cophorin (*19*), glycoprotein fragments (*20*), or band 3 proteins (*21*). From examinations of stoichiometry and correlations of surface reactivity, various authors have suggested that particles may contain dimeric, trimeric, or multimeric associations of polypeptides (*17–22*). In one model system it was calculated that each 8-nm intramembranous particle contained between 10 and 20 tryptic peptide monomers with a combined molecular weight of 45,000 to 85,000 (*20*). Our examinations of "intact" membranes show a degree of association as much as a full order of magnitude greater. However, the presence of 12 protein molecules in a single particle (12 nm in diameter) is not inconsistent with their combined molecular weight ($12 \times 26{,}000 = 312{,}000$) if one recalls that the shadowed ferritin molecule has a diameter of 11 to 12 nm (*23*) and its apoprotein fraction a molecular weight of 480,000 (*24*). For simplicity the purple membrane lipids (25 percent by weight) were not included in the calculation.

Our study provides a clear example of the polypeptide composition of a native membrane particle. The purple membrane helix content is four to five times greater than that calculated in the tryptic peptide reconstitution study (*20*) and a full order of magnitude greater than that of many suggested particle polypeptide contributions. Although we recognize that polypeptide packaging in purple membrane may be unique, such structural complexity may also underlie the other 10-nm particles so commonly found in freeze-fractured biomembranes. If so, simple models of membrane structure, or one-to-one correlations of function and particle occurrence, should be viewed with caution.

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Intravenous Naloxone Administration in Schizophrenia and Affective Illness

Abstract. *Fourteen schizophrenic patients and five patients with affective disorders were given naloxone (0.4 to 10 milligrams) or placebo intravenously in a double-blind fashion. Physicians' ratings of hallucinations, mannerisms and posturing, conceptual disorganization, psychosis, and mood did not change significantly. A single item, unusual thought content, improved significantly on the naloxone day compared to the placebo day. There was no improvement in mood in affectively ill patients rated either by themselves or by physicians. Naloxone did not markedly improve any patient studied, which suggests that the acute blockade of opiate receptors is not associated with global improvement in psychotic symptomatology.*

The recent discoveries of the opiate receptor and endogenous polypeptides that bind to that receptor (*1*) have initiated a search for a peptidergic neuronal system that may influence a variety of behaviors. In humans, endogenous substances that bind to opiate receptors (endorphins) have been demonstrated in cerebrospinal fluid (CSF), brain, and peripheral blood (*2, 3*). Reports of psychotomimetic actions of narcotics and certain narcotic antagonists have led to the suggestion that some behavioral disorders may be associated with an excess of natural opiatelike compounds at specific sites in the central nervous system.

The link between psychotic behavior and endorphins has been suggested by the resemblance of behavioral states induced by endorphins in rats to human catatonia and to neuroleptic-induced catalepsy (*4, 5*). In one study, the investigators reported that reduced symptoms of schizophrenia were associated with a decreased level of endorphin in CSF (*6*). They also found elevated endorphin levels in the CSF of manic patients. In further study linking opiates to mood disorders, cyclazocine, a mixed narcotic agonist-antagonist, had a clinical antidepressant action (*7*). Perhaps the most provocative suggestion is the recent report that naloxone reduces or even eliminates temporarily the auditory hallucinations of chronic schizophrenics (*8*). Naloxone is a pure narcotic antagonist that has been shown to reverse and block opiate effects including analgesia, respiratory suppression, and psychotomimetic and other side effects (*9*). Naloxone has been shown to be effective in reversing the effects induced by endorphins as well (*3, 4*). If excessive endorphin is associated with human behavioral disorders, naloxone would be expected to promptly reverse relevant symptomatology. In this report, the possible antipsychotic and mood-altering effects of naloxone are tested in patients with schizophrenia and affective illness.

Patients participating in this study were all seriously ill inpatients at the National Institute of Mental Health. All were voluntary patients and had signed informed consent. The clinical characteristics of this population are described in Table 1. Naloxone or a matched volume of physiological saline was administered intravenously in a randomized double-blind fashion. The following items were rated on a severity scale of 1 to 7 (not present to severe): hallucinations, mannerisms and posturing, conceptual disorganization, unusual thought content, psychosis, and the mood variables of depression, elation, and dysphoria (*10*). These variables were chosen in order to evaluate the possible antipsychotic and antidepressant effects cited earlier. Blind ratings were performed before and 1 hour after each injection. In addition, each patient was interviewed for 15 min-

utes before and 15 minutes immediately after each injection. Verbal reports of the patient and clinical impressions were also systematically recorded during each interview. Patients completed both a self-rating form, which included mood and thought content items, and a questionnaire concerning side effects. These data are reported as "change units"; ratings from the first hour were subtracted from preinfusion baseline ratings and the sign changed in order for positive numbers to reflect reduction of symptoms.

