These data clearly demonstrate that (i) repeated TP stress can induce a sensitization to a later injection of amphetamine and (ii) a single injection of amphetamine can, conversely, induce a long-lasting sensitization of TP behavior, as reflected by a decreased response to haloperiodol. Collectively, these findings support the hypothesis that TP and amphetamine may be interchangeable in their capacity to induce sensitization. The potential importance of these findings depends on the extent to which they can be generalized to other stressors. In this regard, it has been demonstrated that other, more traditional stressors, such as foot shock and food deprivation, can also induce sensitization to amphetamine (*9*, *10*). Since amphetamine and stress can each induce a sensitization to the other, the question arises of whether the progressive influence of repeated stimulant administration may be due, in part, to the ability of these agents to simulate the effects of stress on the organism. Such a possibility would be greatly enhanced if it could be shown that repeated stress can sensitize an organism to a subsequent stress. Data from our laboratory are in accord with this possibility. For instance, we have shown that food deprivation for 72 hours can diminish the ability of haloperidol to antagonize TP behavior 15 days later (*10*) and that self-stimulation [another known stressor (*11*)] can induce ingestive behaviors that show progressive enhancement upon repetition of this stimulus (*12*).

Our findings might be clinically relevant in several respects. (i) They suggest that even a single administration of a relatively small dose of amphetamine can produce enduring behavioral consequences. Thus, even if individuals previously exposed to amphetamine never develop a psychotic syndrome, they may, nonetheless, display abnormal behavioral responses during stressful situations long after that exposure. (ii) If, as our data suggest, both amphetamine and stress can induce sensitization and may be interchangeable in this regard, it might be predicted that individuals with a vulnerability to stress (such as may occur in certain types of schizophrenia) (*4*) would show an enhanced response to amphetamine. Indeed, a number of studies have shown that schizophrenics appear to be especially sensitive to the psychotogenic effects of amphetamine as well as other stimulants (*13*). (iii) The present findings may also help in understanding the enigma of the extreme variability in amphetamine dosage required to induce psychotic reactions in individuals with no record of schizophrenia (*14*). Thus, those with a history of stress may be much more sensitive to the influence of amphetamine. The last two points are not intended to imply that other environmental, physiological, or psychological factors are not involved, but that stress may be one of many variables which predispose an individual to develop drug-related or naturally occurring psychoses (*15*).

Finally, it should be noted that since amphetamine-induced stereotypy is believed to be mediated by dopamine (*16*), TP sensitization of this response could suggest that repeated stress may sensitize brain dopamine mechanisms. Our recent report that TP and other activating stimuli alter the firing rates of midbrain dopamine-containing neurons is consistent with this possibility (*8*).

SEYMOUR M. ANTELMAN
ALAN J. EICHLER
CYNTHIA A. BLACK
DONNA KOCAN

Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, and *Psychobiology Program, University of Pittsburgh, Pittsburgh, Pennsylvania 15260*

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15. The stressor used here (that is, TP) is a biological one, and produces both biochemical and neuroendocrine changes characteristic of classical noxious stressors [(*7*); S. M. Antelman *et al.*, unpublished observations]. The importance of physical or biological insults in precipitating schizophrenic episodes is indicated by both recent data implicating viral infection in a considerable proportion of schizophrenic patients [D. A. J. Tyrrell, T. J. Crow, R. P. Parry, E. Johnstone, I. N. Farrier, *Lancet* **1979-I**, 839 (1979); T. J. Crow, E. C. Johnstone, D. G. C. Owens, I. N. Ferrier, J. F. MacMillan, R. P. Parry, D. A. J. Tyrrell, *ibid.*, p. 842] and adoption data on monozygotic twins discordant for schizophrenia indicating that only 5.1 percent of the variance in outcome can be accounted for by psychosocial factors [D. Rosenthal, P. H. Wender, S. S. Kety, F. Schulsinger, J. Wilner, R. O. Rieder, *Arch. Gen. Psychiatry* **32**, 466 (1975)].
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Schizophrenia: Elevated Cerebrospinal Fluid Norepinephrine

