transection [65] may also be related to the findings with ECS, since both ECS and acute cervical transection resulted in seizures, acute hypertension, and hypotension which was modified by naloxone treatment.

Others have also demonstrated an endorphin action in baroreflex responses. Schaz and colleagues [93] infused angiotensin II and found that D-Ala-Met enkephalin decreased baroreceptor sensitivity. Petty and Reid [96] used phenylephrine- and sodium nitroprusside-induced activation of baroreflex arcs to uncover reduced baroreceptor sensitivity following injection of an enkephalin analog and an enhancement of baroreceptor reflexes with naloxone. Freye and Arndt [97], Montastruc and associates [98], and Sander *et al.* [87] have also obtained similar results that implicate endorphins in blunting of the baroreflex responses in a number of species. Baroreceptor systems appear to be exquisitely opiate sensitive since even at low doses of endorphins or alkaloid opiates, which have no direct cardiovascular effects, baroreceptor systems may be inhibited.

The collective evidence on this point provides a strong argument for the opinion that endogenous opiate systems are involved in baroreflex responses. Since orthostatic hypotension is an important neurologic problem in certain autonomic diseases (e.g. Shy–Drager's Syndrome), as well as following certain non-opiate drug treatments, it would be important to determine an endorphin involvement in the etiology of such baroreceptor-involved syndromes.

ENDORPHINS AND NEUROLOGIC FUNCTION: SPINAL INJURY AND STROKE

Since our prior work had indicated that endorphins were involved in the pathophysiology of shock, including that produced by rapid spinal cord transection, Faden, Jacobs and I investigated the possibility that endorphins could be indirectly involved in the spinal cord ischemia which often leads to the paralysis associated with spinal trauma [99, 100]. It was initially theorized that, following spinal injury, ischemic damage results from the loss of autoregulation of spinal cord blood flow combined with decreased cord perfusion due to a spinal shock-like state. Thus, if endorphins contribute to this impairment of cardiac and circulatory function following spinal trauma, then naloxone would improve cord perfusion and minimize the ischemic-induced nerve fiber necrosis with its resultant paralysis.

In several studies involving large populations of cats, naloxone was shown to produce a pressor response and to improve spinal cord perfusion following cervical injury in the region of the sixth cervical vertebra. More importantly, however, at the end of 6 weeks the naloxone-treated cats had only minor

* A. Cowan, personal communication.

neurologic impairment, whereas the saline-injected control cats had significant quadriparesis [99, 100]. Following injury, plasma and cerebrospinal fluid levels of endorphins were greatly increased; plasma dopamine levels rose sharply after naloxone injections [74, 100].

These data support an indirect, yet significant, pathophysiologic role for endorphins in spinal cord injury. Not only were endorphin levels elevated at the time of maximum post-injury hypotension, but naloxone produced a pressor response, improved spinal cord perfusion (possibly related to secondary dopamine involvement and microvascular effects), and prevented paralysis. Recent work by Young and associates [101], using thoracic spinal injuries in cats, confirmed these observations. These investigators demonstrated that naloxone improved blood flow in the lateral column white matter and preserved somatosensory evoked potentials 24 hr after injury. Taken together, these results predict that opiate antagonists may be of significant therapeutic value in treating spinal injuries such as would occur following diving accidents or motor vehicle accidents in humans.

If endorphins were involved in the neuronal ischemia following spinal cord injury, could endorphins likewise contribute to the CNS ischemia following stroke or myocardial infarction? We attempted to evaluate the cardiovascular and neurologic effects of naloxone in the gerbil model of stroke [102, 103]. The gerbil is unique for such studies since the circle of Willis is incomplete (posterior communicating arteries are absent, the anterior communicating artery is also absent in about one-third of the animals).

Using aneurism clips, the carotid arteries were bilaterally occluded for 30 min in pentobarbital-anesthetized gerbils. Release of these clips resulted in a naloxone-reversible hypotension. Over the next 6 hr, naloxone-treated (10 mg/kg plus 10 mg naloxone pellet) or saline-treated (1.0 ml/kg plus an inert placebo pellet) gerbils were monitored for functional recovery. Single-blind neurologic evaluations included assessment of time taken to awaken, respiratory rate, ptosis, circling behavior, locomotor and hot plate testing, righting reflexes, opisthotonus, seizures, and survival.

