the US alone or sham-US controls ($P > .05$). The preference behavior of the rats conditioned with PS in this experiment resembled that of their counterparts in experiment 1. These rats did not differ significantly from their controls, nor did they differ significantly from the rats conditioned with IPS or LiCl as the US. Thus PS appears to be of intermediate effectiveness at 10 days of age, ineffective at younger ages, but effective for rats older than 10 days.

The results of these experiments are congruent with studies of odor avoidance learning in adult rats in which both exteroceptive (PS) and interoceptive (LiCl) US's were found to affect behavior (*10*). These results also address the issue of learning and retention of responses conditioned with shock as the US in neonatal rats. It now seems that the failure to obtain reliable conditioning or retention of learned responses based on shock in rats younger than 8 to 10 days of age is related to the locus of application rather than to sensitivity to shock per se. Odors paired with interoceptive US are more easily associated and retained than odors paired with exteroceptive US's, but as the rat matures, exteroceptive aversive stimuli become increasingly effective in establishing associative bonds.

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8. All rats were conditioned against their natural preference for amyl acetate relative to the acetic acid used in testing.
9. In an ancillary study, audible vocalizations were recorded for groups of rats ($N = 4$) receiving either 1.0 mA of IPS or 1.0 mA of PS. There were no significant differences in either the number or the duration of vocalizations. The mean number of vocalizations per blocks of ten trials were 32, 24, and 23 for rats receiving PS and 24, 22, and 16 for IPS.
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18 December 1978; revised 4 May 1979

Cognitive Deficit Caused by Regional Depletion of Dopamine in Prefrontal Cortex of Rhesus Monkey

Abstract. *Depletion of dopamine in a circumscribed area of association cortex in rhesus monkeys produces an impairment in spatial delayed alternation performance nearly as severe as that caused by surgical ablation of the same area. This behavioral deficit can be pharmacologically reversed with dopamine agonists such as* L-*dopa and apomorphine. These data provide direct evidence that dopamine plays an important role in a specific cortical function.*

In primates, including humans, the dorsolateral convexity of the frontal lobe plays a selective role in mediating mnemonic, attentional, and spatial capacities (*1*). In infrahuman primates this region of the cerebral neocortex has high catecholamine levels and synthesis rates, particularly for dopamine (DA), whereas serotonin (5-HT) content and activity in the same cortical tissue is relatively low (*2, 3*). The combination of distinctive behavioral function and differentiated monoamine chemistry makes the frontal association cortex of the rhesus monkey highly suitable for analyzing the role of the putative monoamine neurotransmitters in behavioral processes. We now report that a substantial depletion of DA, along with a more modest depletion of norepinephrine (NE), in the cortex of the principal sulcus on the dorsolateral prefrontal convexity produces a selective impairment of delayed alternation performance similar to that produced by surgical ablation. Moreover, the behavioral deficit resulting from this biochemi-

