available data conclusively establish stereostructure IIa and Ia·HBr (Figure 1). Comparison of this structure with the X-ray structure of the morphinan and benzomorphan ring systems[8-11] reveals that whereas the protonated, axial N lone electron pairs of the latter project *away* from the benzene ring (III), the corresponding lone pair of Ia projects *toward* the phenyl ring (IIb). Since the lack of analgesic activity of Ia and Ib cannot be related to anomalous dissociation behavior (*N*-methylpyrrolidine being somewhat more basic than *N*-methylpiperidine by 0.38 pK_a unit[12]) or to any significant distortions about rings A, B, and C, we conclude that the orientation of the N lone electron pair is a key determinant of productive interactions with the morphine receptor.§ Even if the stereochemistry of IIa were to be inverted about the nitrogen atom in solution or in the free base form at the receptor level (thus causing the *N*-methyl to assume a seemingly more hindered position), it remains that the lone pair would be conformationally twisted outward by some 20–25° relative to the morphinan lone pair (III). It appears probable then that conformational transmission of subtle distortion effects in the lone pair *orientation* of morphinans and related analogs[14,&] may account at least in part for structurally induced variations in their pharmacological properties. It seems likely that this lone pair orientation effect on receptor binding may be equally important for high antagonistic potencies.[6,15,16] The stereochemically controlled mechanism of the lone pair interaction with the analgesic receptor is examined in the following communication.[17]

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§According to a Referee, this conclusion is in contradiction with literature reports[13a] that the quaternary salt *N*-methylmorphine, in which the N lone pair of morphine is unavailable, possesses significant analgesic activity when administered intracerebrally and intraventricularly (hot-plate and licking tests, respectively). However, a detailed perusal of these reports reveals that the effects of *N*-methylmorphine (a blocker of neuromuscular transmission) differ significantly from those induced by morphine. For instance, morphine caused a greater and consistent fall in body temperature; acute tolerance did not develop with *N*-methylmorphine and no cross tolerance developed between morphine and its quaternary analog. The latter did not prevent the development of tolerance to morphine and, most significantly, nalorphine did not prevent the fall in body temperature after application of *N*-methylmorphine but blocked the morphine-induced fall in temperature. Finally, shortly after intraventricular injection of *N*-methylmorphine, a toxic state developed which was characterized by convulsive behavior similar to that induced by other types of quaternary drugs. We conclude on the basis of these observations that *N*-methylmorphine appears not to interact directly with the opiate receptor. It appears firmly established[13b] that morphine antagonists interact directly with the morphine receptors (see ref 2).

& In a personal communication, Dr. Walker has kindly informed us that the five-membered ring C analogs of the benzomorphans reported in that paper are also devoid of analgesic activity.

Clastic Binding on the Opiate Receptor

Sir:

In the preceding communication[1] we have shown that the orientation of the N lone electron pair of morphinans is a key determinant of stereospecific productive binding on the opiate receptor. That the N-protonated form of opiates is the active species[2] is unproved. Electrostatic forces between charges with or without the mediation of a proton bridge[1] can hardly be sensitive to geometrical effects about the charges. Since a regiospecific orientation of the N lone pair of morphinans appears essential for analgesic activity,[1] the protonated form may be tentatively ruled out as the active species. On that basis, the heuristic hypothesis offers itself that the N lone pair of the free base may interact with an electrophilic site whereupon a stereospecific electron transfer leading to oxidation of the *N*-methyl substituent may be operative. We are here tentatively viewing this possible electron injection at the opiate receptor level as forming part of the overall receptor response and not as an extrinsic preliminary step as required by the N-demethylation hypothesis of Beckett, Casy, and Harper[2] (which has since been held invalid[3,4]). Such electronic phenomena at the receptor or enzyme levels shall be conveniently referred to as clastic binding. Earlier, we have demonstrated by the method of deuterium isotope effects that clastic binding is characteristic of

Table I. Comparison of the Analgesic Activities of the Pair Levorphanol ($LNCH_3$)–Deuteriolevorphanol ($LNCD_3$) and the Pair *N*-Ethylnorlevorphanol ($LNCH_2CH_3$)–*N*-Deuterioethylnorlevorphanol ($LNCD_2CH_3$)