With large populations of gerbils, *no* therapeutic effects of naloxone on any of the above measures were observed. Although naloxone improved blood pressure following clip release, an absence of neurological improvement suggests that these two effects were dissociated [102, 103].

Recently, Hosobuchi *et al.* [104] reported that naloxone improved neurologic recovery and survival in gerbils following permanent unilateral carotid ligation (as opposed to the temporary bilateral occlusion model used in our studies). Because of differences in methodology, we attempted to reproduce those studies using a variety of doses of naloxone following unilateral carotid occlusion. Once again, naloxone treatment failed to result in any improvement in neurologic function [103]. Morphine injections did exacerbate these "neurologic" signs; however, this does not necessarily indicate a physiologic role of opiates in stroke. Baskin and Hosobuchi [105] reported a transient naloxone reversal of hemiplegia secondary to cerebral ischemia in two patients, but naloxone had no effect in a third patient with a confirmed focal cerebral infarction. This result [105] contradicts their animal findings [104] since permanent unilateral occlusion of a gerbil carotid artery would superfically seem to be more predictive of a permanent focal cerebral infarction in humans (wherein naloxone was without effect).

The discrepancies noted above cast doubt on the issue of endorphin involvement in experimental stroke models using the gerbil [102]. Nonetheless, recent work by Faden and colleagues [106] demonstrated that naloxone improved somatosensory evoked potentials in dogs subjected to cerebral ischemia induced by carotid injection of air emboli. Since cerebral ischemia can result from many causes of both central and peripheral origin, and since species may show considerable variation, the fundamental hypothesis that endorphins contribute to the neurologic deficits resulting from certain forms of cerebral ischemia requires further specific experimental evaluation.

THYROTROPIN RELEASING HORMONE, CARDIOVASCULAR RESPONSES AND ENDORPHIN ANTAGONISM

As indicated above, it is likely that endorphins contribute substantially to the loss of cardiovascular function and spinal cord perfusion following shock and trauma. However, evidence indicates that endorphins also subserve an important functional role as endogenous analgesics. Thus, the therapeutic use of naloxone in these situations would also be expected to antagonize this analgesic action and thereby have the adverse effect of intensification of traumatic pain [49].

Unlike naloxone, thyrotropin releasing hormone (TRH) is a tripeptide which does not bind to opiate receptors; yet it antagonizes many of the biological effects of endorphins without altering analgesic latencies [6]. Specifically, we and others have shown that TRH functionally antagonizes opiate-induced hypothermia, catalepsy, and other behavioral effects [107, 108]. For this reason, possible therapeutic use of TRH in experimental models of endotoxic and hemorrhagic shock, as well as spinal cord injury, was evaluated.

TRH, in a dose-related way, improved arterial pressure, pulse pressure, heart rate, and respiration rate in experimental shock [109, 110]. Survival was also improved. TRH was shown to be more efficacious than naloxone [111], and its therapeutic effects were mediated through central effector sites which regulate sympatho-medullary outflow [46]. Unlike naloxone, however, direct peripheral effects of TRH were also apparent [46].

At doses of intravenous TRH which produced improvement in cardiovascular variables, no effects upon nociceptive latencies in rats or monkeys were observed [44]. In fact, when combined with analgesic doses of morphine, its antinociceptive properties were slightly enhanced by TRH.*

* J. W. Holaday, B. Cuthbert and J. L. Meyerhoff, unpublished results.

Recently, Faden, Jacobs and I found that TRH injections following spinal cord injury in anesthetized cats resulted in an even greater neurologic recovery than previously obtained with naloxone [112]. Survival was also improved. In the gerbil stroke model, however, TRH was without therapeutic effect [103]. In fact, neurologic signs and survival were worsened by this tripeptide. This finding speaks against common mechanisms of ischemic responses in spinal injury and stroke.

Collectively, TRH appears to have distinctive therapeutic advantages over naloxone in the treatment of experimental shock and spinal injury. Not only is it more efficacious, but it does not appear to interfere with analgesic systems (thus allowing for concomitant opiate injections for pain relief). The effects of TRH in antagonizing the cardiovascular as well as other effects of endogenous opiates appear to be mediated through opposing physiological systems which utilize different receptors, possibly in a manner analogous to the antagonistic interaction between epinephrine and histamine. Nonetheless, a preponderance of evidence indicates that these effects of TRH are independent of its hypothalamic role in regulating pituitary–thyroid function [107].