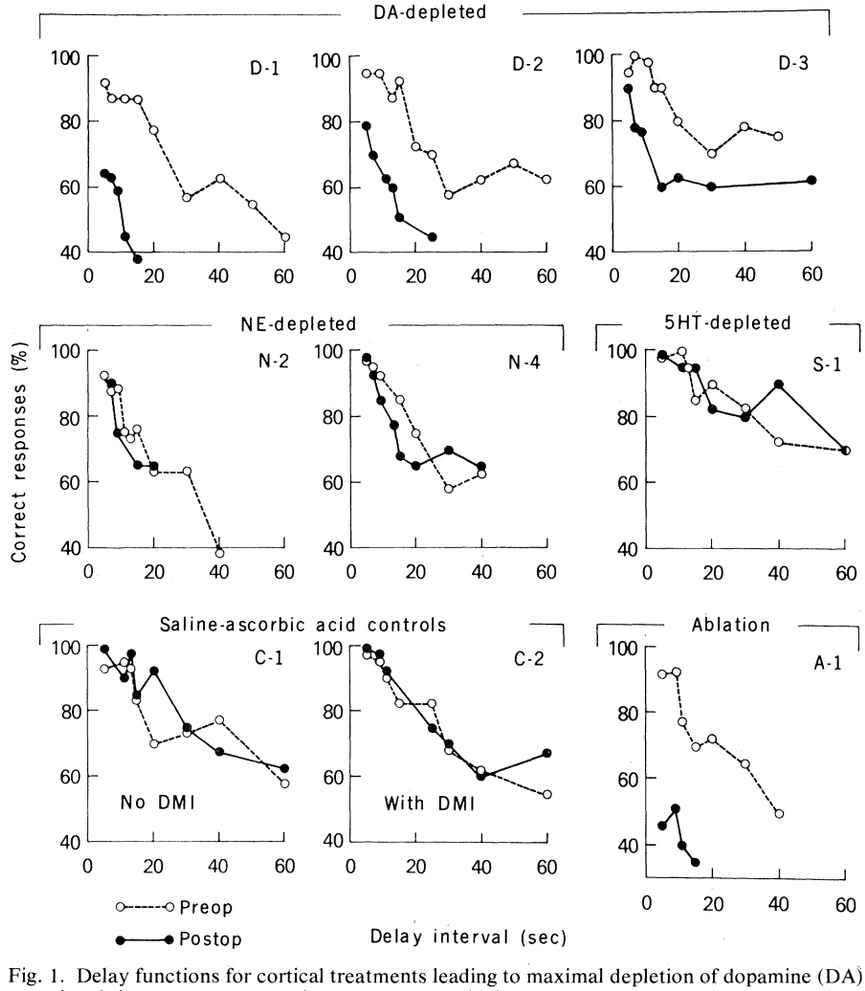

Fig. 1. Delay functions for cortical treatments leading to maximal depletion of dopamine (DA), norepinephrine (NE), or serotonin (5-HT) in the principal sulcus and for ablation. Each point is based on a minimum of 40 test trials at each delay value. Delay values were tested in nonsystematic series with replication in counterbalanced order. Differences between pre- and postoperative functions were significant only for the DA-depleted ($t = 7.94$, d.f. = 57, $P < .001$) and ablated animals ($t = 9.19$, d.f. = 9, $P < .001$). Animals N-2 and N-4 show the deficit range for NE depletion. The 5-HT-depleted (S-1) and ablated (A-1) animals are representative.

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Table 1. Monoamine depletion in selected brain areas. Data are percent depletions (± standard error of mean) of monoamines compared to saline-injected controls (N = 4).

Group	Brain area							
	Principal sulcus			Dorsolateral cortex			Head of caudate	
	NE (%)	DA (%)	5-HT (%)	NE (%)	DA (%)	5-HT (%)	DA (%)	5-HT (%)
6-OHDA (N = 3)	−85 ± 10	−56 ± 15	−31 ± 10	−21 ± 16	−25 ± 25	−23 ± 18	− 8 ± 14	+33 ± 26
6-OHDA + DMI (N = 4)	−76 ± 10	−87 ± 9	+16 ± 9	−13 ± 22	−22 ± 13	+ 8 ± 11	−17 ± 4	+ 7 ± 25
5,6-DHT + DMI (N = 2)	+10 ± 21	−48 ± 2	−70 ± 8	+38 ± 6	−38 ± 1	−26 ± 9	+14 ± 2	−27 ± 5

cal lesion can be pharmacologically reversed by L-dopa or apomorphine. Comparable depletions of NE or 5-HT in the same cortical area had no effect on this behavior. This is the most direct evidence yet obtained that DA may be selectively involved in supporting a specific cortical function.

Fifteen young rhesus monkeys were studied; 14 were trained in a Wisconsin General Test Apparatus on a 5-second spatial delayed alternation problem and on a visual pattern discrimination test. High performance on the former task depends upon the integrity of frontal association cortex, whereas effective performance on the latter depends upon other cortical areas (*4*). Both tasks were given in the same daily session for 20 trials each; task order was randomized from day to day. After the monkeys reached a criterion performance of 90 correct responses per 100 trials on each task, a delay function for the alternation problem was obtained by omitting the visual discrimination trials in daily sessions and giving instead 20 delayed alternation trials at longer delays ranging from 7 to 60 seconds. The effects of catecholamine or indoleamine agonists or stimulants were then examined at a point along the delay function at which individual performance was approximately 75 percent to permit observation of either detrimental or facilitatory drug effects. Where appropriate, dose-response functions were obtained (*5*).