Drug	ED_{50}, mg/kg[a]		$f_{P.R.}$[b]	P.R.
$LNCH_3$	0.074 (0.060–0.091)	$LNCH_3/LNCD_3$	1.30	1.60 (1.23–2.08)
$LNCD_3$	0.118 (0.099–0.140)			
$LNCH_2CH_3$	0.710 (0.58–0.87)	$LNCD_2CH_3/LNCH_2CH_3$	1.38	1.61 (1.17–2.22)
$LNCD_2CH_3$	0.440 (0.34–0.57)			

[a]Dose at which 50% inhibition of the writhing response (phenylquinone) occurs in Swiss albino mice. Twenty-five mice were used per dose level (subcutaneous route) and a total of 130 mice for each compound. [b]For definition, see ref 11. The value of the potency ratio (P.R.) must exceed the value of $f_{P.R.}$ for the pair of substances to differ significantly in potency. Numbers in parentheses are the 95% confidence limits.

substrate interactions with oxidases and dehydrogenases.[5-7] These effects on such enzymes can markedly alter the pharmacological potency of certain substrates[8,9] or even drugs such as morphine.[4] In this latter case, Elison, *et al.*,[4] showed that replacement of the *N*-methyl hydrogens by deuterium *decreased* the analgesic potency by a factor of 1.64 by the subcutaneous route (mouse tail flick assay) and a factor *as high as 3.0* by the intravenous route. No satisfactory explanation for these observations could be offered although Winters[10] suggested that differences in basicity might account for the lower activity of NCD_3 morphine (the latter being more basic than morphine by 0.12 pK_a unit[11]). If the protonated form of morphine were the active species,[2,4] the NCD_3 morphine should have increased rather than decreased activity relative to NCH_3 morphine. Our own earlier analysis of this problem[7] led us to the suggestion that clastic binding (as we now define it above) on the opiate receptor accounts best for these results with NCD_3 morphine. However, cumulative effects of the basicity difference on the rate of partitioning between several compartments prior to binding on the opiate receptor cannot be ruled out as a potential source of the potency differences although the much larger isotope effect (3.0) observed by the intravenous[4] route does not support this hypothesis. We now wish to submit concrete evidence that clastic binding and not basicity differences is the most probable source of the potency difference between NCH_3 and NCD_3 morphine at the opiate receptor level.

Since clastic binding has been observed only with specific substrates and not with inhibitory nonsubstrate analogs,[6] it occurred to us that conventional binding (as opposed to clastic) may now obtain through the simple expedient of substituting the NCH_3 of opiates by another alkyl group such as NCH_2CH_3. Accordingly, a comparison of the agonist potencies of a pair such as NCH_2CH_3–NCD_2CH_3 within the same family of opiates may allow a definite conclusion as to the relative role of deuterium-induced basicity differences on potency because clastic binding on the receptor may be selectively associated with NCH_3 groups. We therefore prepared NCD_3 and NCD_2CH_3 (>99% labeled) norlevorphanols by conventional procedures and compared their analgesic potencies in mice (writhing syndrome) with that of their protio analogs. The results are shown in Table I where it can be seen that levorphanol is more active than its NCD_3 counterpart by a factor of 1.60, a potency difference in excellent agreement with the morphine results.[4] However, and most importantly, this isotope effect on potency is not only absent with the NCD_2CH_3 analog *but is actually reversed, the deuterioethyl compound being 1.61 times more active than its protio counterpart.* Clearly, then, the *convergent* differences in basicity introduced by deuterium substitution in the NCH_3 and NCH_2CH_3 groups, respectively, cannot serve to explain the *divergences* in the potency ratios. The results with the NCD_2CH_3–NCH_2CH_3 pair of opiate agonists find an exact parallel in our previous observations[5,8] with tyramine and its α-deuterated analog where the greater adrenergic potency of the latter[8] could be linked to a decreased rate of degradation by an extrinsic or peripheral monoamineoxidase.[5] At present, this leaves only one reasonable explanation for the reduced potency of NCD_3 levorphanol relative to its protio analog: *clastic binding on the opiate receptor complex itself.* In other words, the opiate receptor complex would possess an intrinsic and specific oxidative *N*-demethylase activity[7] (clastic binding being characteristic of substrate interactions with oxidative *N*-dealkylases[6,7]). The well-established stereoelectronic specificity of related oxidases[6,7] demands a favorable orientation of the N lone electron pair and of the NCH_3 group if clastic binding is to occur. This orientation requirement has been demonstrated in the preceding communication.

We tentatively conclude that clastic binding, which is tantamount to injecting electrons at the receptor level, may help create interneuronal connections that would be naturally forbidden, thus allowing perhaps for the multiplicity of biological effects (besides analgesia) associated with several classes of narcotics.

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