Abstract. *Concentrations of norepinephrine in cerebrospinal fluid are higher in schizophrenic patients, particularly in those with paranoid features, than in normal volunteer subjects of the same age. This observation supports recent reports of elevated concentrations of norepinephrine in specific brain areas adjacent to the cerebral ventricles of paranoid schizophrenic patients. Overflow of the amine from periventricular regions into the cerebrospinal fluid may reflect abnormally high release or diminished enzymatic destruction of norepinephrine in patients with schizophrenia.*

Indirect pharmacological evidence provides the basis for speculations about the role of catecholamines in schizophrenia (*1*). Neuroleptic agents effective in the management of schizophrenia block dopamine receptors and the limbic noradrenergic system that generates adenosine 3′,5′-monophosphate (cyclic AMP) (*2*). High doses of amphetamines, which enhance release of brain catecholamines, can produce symptoms similar to paranoid schizophrenia (*3*). Furthermore, reserpine, which depletes brain catecholamines, alleviates some of the symptoms

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Table 1. Comparison of schizophrenic subgroups and control subjects. Values are means ± standard errors, and comparisons are by two-tailed t-tests.

Group	N	Age (years)	NE in CSF (pg/ml)	Blood pressure (mm-Hg)	Pulse (beats per minute)	Bunney-Hamburg psychosis rating
Control	29	29 ± 2.4	91 ± 6*	121 ± 2.6/ 75 ± 2.2‡	80 ± 1.9†	
All schizophrenics	35	25 ± 1.2	125 ± 11	123 ± 2.2/ 80 ± 1.0	95 ± 1.8	6.2 ± 0.4
Paranoid	14	26 ± 1.5	144 ± 20	122 ± 2.4/ 80 ± 1.3	92 ± 2.6	5.7 ± 0.8
Undifferentiated	10	27 ± 3.7	101 ± 11	126 ± 6.8/ 80 ± 2.4	100 ± 4.5	7.4 ± 0.7
Schizoaffective	11	25 ± 1.5	122 ± 21	120 ± 2.1/ 80 ± 1.8	95 ± 2.4	5.6 ± 0.7

*Less than all schizophrenics, $P < .01$; less than paranoids, $P < .02$. †Less than all schizophrenics, $P < .001$. ‡Less than all schizophrenics, $P < .05$.

of schizophrenia (*4*). The dopamine hypothesis of schizophrenia, however, is not accepted universally (*5*). In recent preliminary studies (*6, 7*), elevated concentrations of norepinephrine (NE) were found in specific areas of the brains of schizophrenic patients studied at autopsy. The limbic system, which controls emotional and cognitive behaviors similar to those disrupted in schizophrenia, is richly innervated by noradrenergic and dopaminergic neurons. Evidence suggests limbic system dysfunction in at least some cases of schizophrenia (*8*). Since the structures that compose the limbic system are adjacent to the cerebral ventricles, NE released in these areas may reach the cerebrospinal fluid (CSF) and thus reflect the activity of the limbic noradrenergic neurons (*9*).

We measured NE concentrations in the CSF of 35 schizophrenic patients and 29 healthy volunteers who were admitted to the clinical center at the National Institutes of Health (NIH). All gave written informed consent for their participation in the research procedures. Using Spitzer's research diagnostic criteria (*10*), two psychiatrists evaluated the schizophrenic patients before admission and during hospitalization to confirm the diagnostic categories—paranoid ($N = 14$), undifferentiated ($N = 10$), and schizoaffective ($N = 11$). The specially trained nursing staff completed the 15-point Bunney-Hamburg rating scale for psychosis twice daily for each patient. Control subjects (who had no personal or family history of psychotic illness) were admitted to the same wards as the patients and placed on the same diet (low in monoamines, alcohol-free, and caffeine-restricted) as that of the schizophrenic patients. Subjects received no medication for at least 2 weeks before we obtained CSF by lumbar puncture (at 9:00 a.m., after 9 hours of strict bed rest and no food or drink) (*11*). The nursing staff recorded blood pressure (by auscultation) and pulse rate (by radial palpation) four times a day for each subject.