Most patients were tested in the drug-free state, and others were tested while being treated on standard maintenance therapy (see Table 1) to replicate the study conditions of Gunne *et al.* (*8*). For the most part, 0.4 mg of naloxone was used, both in order to replicate Gunne *et al*, and because this dose temporarily reverses narcotic overdoses.

Patients ranged in age from 20 to 59 years (Table 1). The patients were chronically ill, having a mean duration of illness of 7.6 years.

No global clinical improvement in the schizophrenic group was noted during the placebo or naloxone day (Table 2). Of the eight items studied, only unusual thought content demonstrated a statistically significant improvement ($P < .04$, two-tailed sign test) when the naloxone and placebo days were compared. Although 10 of 14 patients had a slight decrease in scores when the eight rating measures were combined, this did not achieve statistical significance (*11*). It should be noted that the change scores

Table 1. Patient characteristics. Chronicity refers to the duration of the patient's history of illness. Fluphenazine was injected intramuscularly; other drugs were taken orally.

Patient	Diagnosis	Age	Sex	Chronicity	Current medication	Hallucinations	Naloxone dosage (mg)
A.D.	Schizophrenia	26	M	9 years	Thioridazine, 400 mg/day for 5 months	Yes	0.4
G.D.	Schizophrenia	27	M	7 years	Fluphenazine decanoate, 50 mg every 2 weeks for 5 months	No	0.4
W.J.	Schizophrenia	28	M	12 years	Reserpine, 12 mg/day for 1 month	Yes	0.4
P.M.	Schizophrenia	20	M	7 years	Haloperidol, 20 mg/day for 7 months	Yes	0.4
H.M.	Schizophrenia	26	M	7 years	Drug-free for 1 month	No	0.4
M.R.	Schizophrenia	22	M	2 years	Drug-free for 1 month	Yes	0.4
N.R.	Schizophrenia	19	M	6 months	Fluphenazine decanoate, 25 mg every 2 weeks for 1 month; Cogentin, 4 mg/day for 1 month	Yes	6
B.H.	Schizophrenia	53	F	23 years	Drug-free for 1 month	Yes	10
T.E.	Schizophrenia	18	M	2 months	Drug-free for 3 months	No	6
R.D.	Schizophrenia	18	F	3 years	Drug-free for 3 months	Yes	0.4
H.B.M.	Schizophrenia	31	F	8 years	Drug-free for 1 month	Yes	0.4
D.W.	Schizophrenia	32	M	8 years	Drug-free for 1 month	No	0.4
Q.C.	Schizoaffective	23	F	5 years	Drug-free for 3 months	No	0.4
G.H.	Schizoaffective	18	F	3 years	Drug-free for 3 months	No	0.4
Y.N.	Depression	49	F	8 months	Drug-free for 3 weeks	No	0.4, 0.8, 1.2
C.G.	Depression	46	M	5 years	Drug-free for 1 month	No	2
K.D.	Hypomania	23	F	8 years	Drug-free for 1 month	No	2
W.M.	Hypomania	55	F	20 years	Lithium carbonate, 1.8 g/day for 4 months; haloperidol, 8 mg/day for 8 days	No	2
B.A.	Cyclic psychosis	38	F	20 years	Fluphenazine decanoate, 20 mg/day every week for 5 months	Yes	0.4

Table 2. Change in behavior ratings of schizophrenic patients during the first hour after infusion of naloxone (N) or placebo (P). Items were rated on a severity scale of from 1 (not present) to 7 (severe). Ratings for the first hour were subtracted from baseline ratings made before the infusions, and the signs were changed in order for positive numbers to reflect improvement as seen in diminished symptoms.