FUTURE DIRECTIONS

A major deficiency in the work described above, in which naloxone was used as an experimental tool, is the absence of solid evidence as to which of the several endorphin systems are involved. Are neuronally released endorphins within central autonomic pathways more important than endorphins released as hormones from pituitary or adrenal glands? Are endorphins functioning as neuromodulators of other hormones and neurotransmitters? What specific opiate receptor subtypes are involved in cardiovascular responses to endorphins?

Evidence reviewed above suggests that adrenal enkephalins are less important than neuronal enkephalins in endotoxic shock and possibly hemorrhagic shock as well. Spinal shock may involve adrenal enkephalin effects, although central parasympathetic involvement was established. Nonetheless, to measure elevations in circulating endorphins during shock or to extirpate endorphin-containing glands may have little functional relevance to the cardiovascular effects of endogenous opiates released in discrete areas which act upon specific receptor populations. A more direct analysis is needed on a cause-and-effect level.

As to endorphins as neuromodulators, the data of Eiden and Ruth [27] indicate that adrenal enkephalins may alter the direct cardiac effects of catecholamines. Kiang and Wei [113] have shown that dynorphin, a potent opiate peptide found in the posterior pituitary and spinal cord, sensitizes rats to the bradycardiac effects of morphine; possible actions at kappa receptors were implicated. Thus, one type of endorphin, under certain situations, may function indirectly as a regulatory peptide to modulate cardiovascular actions of other endorphins, hormones or transmitters.

The characterization of opiate receptor subtypes which mediate cardiovascular effects of endorphins and opiate alkaloids has been hindered by the absence of specific receptor antagonists. Recently, however, work in my laboratories [114] has shown that endotoxic shock hypertension is specifically reversed by a novel delta antagonist which has no effect upon analgesic responses to morphine (presumably mu mediated). This compound has an enormous potential for reversing shock without blocking analgesia derived from internal or external opiates. Other studies, using a selective mu antagonist, have provided preliminary evidence that opiate bradycardia and baroreceptor effects are mediated by mu receptor actions [115].

The evidence summarized above amply supports the hypothesis that endorphins contribute to the pathophysiology of shock. Teleologically, however, why would a system evolve to provide pain relief and then contribute to the demise of the organism through the perpetuation of circulatory shock? What selective advantage would be conferred by such an apparently maladaptive response? We have speculated that hypotension may be a protective mechanism in an animal with a major arterial bleeder, assisting the coagulative sealing of the wound by reducing the pressure head in the blood vessel [116, 117]. Alternatively, it may be suggested that this "maladaptive" response merely reflects an evolutionary imperfection which persists despite apparent negative selective pressures. Neither of these arguments provides a satisfactory explanation, however. One way to rationalize the issue as to an "adaptive" endorphin role in pain relief and "maladaptive" role in circulatory shock is to consider that the complex endorphin systems may well be functionally independent. For example, since preliminary evidence indicates that endotoxic shock is mediated at delta opioid receptors [114] and analgesia is mu-receptor mediated [11, 13], these two receptor subpopulations may be independently activated (or inactivated) to allow for a selectivity of responses. Nonetheless, the philosophical question as to the adaptive significance of endorphins (or toxic factors) to the etiology of circulatory shock eludes a scientific answer.

The products of basic endorphin research have great potential for extrapolation to the clinical environment. Opiate antagonists, including those with receptor level actions as well as TRH, may be of significant therapeutic value in treating circulatory shock and ischemia due to bacterial infections, hemorrhage, anaphylactic responses, or even neurogenic causes. It is further possible that these substances will be useful in treating spinal injury, certain forms of stroke, or even orthostatic hypotension. Indeed, preliminary clinical trials have yielded encouraging evidence that naloxone has therapeutic benefit in humans suffering from various forms of circulatory shock [118–121].

It is important to note, however, that, although naloxone and TRH are already clinically available for other purposes and have a very high therapeutic index (at least 1 : 100), it is most premature to suggest their unrestrained use in unestablished clinical situations until further basic science data are available and until prospective, randomized, double-blind clinical evaluations are accomplished. To do other-

wise jeopardizes the patient and may ultimately contribute to an unwarranted acceptance or rejection of these potentially useful drugs.