The clinicians collected, processed, and preserved the CSF of patients and controls identically but in a manner different from that used in our previous studies, in which different concentrations of NE were found in normal subjects (*9*). Previously, the 4 ml of CSF required for NE analysis was collected into tubes containing 10 mg of ascorbic acid and frozen immediately on dry ice. In the present study, CSF was collected into tubes without ascorbic acid and was placed immediately on wet ice, 10 mg of ascorbic acid was added to 4 ml of this CSF within 30 minutes, and the samples were frozen at −70°C. We have discussed the methodological variations in greater detail elsewhere (*12*). The investigators who assayed the samples were blind to the diagnoses.

Mean concentrations of NE in CSF for all the schizophrenic patients and for those with paranoid schizophrenia were higher than those of control subjects [$P < .01$ and .02, respectively (two-tailed t-test; see Table 1)]. The NE concentrations in paranoid patients tended to be higher than in those with undifferentiated schizophrenia ($P < .1$), although one-way analysis of variance revealed no significant differences in the mean concentrations of NE in CSF, pulse rates, or blood pressures among the three schizophrenic subgroups. One-way analysis of variance of the control group and the three schizophrenic subgroups showed intergroup differences for NE concentration [$F(3, 60) = 3.8$, $P < .02$] and pulse rate [$F(3, 60) = 7.9$, $P < .001$]. The Newman-Keuls and Duncan tests were then used to contrast these intergroup differences. These tests indicated that for NE concentrations, the control group was significantly different from the paranoid subgroup only, and that for pulse rates, the control group was different from each of the three schizophrenic subgroups. The entire group of schizophrenic patients had higher mean diastolic blood pressure and pulse rate than the controls [$P < .05$ and .001, respectively (two-tailed t-test; see Table 1)]. One paranoid patient's NE concentration was 320 pg/ml (greater than 2 standard deviations from the mean), but even when this patient was omitted, the mean NE concentration for the paranoid patients (130 ± 16 pg/ml) remained significantly higher than for the controls ($P < .025$). The cardiovascular status of this patient was unremarkable; the pulse rate was 84 beats per minute and the blood pressure 120/81 mm-Hg. Of the three patient subgroups, those with undifferentiated schizophrenia had the highest mean pulse rate and psychosis score and the lowest mean NE concentration. Paranoid schizophrenic patients had the highest mean NE concentration and were the only subgroup to be significantly higher in this parameter than the controls; they also had the lowest mean pulse rate of the schizophrenic subgroups. Psychosis ratings, NE concentrations in CSF, pulse rates, and blood pressures were not correlated with each other or with any of the other parameters measured when evaluated with the Spearman rank-order correlation statistic.

The elevated pulse rates and diastolic blood pressures in the patients may reflect increased sympathetic or diminished parasympathetic nervous system activity. Although the patients reported less discomfort than the control subjects (*13*), the lumbar puncture (or the anticipation of the procedure) may cause greater anxiety in patients than in normal subjects. In spite of efforts to adequately inform the subjects about the procedures, some of the patients, particularly those with paranoia, may not have understood or fully believed the explanation for the lumbar puncture procedure. The elevated concentrations of NE in CSF in the paranoid patients do not seem to be directly related to anxiety, since they had the lowest mean pulse rate (a good index of anxiety level) and the highest mean NE concentration of the three schizophrenic subgroups.

These data are consistent with several recent reports (*6, 7*) of elevated concentrations of NE in specific brain areas of schizophrenic subjects, particularly

paranoid schizophrenics (*6*). Although schizophrenia may be a group of disorders characterized by similar symptoms but biochemically heterogeneous, paranoid schizophrenia may represent a more homogeneous population (*14, 15*). Evidence for this idea (other than studies reporting NE levels noted above) derives from reports that platelet monoamine oxidase (MAO) activity is reduced (*14*) and that urinary excretion of phenylethylamine (PEA) is increased (*15*) in the paranoid subgroup of schizophrenic patients. Phenylethylamine is an endogenous amine that is structurally and pharmacologically related to NE and amphetamine (*15*).