Patient	Hallucinations		Mannerisms and posturing		Conceptual disorganization		Unusual thought content*		Psychosis		Depressive mood		Elation		Dysphoric affect	
	P	N	P	N	P	N	P	N	P	N	P	N	P	N	P	N
W.J.	−1	0	1	1	5	5	−2	1	0	0	−3	2	1	2	−3	0
H.M.	0	0	−1	0	−1	0	−2	0	−1	0	−1	−1	0	0	0	0
A.D.	−1	0	1	0	1	−1	−2	0	0	0	0	0	−1	0	−1	0
P.M.	−2	−1	0	0	−1	0	0	3	1	−1	1	2	0	2	1	0
G.D.	0	0	−1	0	0	0	1	0	0	−1	0	0	0	0	0	0
M.R.	0	0	0	−2	0	−1	−1	0	0	0	0	0	0	0	0	0
N.R.	0	0	1	0	0	0	0	1	0	1	0	0	0	0	0	2
B.H.	0	0	−1	−2	0	−1	0	−2	−1	−1	0	0	1	−1	−1	−3
T.E.	0	0	0	0	0	0	0	0	0	0	−1	0	0	0	−1	0
Q.C.	2	0	1	−1	0	0	−1	1	0	−1	1	0	0	0	1	1
R.D.	0	0	−1	0	0	1	0	2	0	1	−1	−1	1	2	2	1
D.W.	0	0	0	0	0	0	0	0	0	0	−2	1	1	0	−1	0
H.B.M.	0	0	0	1	0	0	0	2	0	0	1	0	0	0	0	0
G.H.	0	0	−1	−1	0	1	−1	0	0	1	0	2	−1	−1	−1	1
Totals	−2	−1	−1	−4	4	4	−8	8	−1	−1	−5	5	2	4	−4	2

*$P < .04$, two-tailed sign test

Table 3. Change of behavior ratings of affectively ill patients made by an observer and by the patients during the first hour after infusion. Observer items were rated on a scale of from 1 (not present) to 15 (severe). The self-rating items were scored from 1 (not present) to 7 (very marked). Change units are as described for Table 2. Patient Y.N. received three paired and randomized naloxone and placebo injections.

Patient	Observer								Self rating					
	Depression		Elation		Psychosis		Mania		Depression		Elation		Unusual thoughts	
	P	N	P	N	P	N	P	N	P	N	P	N	P	N
Y.N. 1	0	0	0	0	0	0	0	0	0	−1	0	0	2	5
Y.N. 2	0	0	0	0	0	0	0	0	1	0	0	0	−1	−1
Y.N. 3	0	0	0	0	0	0	0	0	0	−2	0	0	0	−1
C.G.	0	0	0	0	0	0	0	−1	1	0	0	0	0	0
W.M.B.	0	1	1	0	1	−1	3	0	Unable to complete self-rating					
K.D.	0	−2	0	2	0	1	0	−1	0	2	0	0	0	0
B.A.	0	0	1	0	0	0	0	0	−2	−2	−2	−3	−1	0
Total	0	−1	2	2	1	−2	3	−2	0	−3	−2	−3	0	3

themselves are quite small. Fifty-eight percent of all scores did not change from baseline to the 1-hour rating point postinjection and another 30 percent changed by only one unit.

In contrast to the previous report (*8*), hallucinations were not altered after naloxone injection. Of the 14 schizophrenic patients in this study, 8 reported auditory hallucinations on both the placebo and active compound or had obvious behavioral signs of hallucinations (such as speaking to persons not present). The hallucinations in three patients were rated slightly worse on the placebo day, and one was rated as improved. After the naloxone injection, one patient had an increase in hallucinations. No patient showed a decrease in hallucinations.

Eight patients reported "hearing voices that others don't hear" on their self-rating forms. Five of eight reported no change in this auditory hallucination item on the naloxone day. Two failed to complete this item on the naloxone day, and only one patient reported a decrease in his hallucinations. However, this patient reported even greater improvement on the placebo day.

After breaking the blind, we examined the interview data for the naloxone day for reports of hallucinations. A few clinical examples illustrate the lack of effect of naloxone on this aspect of the psychotic process. Patient P.M. did not spontaneously report hallucinations prior to the naloxone, but shortly after receiving naloxone, he responded, "I'm mad, they're bugging me" and "they're telling me I'm their slave." Patient A.D. reported voices saying "get out of the hospital" and "get better grades." He stated that "the voices stopped as the needle went in" but claimed to hear voices during the actual naloxone injection. Over the next 2 hours, he continued to report voices saying "get out of the hospital" and "go to southwest Washington." Patient H.M. reported hearing "sounds I heard at college" and "I hear people playing tennis and the sounds of the book-bin shutting." After the naloxone infusion, he continued to report these "sounds from college." Patient W.J. spoke loudly to imaginary persons. He would yell, "they're trying to get me" and would talk, both before and after the injection of naloxone, with "Mr. Napp," a figure he equated with the devil.