Acknowledgements—I wish to thank Drs. A. I. Faden, G. L. Belenky, R. J. D'Amato and the many other collaborators who helped to make this commentary possible, Dr. N. J. Gurll for critical comments, and Pat Conners for preparation of the manuscript.

REFERENCES

1. C. F. Schmidt and A. E. Livingston, *J. Pharmac. exp. Ther.* **47**, 411 (1933).
2. S. D. Gokhale, O. D. Gulati and N. Y. Joshi, *Br. J. Pharmac. Chemother.* **21**, 273 (1963).
3. A. G. J. Evans, P. A. Nasmyth and H. C. Stewart, *Br. J. Pharmac. Chemother.* **7**, 542 (1952).
4. M. R. Fennessy and J. F. Rattray, *Eur. J. Pharmac.* **14**, 1 (1971).
5. W. Feldberg and W. D. M. Paton, *J. Physiol., Lond.* **114**, 490 (1951).
6. J. W. Holaday and H. H. Loh, in *Hormonal Proteins and Peptides* (Ed. C. H. Li), Vol. 10, pp. 205–91. Academic Press, New York (1981).
7. J. J. Jacob, E. C. Tremblay and M-C. Colombel, *Psychopharmacologia* **37**, 217 (1974).
8. J. W. Holaday, E. Wei, H. H. Loh and C. H. Li, *Proc. natn Acad. Sci. U.S.A.* **75**, 2923 (1978).
9. R. Guillemin, T. Vargo, J. Rossier, S. Minick, N. Ling, C. Rivier, W. Vale and F. Bloom, *Science* **197**, 1367 (1977).
10. H. Akil, J. Madden, R. L. Patrick and J. D. Barchas, in *Opiates and Endogenous Opiate Peptides* (Ed. H. W. Kosterlitz), pp. 63–70. Elsevier/North-Holland Biomedical Press, Amsterdam (1976).
11. W. R. Martin, C. G. Eades, J. A. Thompson, R. E. Huppler and P. E. Gilbert, *J. Pharmac. exp. Ther.* **197**, 517 (1976).
12. J. A. H. Lord, A. A. Waterfield, J. Hughes and H. W. Kosterlitz, *Nature, Lond.* **267**, 495 (1977).
13. E. T. Iwamoto and W. R. Martin, *Mednl Res. Rev.* **1**, 411 (1981).
14. R. Elde, T. Hökfelt, O. Johansson and L. Terenius, *Neuroscience* **1**, 349 (1976).
15. T. Hökfelt, R. Elde, O. Johansson, L. Terenius and L. Stein, *Neurosci. Lett.* **5**, 25 (1977).
16. J. Hughes, H. W. Kosterlitz and T. W. Smith, *Br. J. Pharmac.* **61**, 639 (1977).
17. S. F. Atweh and M. J. Kuhar, *Brain Res.* **124**, 53 (1977).
18. S. W. Young, J. K. Wamsley, M. A. Zarbin and M. J. Kuhar, *Science* **210**, 76 (1980).
19. R. R. Goodman, S. H. Snyder, M. J. Kuhar and W. S. Young, *Proc. natn Acad. Sci. U.S.A.* **77**, 6239 (1980).
20. S. J. Watson and J. Akil, in *Hormonal Proteins and Peptides* (Ed. C. H. Li), Vol. 10, pp. 171–201. Academic Press, New York (1981).
21. R. A. Galosy, L. K. Clarke, M. R. Vasko and I. L. Crawford, *Neurosci. Biobehav. Rev.* **5**, 137 (1981).
22. J. W. Holaday and A. I. Faden, in *Neurosecretion and Brain Peptides; Implications for Brain Function and Neurological Disease* (Eds. J. Martin, S. Reichlin and K. Bick), pp. 421–34. Raven Press, New York (1981).
23. H. N. Sapru, R. N. Willette and A. J. Krieger, *J. Pharmac. exp. Ther.* **217**, 228 (1981).
24. J. W. Holaday, *A. Rev. Pharmac.*, in press.
25. R. E. Lang, U. B. Bruckner, K. Hermann, B. Kempf, W. Rascher, V. Sturm, T. Unger and D. Ganten, *Adv. Biochem. Psychopharmac.* **33**, 363 (1982).
26. I. Hanbauer, S. Govoni, E. A. Majane, H. Y. T. Yang and E. Costa, *Adv. Biochem. Psychopharmac.* **33**, 209 (1982).
27. L. E. Eiden and J. A. Ruth, *Peptides*, in press.