The major metabolite of NE in human brain tissue is 3-methoxy-4-hydroxyphenylglycol (MHPG). Most studies of MHPG in CSF find no significant differences between schizophrenic patients and normal subjects (*16*). However, activity of MAO, an enzyme involved in the conversion of NE to MHPG, tends to be low in schizophrenics (*14*). Patients with paranoid schizophrenia may have the lowest MAO activity, and the activities of other schizophrenic subtypes appear to lie intermediate between those of paranoid schizophrenics and those of normal subjects (*14*). Release of NE in the brain could be normal in schizophrenics, but if degradation of NE by MAO is retarded, then schizophrenic patients could have elevated concentrations of free NE that could reach the CSF and normal concentrations of the metabolite MHPG. Note that patients with paranoid schizophrenia have the highest concentrations of free NE in CSF; this is the same subgroup that Potkin *et al.* (*14*) report to have the lowest MAO activity. If these data are substantiated, one might hypothesize that the excess NE may induce a psychosis, similar to that produced by chronic ingestion of catecholamine-releasing drugs such as amphetamine, in which paranoid features are prominent (*3*).

If the elevated excretion rate of PEA in the paranoid patients (*15*) could be taken to indicate increased PEA metabolism in brain or even in the limbic system, where levels are high in normal subjects compared to other brain areas, what might these data imply with respect to the paranoid schizophrenic process? First, these data suggest that the paranoid subgroup may be more homogeneous. Second, PEA may be an endogenous psychotomimetic itself, a precursor of dopamine and NE (nonspecific hydroxylases are present in the brain), a modulator of catecholamine release and metabolism, or an insignificant by-product. If there is a physiologic role for PEA, the present trend toward evoking elevated NE activity in schizophrenia would implicate PEA as a releaser or precursor that increases NE levels.

The elevated concentrations of NE in the CSF of schizophrenic patients should be interpreted with caution, especially with respect to the paranoid subgroup, because of the considerable overlap between patients and controls and because our diagnostic abilities with regard to subgrouping schizophrenic patients remain tentative since most schizophrenic patients demonstrate paranoid delusions at some time in their clinical history. For example, one patient diagnosed as schizoaffective also had marked paranoid features and a NE concentration of 309 pg/ml. The results, however, are consistent with the view that in schizophrenics (*6, 7*)—particularly in some paranoid patients (*6*)—there are increased concentrations of NE in CSF, which implies enhanced release or diminished metabolism of the free amine in areas of the brain that are adjacent to the cerebral ventricles. However, the relation of the pathophysiology of schizophrenia to a defect in central noradrenergic neurotransmission remains to be elucidated.

C. R. LAKE*
Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, Maryland 20014
D. E. STERNBERG†
D. P. VAN KAMMEN
J. C. BALLENGER‡
Biological Psychiatry Branch, National Institute of Mental Health,
M. G. ZIEGLER§
Laboratory of Clinical Science, National Institute of Mental Health
R. M. POST
Biological Psychiatry Branch, National Institute of Mental Health
I. J. KOPIN
Laboratory of Clinical Science, National Institute of Mental Health
W. E. BUNNEY
Biological Psychiatry Branch, National Institute of Mental Health

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* Present address and reprint requests: Departments of Psychiatry and Pharmacology, Uniformed Services Medical School, Bethesda, Md. 20014.
† Present address: Department of Psychiatry, Yale University, New Haven, Conn. 06519.
‡ Present address: Department of Psychiatry, University of Virginia, Charlottesville 22903.
§ Present address: Departments of Clinical Pharmacology and Medicine, University of Texas Medical Branch, Galveston 77550.

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