The results of the injections in patients suffering from affective disorders are reported in Table 3. Additionally, two severely depressed patients, not reported in these tables, were given naloxone for 3 days in higher doses (*12*) in a nonblind experiment in which there was no improvement.

The failure to demonstrate clear-cut improvement in schizophrenic patients or mood effects in affectively ill patients may reflect the absence of excessive endorphin in these patients or the lack of pathogenic effects of such an excess. Alternative explanations, such as the dosage of naloxone used, a nonrepresentative clinical sample in a diagnostically heterogeneous illness, or rating measures insensitive to specific symptoms, are possible but less likely. The higher doses administered to selected patients were without prominent effects. Even transient changes were not observed. Patients represented a variety of diagnostic subtypes. Although subtle improvement might go undetected in a study using behavior rating measures, there was certainly no dramatic improvement in any of the 19 patients studied. The finding of improvement in unusual thought content is puzzling. This item rates unusual, bizarre, psychotic verbal productions of the patients. Other measures of psychosis and cognitive impairment in schizophrenia, such as conceptual disorganization, failed to demonstrate improvement. A single significant *P* value among eight comparisons, several of which are interrelated, is not impressive. This finding does deserve to be examined in subsequent studies, however. The finding of catalepsy in animals given endorphins and its reversal by naloxone (*4, 5*) remains interesting. However, in our study, mannerisms and posturing, which have some similarity in man to these motor effects in animals, failed to improve. Of 14 patients, 13 were rated as showing a mild or greater degree of mannerisms and posturing at least once on each day of study. Nonetheless, further testing of naloxone in patients with catatonia or other neuromuscular symptoms is warranted. Taken together, these data suggest that acute blockade of opiate receptors is not associated with prominent alterations in schizophrenic or affective behavior.

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10. These items were selected from the Brief Psychiatric Rating Scale [J. E. Overall and D. R. Gorham, *Psychol. Rep.* **10**, 799 (1962)]; the Bunney-Hamburg rating scale [W. E. Bunney, Jr., and D. A. Hamburg, *Arch. Gen. Psychiatry* **9**, 280 (1963)], and an amphetamine interview rating scale used at the National Institute of Mental Health.
11. The sign test was chosen because these individual scales do not meet the conditions for parametric tests. A paired *t*-test was used for the sum of the eight rating measures because the sum more nearly approximates parametric conditions.
12. In these nonblind patients, the following doses of naloxone were administered on consecutive days: D.C. 2, 4, and 6 mg; Z.L. 0.8, 1.2, and 2.0 mg.
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Androgen Concentration in Motor Neurons of Cranial Nerves and Spinal Cord

Abstract. *After injection of [^{3}H]dihydrotestosterone, a major testosterone metabolite, radioactivity is concentrated in nuclei of certain cells in the midbrain, pons, medulla oblongata, cerebellum, and spinal cord. While there is some overlap between androgen and estrogen target neuron distribution, certain motor neurons appear to be selectively labeled by androgen; in contrast, estrogen localization prevails in sensory neurons. These results may help to explain why male sexual behavior in some rodents is not fully activated with dihydrotestosterone alone but in addition requires estradiol, a testosterone metabolite.*

The central action of androgen on the modulation of reproductive functions is thought to be mediated through the preoptic-hypothalamic region (*1*). Androgen target neurons have been detected in this region (*2*). In addition, target sites for androgen have been identified in extrahypothalamic sites, such as the septum, the amygdala, the hippocampus, and the epithalamus (*3*). This study was undertaken to search for and anatomically define androgen target cells in the lower brainstem and spinal cord. Isotopically labeled 5α-dihydrotestosterone (DHT) was used because it is a major metabolite of testosterone, which is found in the brain and not converted to estradiol (*4*). Androgen-concentrating cells were found to be widely distributed in the lower brainstem, that is, midbrain, pons, and medulla oblongata, and in the spinal cord, with a preferential localization of androgen in motor neurons of cranial nerves and of the spinal cord.