28. J. Flórez and A. Mediavilla, *Brain Res.* **138**, 585 (1977).
29. R. E. Lang, U. B. Bruckner, B. Kempf, W. Rascher, V. Sturm, T. Unger, G. Speck and D. Ganten, *Clin. expl Hypertension*, in press.
30. J. W. Holaday and A. I. Faden, *Nature, Lond.* **275**, 450 (1978).
31. J. W. Holaday, P. Y. Law, H. H. Loh and C. H. Li, *J. Pharmac. exp. Ther.* **268**, 176 (1979).
32. R. P. Gilbert, *Physiol. Rev.* **40**, 245 (1960).
33. A. I. Faden and J. W. Holaday, *J. Pharmac. exp. Ther.* **212**, 441 (1980).
34. D. G. Reynolds, N. J. Gurll, T. Vargish, R. Lechner, A. I. Faden and J. W. Holaday, *Circulat. Shock* **7**, 39 (1980).
35. D. J. M. Wright and M. P. I. Weller, *Br. J. Pharmac.* **70**, 99P (1980).
36. R. M. Raymond, J. M. Harkema, W. V. Stoffs and T. E. Emerson, *Surgery Gynec. Obstet.* **152**, 159 (1981).
37. F. N. Gahhos, R. C. J. Chiu and E. G. Hinche, *Circulat. Shock* **8**, 188 (1981).
38. J. M. Weld, T. E. Nugent, J. D. Combie, W. E. Woods and T. Tobin, *Equine Vet. J.*, in press.
39. N. J. Gurll, D. G. Reynolds, T. Vargish, S. A. Lutz and E. Ganes, *Physiologist* **24**, 11 (1981).
40. M. Rees, J. G. Payne and J. C. Bowen, *Surgery* **91**, 81 (1982).
41. J. J. Kaufman, *Lancet* **i**, 559 (1982).
42. H. F. Janssen, J. L. Pugh and L. O. Lutherer, *Adv. Shock Res.* **7**, 117 (1982).
43. H. F. Janssen and L. O. Lutherer, *Brain Res.* **194**, 608 (1980).
44. J. W. Holaday and A. I. Faden, in *Advances in Pharmacology and Therapeutics* (Eds. H. Yoshida, Y. Hagihara and S. Ebashi), Vol. II, pp. 45–55. Pergamon Press, New York (1982).
45. P. L. Rios and J. Jacob, *Archs Inst. Pasteur Tunis* **58**, 313 (1981).
46. J. W. Holaday, R. J. D'Amato, B. A. Ruvio and A. I. Faden, *Adv. Biochem. Psychopharmac.* **33**, 353 (1982).
47. M. R. Dashwood and W. Feldberg, *J. Physiol., Lond.* **300**, 22P (1979).
48. V. Manugian, S. Koyama, H. L. Santiesteban, W. S. Ammons and J. W. Manning, *Fedn Proc.* **40**, 522 (1981).
49. G. L. Belenky, B. A. Ruvio and J. W. Holaday, *Abstr. Soc. Neurosci.* **7**, 798 (1981).
50. J. W. Holaday, B. A. Ruvio and J. Sickel, *Circulat. Shock* **9**, 169 (1982).
51. N. J. Gurll, D. G. Reynolds, T. Vargish, E. Ganes, E. Mougey and J. W. Holaday, in press.
52. A. I. Faden and J. W. Holaday, *Science* **205**, 317 (1979).
53. T. Vargish, D. G. Reynolds, M. J. Gurll, R. Lechner, J. Holaday and A. I. Faden, *Circulat. Shock* **7**, 31 (1980).
54. N. J. Gurll, T. Vargish, D. G. Reynolds and R. B. Lechner, *Surgery* **89**, 364 (1981).
55. N. J. Gurll, D. G. Reynolds, T. Vargish and R. Lechner, *J. Pharmac. exp. Ther.* **220**, 621 (1982).
56. N. J. Gurll, D. G. Reynolds, T. Vargish and R. Lechner, *J. Pharmac. exp. Ther.* **220**, 625 (1982).
57. G. Feuerstein, R. Ailam and F. Bergman, *Eur. J. Pharmac.* **65**, 93 (1980).
58. M. T. Curtis and A. M. Lefer, *Am. J. Physiol.* **239**, H416 (1980).
59. J. C. Schadt and D. H. York, *Can. J. Physiol. Pharmac.*, in press.
60. J. W. Holaday, M. O'Hara and A. I. Faden, *Am. J. Physiol.* **241**, H479 (1981).
61. M. L. Patton, N. J. Gurll, D. G. Reynolds, T. Vargish

