significantly at the first minute. F (4, 100) = 9.04, $P < .001$, and at the tenth minute, F (4,100) = 4.89, $P < .001$, but not at 30 and 60 minutes. Individual group comparisons with t-tests indicate that the groups pretreated with β-endorphin and (−)-morphine responded in a manner significantly different from that of the groups given (+)-morphine and SP at these times and from that of the control group at the first minute.

12. For example, it has been shown that the inhibitory action of clonidine in mouse vas deferens is due to its action at presynaptic α adrenoceptors, whereas the inhibitory action of opiates is mediated by presynaptic opiate receptors [M. G. C. Gillan, H. W. Kosterlitz, L. E. Robson, A. A. Waterfield, *Br. J. Pharmacol.* **66**, 601 (1979)]. The former is selectively blocked by phentolamine, the latter by naloxone. In rat vas deferens, both phentolamine and naloxone exert stimulatory actions that may be due in part to a blockade of the α-adrenoceptor or opiate receptor, respectively.
13. B. J. Meyerson and L. Terenius, *Eur. J. Pharmacol.* **42**, 191 (1977).
14. These two may correspond to the high- and low-affinity opiate receptor-binding sites reported by G. W. Pasternak and S. H. Snyder [*Nature* **253**, 563 (1975)]. Whether the excitatory or inhibitory action is expressed probably depends on the ratio of excitatory:inhibitory receptors activated by the opiate.
15. The lack of excitatory action of etorphine in this assay in vitro parallels previous findings in vivo. A high dose of etorphine administered in the periaqueductal gray region (a site previously determined as mediating morphine analgesia) (*2*) in rats resulted in analgesia but not hyperreactivity, whereas morphine administered in this same brain region resulted in analgesia and hyperreactivity (*2*) [B. E. Thorn and R. A. Levitt, *Neuropharmacology* **19**, 203 (1980)].
16. I thank K. C. Rice for the gifts of (+)-morphine and (+)-naloxone. β-Endorphin (camel) and substance P were obtained from Peninsula Laboratories, Inc. This work was supported by grant DA 00367 from the National Institute of Drug Abuse.

7 May 1980; revised 18 June 1980

Elevated Cerebrospinal Fluid Norepinephrine in Schizophrenics: Confounding Effects of Treatment Drugs

The report by Lake *et al.* (*1*) presents evidence that the mean concentration of norepinephrine in the cerebrospinal fluid of a group of schizophrenics was elevated compared to that in healthy controls. A difficulty in studies of this type is the possible confounding effects of drugs used in the treatment of schizophrenia. Lake *et al.* report that the subjects received no medication for at least 2 weeks prior to the study. However, neuroleptic agents persist in the body for much longer periods of time. For example, chlorpromazine may be detected in the urine months after its administration has been discontinued (*2*). Furthermore, it is possible that drugs have persisting effects even after their disappearance from the body. Therefore, the effects of drugs used in the treatment of schizophrenia should be considered in the interpretation of the results reported by Lake *et al.*

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2. W. Martindale, *The Extra Pharmacopoeia* (Pharmaceutical Press, London, ed. 27, 1977).

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The comment by Lipsky is appropriate and warranted. Most of our 35 schizophrenic patients had been medication-free for more than 2 weeks before being studied, and the mean time since receiving the last dose of psychotic medication was about 4 ± 0.6 weeks, excluding several patients who had never been given antipsychotic drugs. [The concentrations of norepinephrine (NE) in the cerebrospinal fluid (CSF) of the patients who had never received antipsychotic drugs were similar to those measured in the patients who had received such drugs.] These periods are inadequate to ensure complete elimination of neuroleptic drugs, but to withhold therapeutic medication for 2 weeks is difficult; to withhold it for longer periods may be unethical.

There were elevated levels of NE in the CSF of the schizophrenic patients (*1*). The question by Lipsky seems to be whether some persisting antipsychotic drug effect could have been responsible for the elevation. The primary catabolite of brain NE metabolism is 3-methoxy-4-hydroxyphenylglycol (MHPG), and chlorpromazine lowers CSF levels of MHPG in schizophrenic subjects (*2*). In animals a variety of neuroleptic drugs significantly reduce brain NE levels (*3*). Eleven of the patients in our study were subsequently given pimozide, an antipsychotic drug, and restudied after at least 4 weeks of daily drug administration. Norepinephrine levels at the time of the second lumbar CSF tap were significantly reduced ($t = 3.04$, $P < .01$; Student's paired t-test) (*4*, *5*).

It appears that at least some antipsychotic drugs are associated with a decrease rather than an increase in NE levels. Thus, our finding of elevated levels of NE in CSF of schizophrenics is not explained by the effects of residual antipsychotic drugs.

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