After training and testing were completed, the animals were prepared for surgery. A frontal craniectomy was performed and the principal sulcus in each hemisphere exposed. Microquantities of selective toxins or control solutions were administered bilaterally in multiple injections 3 mm deep and extending around the entire perimeter of the principal sulcus at 3-mm intervals. One group (N = 4) received intracortical injections of the selective catecholaminergic toxin 6-hydroxydopamine (6-OHDA) (100 μg per injection site). In an effort to achieve maximal depletion of DA, the animals in this group were given intraperitoneal injections of desmethylimipramine (DMI) (total dose, 35 mg per kilogram of body weight), a selective blocker of noradrenergic membrane reuptake, before and after surgery (*6*). Controls for neural toxicity and nonspecific neural damage included animals that received intracortical injections of 6-OHDA without DMI (N = 3) or a selective indoleaminergic toxin, 5,6-dihydroxytryptamine (5,6-DHT) (9 μg per injection site), also preceded and followed by DMI (N = 2) (*7*). Additional controls (N = 4) for tissue damage at injection sites received intracortical injections of the vehicle, ascorbic acid in saline (1 mg/ml). Three of these controls were treated with DMI and one was not. In two additional cases the cortex in the principal sulcus was surgically removed in each hemisphere. Finally, one monkey was prepared for histological analysis. This monkey received multiple injections of 6-OHDA in one hemisphere, saline injections in the other, and was treated with DMI. The animal was killed 2 months after treatment. Its brain was embedded in celloidin and cut at 25-μm thickness. Sections stained with thionine were examined microscopically to determine the extent of cortical damage after intracerebral injections and to detect possible ret-

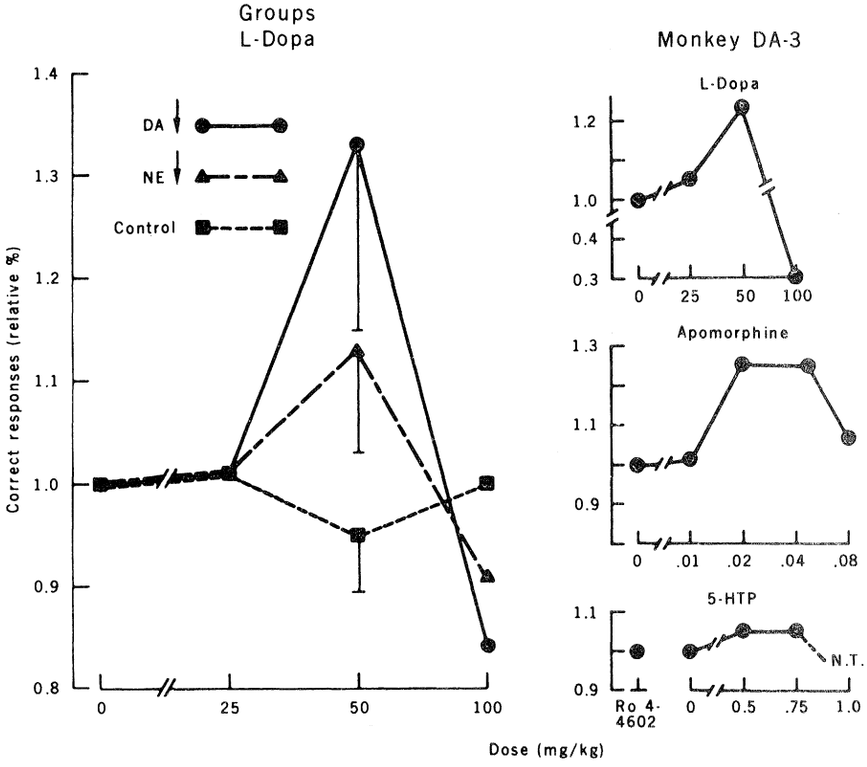

Fig. 2. Dose-response functions for the DA-depleted (N = 3), NE-depleted (N = 3), and saline control animals (N = 3). L-Dopa was given intraperitoneally 45 minutes before testing and 15 minutes after treatment with the peripheral L-dopa decarboxylase inhibitor Ro4-4602 (20 mg/kg, intraperitoneally). Data for each drug session were compared to mean performance on matched saline test sessions and relative performance values were derived (y-axis; 1.0 indicates no difference from saline). Dose-response functions are shown for a representative animal treated with L-dopa (and Ro4-4602), apomorphine (intramuscularly, 5 minutes before test), and 5-HTP [intraperitoneally, 45 minutes before test and 15 minutes after Ro4-4602 (20 mg/kg, intraperitoneally)]; *N.T.*, animal would not perform at this dose.

rograde changes in the relevant sector of the dorsomedial nucleus of the thalamus which projects to the principal sulcus (*8*).