and E. M. Ganes, *Circulat. Shock* **9**, 178 (1982).
62. G. Feuerstein, C. C. Chiueh and I. J. Kopin, *Eur. J. Pharmac.* **75**, 65 (1981).
63. J. C. Schadt and D. H. York, *J. Autonomic Nerve Syst.*, in press.
64. N. J. Gurll, D. G. Reynolds, T. Vargish and E. Ganes, *Fedn Proc.* **41**, 1135 (1982).
65. J. W. Holaday and A. I. Faden, *Brain Res.* **189**, 295 (1980).
66. A. I. Faden, T. P. Jacobs and J. W. Holaday, *J. Autonomic Nerve Syst.* **2**, 295 (1980).
67. H. DeGeest, M. N. Levy, H. Zieski and R. I. Lipman, *Circulat. Res.* **17**, 222 (1965).
68. O. H. Viveros, E. J. Diliberto, E. Hazum and K. J. Chang, *Molec. Pharmac.* **16**, 1101 (1979).
69. M. R. Dashwood and W. Feldberg, *J. Physiol., Lond.* **281**, 30P (1978).
70. J. P. Huidobro-Toro and J. M. Musacchio, *Archs int. Pharmacodyn. Thér.* **251**, 310 (1981).
71. R. E. Lind, N. J. Gurll, J. T. Jenkins and D. G. Reynolds, *Surg. Forum* **31**, 48 (1980).
72. M. T. Curtis and A. M. Lefer, *Experientia* **37**, 403 (1981).
73. L. J. Eddy, D. W. Joiner and T. M. Glenn, *Fedn Proc.* **41**, 1135 (1982).
74. A. I. Faden, T. P. Jacobs, G. Feuerstein and J. W. Holaday, *Brain Res.* **213**, 415 (1981).
75. D. J. Goldstein, A. B. Pitterman, M. Frech, G. Kelly, J. J. Pisano and H. R. Keiser, *Life Sci.* **31**, 341 (1982).
76. P. Rubin, T. F. Blaschke and C. Guilleminault, *Circulation* **63**, 117 (1981).
77. J. O. Arndt and E. Freye, *Nature, Lond.* **277**, 399 (1979).
78. A. A. Artru, P. A. Steen and J. D. Michenfelder, *Anesthesiology* **52**, 217 (1980).
79. C. Farsang and G. Kunos, *Br. J. Pharmac.* **67**, 247 (1979).
80. R. B. Resnick, A. M. Washton and H. Lal, in *Endogenous and Exogenous Opiate Agonists and Antagonists* (Ed. E. L. Way), pp. 565–6. Pergamon Press, Oxford (1980).
81. C. Farsang, M. D. R. Gonzales, L. Mucci and G. Kunos, *J. Pharmac. exp. Ther.* **214**, 203 (1980).
82. D. J. Pettibone and G. P. Mueller, *Endocrinology* **109**, 798 (1981).
83. B. Delbarre, D. Senon, M. Dufraisse and M. DuPont, *Abstr. Soc. Neurosci.* **4**, 19 (1978).
84. T. Yukimura, T. Unger, W. Rascher, R. E. Lang and D. Ganten, *Clin. Sci.* **61**, 347S (1981).
85. R. H. Moore and E. A. Dowling, *Regul. Peptides* **1**, 77 (1980).
86. G. E. Sander, T. D. Giles, A. C. Quiroz, D. H. Coy and A. J. Kastin, *Clin. Res.*, in press.
87. G. E. Sander, T. D. Giles, A. J. Kastin, A. C. Quiroz, A. Kaneish and D. H. Coy, *Peptides* **2**, 403 (1981).
88. P. Bolme, K. Fuxe, L. F. Agnati, R. Bradley and J. Smythies, *Eur. J. Pharmac.* **48**, 319 (1978).
89. N. Zamir and M. Segal, *Brain Res.* **160**, 170 (1979).
90. N. Zamir, R. Simantov and M. Segal, *Brain Res.* **184**, 299 (1980).