Adrenal glands and testes were surgically removed from two 60-day and two 26-day-old male Sprague-Dawley rats. After 96 hours the animals were injected intravenously with [1,2-^{3}H]dihydrotestosterone (5α-androstan-17β-ol-3-one) (44 c/mmole). The adult rats were injected with 1.0 μg and the immature rats with 2.0 μg of labeled DHT per 100 g of body weight. The animals were killed 1 hour afterward. Midbrain, pons, medulla oblongata with cerebellum, and different segments (cervical, thoracic, and lumbar) of the spinal cord were dissected, mounted on tissue holders, and frozen in liquefied propane (−180°C). Serial frozen sections (4-μm thickness) were cut in a wide-range cryostat (Harris Manufacturing Co., North Billerica, Massachusetts) and dry- or thaw-mounted on slides coated with photographic emulsion (Kodak NTB-3). After autoradiographic exposure for 5 to 15 months, slides were photographically processed and stained with methylgreen pyronin (*5*).

Cells with radioactivity concentrated in the nucleus were found in areas of the midbrain, pons, medulla oblongata, cerebellum, and spinal cord of all animals studied (Fig. 1). The topographic distribution of labeled cells appears to be similar in brains of adult and immature male rats; possible quantitative differences cannot be excluded. The labeled cells are mainly neurons but include certain ependymal and subependymal cells in the region of the fourth ventricle and spinal canal. Ependymal and subependymal cells with concentrations of radioactivity in the nucleus are most apparent in the collicular recess organ (*6*) and the area postrema. Accumulation of radioactivity is also seen in the lumen of blood vessels and ventricles. This is consistent with the presence of sex steroid–binding proteins in plasma and suggests transport of androgens through the cerebrospinal fluid.

The wide distribution of androgen-concentrating cells (*7*) is striking. Throughout the reticular formation in the mesencephalon, pons, and medulla oblongata, moderate to strong concentration of radioactivity is seen in neurons of different sizes and shapes (Fig. 1c). Androgen appears to be specifically concentrated in motor neurons in nuclei of cranial nerves and in motor neurons of the spinal cord (Fig. 1, b and d and Fig. 2). Androgen is also concentrated in the

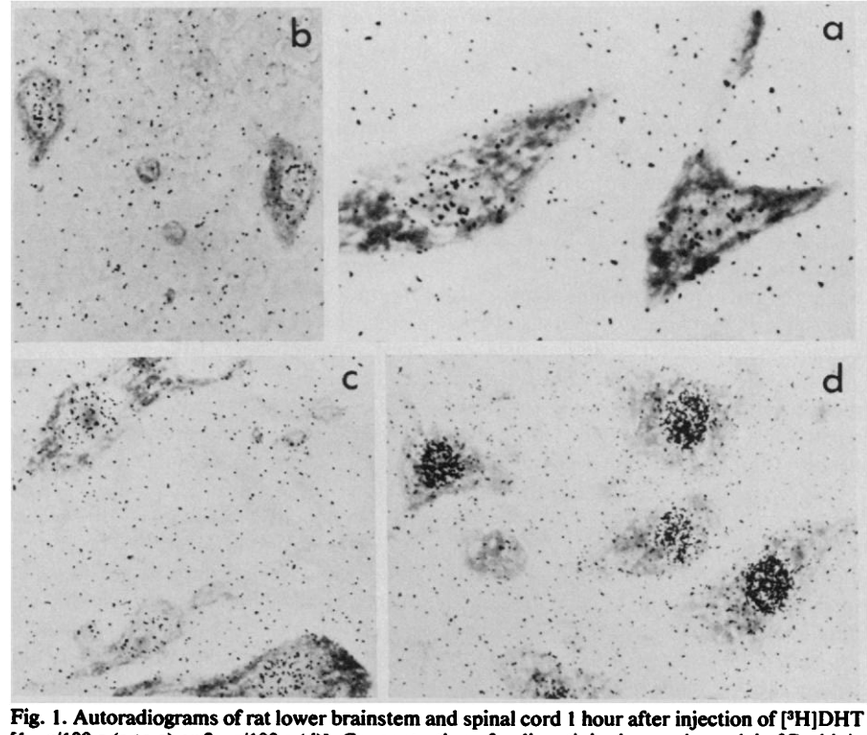

Fig. 1. Autoradiograms of rat lower brainstem and spinal cord 1 hour after injection of [^{3}H]DHT [1 μg/100 g (a to c) or 2 μg/100 g (d)]. Concentration of radioactivity is seen in nuclei of Purkinje cells (a), motor neurons of the seventh nerve (b), neurons of the reticular formation (c), and α-motor neurons in lamina IX of the thoracic segment of the spinal cord (d). Exposure times were 360 days (a), 290 days (b), 330 days (c), and 300 days (d). Stained with methylgreen pyronin (× 520).