Following a postoperative recovery period of at least 1 week, the animals were retested on the delayed alternation and visual discrimination problems, their delay functions were remapped, and drug effects were reevaluated. When the postoperative testing was completed, which usually required 4 to 10 months, the animals were killed, and their brains were rapidly removed, dissected over ice, and frozen until assayed. Appropriate cortical and subcortical tissue samples from 13 animals were subjected to cation exchange chromatography and fluorimetric assay for 5-HT, DA, and NE (*2*).

Each treatment produced a distinctively different pattern of monoamine depletion in the cortex of the principal sulcus (Table 1). Those animals injected with 6-OHDA and DMI showed an average depletion of 87 percent for DA and 76 percent for NE, compared to monoamine content in the same area in vehicle-injected controls. A complementary pattern of depletion was found in 6-OHDA–injected animals not treated with DMI: average DA depletion was 56 percent and that for NE was 85 percent (*9*). The 5-HT content was not appreciably affected in either group. In contrast to both groups injected with 6-OHDA, animals treated with 5,6-DHT showed 70 percent depletion of 5-HT in the principal sulcal cortex while DA was lowered 48 percent and NE was essentially unaffected (Table 1). The monoamine content of adjacent cortical and subcortical areas, including the remainder of the dorsolateral cortex and the caudate nucleus, was within normal limits in all cases (Table 1). The substantial reduction in monoamine levels 4 to 10 months after treatment with the toxins indicates relatively permanent depletion.

All animals recovered rapidly and displayed normal appetitive behavior and motor activity in their home cages. Further, none exhibited deficits on the visual discrimination problem. However, spatial delayed alternation performance was differentially affected by the experimental treatments. Intracortical injections of 6-OHDA accompanied by DMI, which produced an 87 percent depletion of DA in the principal sulcus, induced a behavioral impairment approaching in severity that exhibited by monkeys with surgical resection of the same tissue (Fig. 1, monkeys D-1, D-2, and D-3; A-1). In contrast, a slight but nonsignificant deficit was observed in animals with an average NE depletion of 85 percent (Fig. 1, monkeys N-2 and N-4), and no impairment was found in the group with maximal 5-HT depletion (Fig. 1, monkey S-1) or in animals injected with vehicle with DMI (Fig. 1, monkey C-2) or without DMI (Fig. 1, monkey C-1).

Postoperative dose-response functions show that the behavioral deficit produced by the DA depletion is reversible. L-Dopa facilitated the delayed-alternation performance of the DA-depleted group (Fig. 2). A dose of 50 mg/kg resulted in a mean 30 percent increment in performance over that observed regularly for nondrug sessions. At optimal dose L-dopa restored performance to predeficit levels for the DA-depleted animals. This catecholamine precursor had no significant effect on the performance of the NE-depleted or control animals (Fig. 2) or on the performance of animals with surgical ablations (not shown). Doses lower than 50 mg/kg had little effect while higher doses resulted in agitated behavior and degraded or eliminated test performance. The specific DA agonist apomorphine also ameliorated the deficit in two of the four monkeys (*10*), while the 5-HT precursor 5-hydroxytryptophan (5-HTP) was totally ineffective (Fig. 2). None of these drugs affected performance preoperatively. The noradrenergic agonist clonidine produced a moderate nonspecific enhancement of delayed alternation performance in all animals (*11*), while diazepam, which was tested only in selected animals, produced no consistent facilitation.

The finding that DA depletion can be restricted to a circumscribed area of prefrontal cortex and produce a behavioral deficit in a selective function of that area adds to the growing body of evidence that DA in prefrontal cortex may function as a neurotransmitter independent of its precursor role (*12*). Apparently the DA loss must be quite severe (nearly 90 percent) before it induces behavioral impairment; treatments that reduce DA by 56 percent did not alter the behavior under examination. The loss in delayed alternation performance appears to be attributable specifically to substantial depletion of DA, because treatments that produce comparable depletions of NE or 5-HT, in combination with modest DA depletion and comparable nonspecific cortical damage, fail to produce significant impairment.