91. T. Yukimura, G. Stock, H. Stumpf, T. Unger and D. Ganten, in *Advances in Endogenous and Exogenous Opioids; Proceedings of the International Narcotics Research Conference* (Ed. J. Takagi), pp. 370–3. Kodansha Ltd., Tokyo (1981).
92. C. P. Martucci and E. F. Hahn, *Endocr. Res. Commun.* **6**, 291 (1979).
93. K. Schaz, G. Stock, W. Simon, K-H. Schlör, T. Unger, R. Rockhold and D. Ganten, *Hypertension* **2**, 395 (1980).
94. B. R. Dworkin, R. J. Filewich, N. E. Miller, N. Cragimyle and T. G. Pickering, *Science* **205**, 1299 (1979).
95. G. L. Belenky and J. W. Holaday, *Brain Res.* **177**, 414 (1979).
96. M. A. Petty and J. L. Reid, *Hypertension* **3**, I-142 (1981).
97. E. Freye and J. O. Arndt, *Naunyn-Schmiedeberg's Archs Pharmac.* **307**, 123 (1979).
98. J. L. Montastruc, P. Montastruc and F. Moralesolivas, *Br. J. Pharmac.* **74**, 105 (1981).
99. A. I. Faden, T. P. Jacobs and J. W. Holaday, *Science* **211**, 493 (1981).
100. A. I. Faden, T. P. Jacobs, E. H. Mougey and J. W. Holaday, *Ann. Neurol.* **10**, 326 (1981).
101. W. Young, E. S. Flamm, H. B. Demopoulos, J. J. Tomasula and V. DeCrescito, *J. Neurosurg.* **55**, 209 (1981).
102. J. W. Holaday and R. J. D'Amato, *Science,* in press.
103. J. W. Holaday and R. J. D'Amato, *Life Sci.* **31**, 385 (1982).
104. Y. Hosobuchi, D. S. Baskin and S. K. Woo, *Science* **215**, 69 (1982).
105. D. S. Baskin and Y. Hosobuchi, *Lancet* **i**, 272 (1981).
106. A. I. Faden, J. Hallenbeck and C. Brown, *Neurology* **32**, 1083 (1982).
107. J. W. Holaday, L. F. Tseng, H. H. Loh and C. H. Li, *Life Sci.* **22**, 1537 (1978).
108. Y. Taché, M. Lis and R. Collu, *Life Sci.* **21**, 841 (1977).
109. J. W. Holaday, R. J. D'Amato and A. I. Faden, *Science* **213**, 216 (1981).
110. J. W. Holaday, B. A. Ruvio and A. I. Faden, *Eur. J. Pharmac.* **74**, 101 (1981).
111. J. W. Holaday and A. I. Faden, in *Advances in Endogenous and Exogenous Opioids; Proceedings of the International Narcotic Research Conference* (Ed. H. Takagi), pp. 367–9. Kodansha Ltd., Tokyo (1981).
112. A. I. Faden, T. P. Jacobs and J. W. Holaday, *New Engl. J. Med.* **305**, 1063 (1981).
113. J. G. Kiang and E. G. Wei, *Fedn Proc.* **41**, 1468 (1982).
114. J. W. Holaday, B. A. Ruvio, L. Robles and C. Johnson, *Life Sci.*, **31**, 2209 (1982).
115. J. W. Holaday and S. J. Ward, *Abstr. Soc. Neurosci.* 8 (1982).
116. A. I. Faden and J. W. Holaday, *J. infect. Dis.* **142**, 229 (1980).
117. J. W. Holaday and A. I. Faden, *J. infect. Dis.* **143**, 863 (1981).
118. M. Tiengo, *Lancet* **i**, 690 (1980).
119. W. P. Peters, M. W. Johnson, P. A. Friedman and W. E. Mitch, *Lancet* **i**, 529 (1981).
120. K. Lenz, W. Bruml, A. Gassner, K. Hruby, G. Kleinberger and A. Laggner, *Lancet* **i**, 834 (1981).
121. W. R. Swinburn and P. Phelen, *Lancet* **i**, 167 (1982).