In addition, the behavioral deficit could be reversed by the DA precursor L-dopa, and in some cases by the selective DA agonist apomorphine, while neither the indoleaminergic precursor 5-HTP nor the noncatecholaminergic drug diazepam improved performance. An unexplained general enhancement in performance for all animals was observed after treatment with the noradrenergic agonist clonidine. The mechanism by which the specific DA agonists improved performance is not known. However, since 6-OHDA selectively destroys presynaptic terminals, many postsynaptic receptor sites should still be available for occupation by agonists such as apomorphine and should be supersensitive to both endogenous and exogenous sources of DA (*13*). This possibility is consistent with our finding that various drugs did not ameliorate the behavioral impairment of animals with surgical lesions in whom such receptor sites were destroyed.

The present results do not imply that spatial delayed alternation function is exclusively dependent on DA. Other putative neurotransmitters not manipulated in the present study may also play a role. Nor is it known whether other functions of frontal association cortex in addition to spatial delayed alternation performance are similarly DA-dependent. Various types of behaviors depend upon normal levels of DA in the central nervous system (*14*). In addition it has been suggested that learning and memory processes depend upon a dopaminergic reward network intimately involving the prefrontal cortex (*15*). Further work is required to integrate these findings and to specify the precise neurohumoral or synaptic mechanisms by which DA supports cortical function. Nevertheless, the present results establish a prominent role for DA in primate cortical function and provide a promising basis for the study of the therapeutic possibilities of drug treatment in recovery from biochemical deficiencies that affect cognition.

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5. Dose-response functions for each animal were obtained by selecting the delay value (from each animal's delay function) at which 75 percent correct performance was obtained. Drug sessions consisted of a 20-trial block at this test delay value and a 20-trial block at 5-second delay, with the order of the blocks counterbalanced across sessions. Data from the 5-second block provided a check on motivation and other general factors affecting performance. Data from the test block were used to construct dose-response functions. Each animal was tested at least twice at each drug dose, and a saline control session was interspersed between each drug test. Dose-response functions were computed for individuals and groups by comparing drug performance to saline performance (mean correct responses after drug divided by mean correct response after saline).
6. Direct infusion of 6-OHDA into neural tissue results in selective damage to catecholaminergic neurons or neuron terminals (or both) (*16*). Noradrenergic neurons exhibit greater selective uptake of the toxin and at appropriate dose levels are selectively destroyed (*17*). Systemic treatment with DMI inhibits noradrenergic membrane reuptake and as a result protects noradrenergic neurons from the cytotoxic effects of 6-OHDA (*18*). The focus of damage is thus shifted to dopaminergic neurons. Substitution of the indoleamine 5,6-DHT for 6-OHDA similarly shifts the focus of damage to serotonergic neurons (*19*).
7. Total quantity of toxin or vehicle varied somewhat between animals, depending upon variation in the length of the principal sulcus. The number of injection sites per hemisphere ranged from 13 to 18 (mean ~ 15). Thus total 6-OHDA dose averaged 3 mg (as free base) and total 5,6-DHT dose averaged 0.27 mg (as free base).
8. Light-microscopic examination of histological preparations revealed that cellular damage in the principal sulcus was confined largely to tracks caused by needle penetrations. Such damage was no greater in the hemisphere injected with 6-OHDA than in the one injected with saline. In both hemispheres, cortex between and adjacent to injection sites in the banks and depths of the principal sulcus and on the dorsal and inferior convexities appeared to be undamaged. Further, the dorsomedial nucleus in the thalamus was intact, except for miniscule islands of chromatolysis and degeneration corresponding to the discontinuous cortical damage at needle penetration sites. The finding that neurons which project to frontal cortex are spared provides evidence that 6-OHDA can be injected intracerebrally without producing widespread nonspecific cortical damage.
9. The degree of protection exerted by DMI on NE terminals was considerably less than expected. The resistance of the monkey to the neurochemical effects of 6-OHDA has been noted [G. R. Breese, R. D. Cooper, A. S. Hollister, G. Kraemer, W. T. McKinney, in *Chemical Tools in Catecholamine Research*, G. Jonsson, T. Malmfors, C. Sachs, Eds. (North-Holland, Amsterdam, 1975), vol. 1, pp. 335-342].
10. The short duration of apomorphine's behavioral action probably contributed to its less reliable therapeutic action. The test procedure took about 20 minutes to complete. Whereas L-dopa was effective for several hours, peak apomorphine effect appeared within 10 to 15 minutes, then rapidly diminished.
11. Clonidine enhanced spatial delayed alternation performance of virtually all animals, both pre- and postoperatively. At optimum dose level (0.01 to 0.04 mg/kg) the mean performance enhancement was as follows: preoperative (N = 4), +11 percent; operated saline controls (N = 4), +23 percent; NE-depleted (N = 2), +18 percent, DA depleted (N = 3), +14 percent; 5-HT depleted (N = 2), +15 percent; and ablated (N = 1), +23 percent.

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20. T.J.B. was supported by postdoctoral fellowship MH 05202 and funds from Grinnell College. The Ro4-4602 was donated by Hoffmann-La Roche, Inc., Nutley, N.J.

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5 September 1978; revised 24 April 1979

Lithium Transport Across Red Cell Membrane: A Cell Membrane Abnormality in Manic-Depressive Illness

Abstract. *In the families of manic-depressive patients, relatives with a history of affective disorders had a significantly higher ratio of mean red cell lithium to plasma lithium in vitro than relatives with no such history. A genetically controlled abnormality in lithium-sodium transport, the mechanism that determines the lithium ratio, may play a role in the etiology of some forms of affective disorders.*

An abnormality in cell membrane function, reflected in altered transport of lithium across cell membranes, may play a role in the etiology of affective disorders (*1*). Using the red cell as a model, we have demonstrated in normal individuals that genetic factors contribute to variability in the distribution of lithium across the red cell membrane, that is, in the ratio of lithium concentration in red cells to that in plasma (lithium ratio) (*2*). An initial study indicated that manic-depressive (bipolar) patients had a significantly higher mean lithium ratio in vivo than normal individuals (*3*). This result suggested that a disturbance in cell membrane function is associated with the pathophysiology of bipolar illness. Before concluding, however, that a genetically controlled biological trait plays a role in the etiology of a psychiatric disorder, one must demonstrate that the biological trait and the psychiatric disorder are transmitted nonindependently within pedigrees (*4*).

We have assessed the lithium ratio in vitro and the psychiatric diagnosis in 66 adult first-degree relatives of 31 bipolar I patients (having both incapacitating manic and depressive states) who were diagnosed according to the Research Diagnostic Criteria (RDC) (*5*). The relatives studied had been drug-free for 1 week and alcohol-free, according to self-report, for 48 hours before participation. Relatives taking medication regularly for a medical or psychiatric illness were excluded from the study.

To determine the lithium ratio, we incubated red cells in the presence of 1.5 mM lithium chloride for 24 hours. The red cell and extracellular lithium concentrations were then determined by atomic emission spectrophotometry. This procedure yields a lithium ratio that is highly correlated (r = .85, P < .001) with the lithium ratio in vivo (*6*). We (E.D., S.E., and R.S.) diagnosed the first-degree relatives according to the RDC by using the *Schedule for Affective Disorders and Schizophrenia—Lifetime Version* (*7*). We did not know the lithium ratios at the time of diagnosis. The laboratory technicians, in turn, did not know the identity or diagnosis of relatives when they conducted the lithium assays.

Of the 66 relatives studied, 16 had a history of a major affective illness, 28 had a history of a minor affective illness, and 22 had no history of affective illness (*8*). The distribution of the lithium ratios of the relatives in each of the three diagnostic groups is shown in Fig. 1. A general linear model two-way analysis of variance (*9*) (the factor entered first was membership in one of the three diagnostic groups and the factor entered second was family membership) indicated significant differences among the mean lithium ratios of the diagnostic groups [F(2, 33) = 3.68, P < .04]. Relatives with a history of major and minor affective illness had significantly higher mean lithium ratios [0.17 ± 0.05 (standard deviation) and 0.18 ± 0.04, respectively] than did relatives with no history of affective illness (0.15 ± 0.03) (t = 2.09, P < .05; and t = 2.45, P < .025, respectively). The differences among means of the groups were not attributable to differences in age, sex, ethnic origin, previous psychotropic medication, or alcoholism (*10*).

Of the 31 bipolar I patients, 15 had on-

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