Possible Etiology of Schizophrenia: Progressive Damage to the Noradrenergic Reward System by 6-Hydroxydopamine

Abstract. *Single or repeated intraventricular injections of 6-hydroxydopamine caused marked and long-lasting deficits in brain self-stimulation and other rewarded behaviors in the rat. The behavioral deficits, as well as the depletion of brain norepinephrine induced by 6-hydroxydopamine, were prevented by prior treatment with chlorpromazine. Episodic or continuous formation of endogenous 6-hydroxydopamine in man as a result of a genetically determined enzymatic error could selectively damage the binding capacity and, eventually, the structural integrity of the noradrenergic reward mechanism. Such damage might cause the fundamental symptoms and long-term downhill course of schizophrenia.*

We propose in this report a novel physiological and chemical etiology for schizophrenia. Our work is based on Thudichum's (*1*) concept that "many forms of insanity" are caused chemically by "poisons fermented within the body." The essential properties of the offending chemical have been outlined by Hollister (*2*): "In short, what is required is an endogenous toxin, highly active and highly specific in its action at minute doses, continuously produced, for which tolerance does not develop."

Current biochemical theories, which use mescaline or LSD (lysergic acid diethylamide) as a model, generally attribute hallucinogenic or psychotomimetic properties to the toxic metabolite (*3, 4*). Such formulations may be criticized on two grounds. First, in view of the chronic and even lifelong duration of schizophrenia, it seems unlikely that a mescaline-like substance would be produced in adequate quantities continuously over many decades without the development of tolerance. Second, many authorities now question the assumption that hallucinogenic drugs induce a "model psychosis." These agents do not reproduce the fundamental symptoms of schizophrenia, and the differences between the drug states and schizophrenic reactions are easily distinguished (*5*). The wide variety of mental changes caused by the drugs, such as hallucinations and delusions, tend rather to resemble the accessory symptoms of schizophrenia.

According to Bleuler (*6*), "the fundamental symptoms consist of disturbances of association and affectivity." Specifically, this author suggests that schizophrenic associations lose their continuity because the thoughts "are not related and directed by any unifying concept of purpose or goal." At the same time, emotional responsivity is diminished and eventually reduced to indifference, so that "many schizophrenics in the later stages cease to show any affect for years and even decades." In Rado's (*7*) view, the disturbance of affect stems from the fact that the "pleasure resources are inherently deficient." Finally, Blueler and others emphasize that the course of the disease "is at times chronic, at times marked by intermittent attacks, and which can stop or retrograde at any stage, but does not permit a full *restitutio ad integrum.*" A distinctive feature of our theory is that it explains both the fundamental symptoms of schizophrenia and its long-term downhill course.

Physiological (*8*), histochemical (*9*), and psychopharmacological (*10*) work has led to the suggestion (*11*) that rewarded or goal-directed behavior is controlled by a specific system of norepinephrine-containing neurons in the brain. The cells of origin of this system are localized in the lower brain stem, and the axons ascend via the medial forebrain bundle to form noradrenergic synapses in the hypothalamus, limbic system, and frontal cortex. Electrical stimulation of the medial forebrain bundle serves as a powerful reward and also elicits species-typical consummatory responses, such as feeding and copulation, which produce pleasure and permit the satisfaction of basic needs (*8*). Electrolytic lesions of the medial forebrain bundle, or pharmacological blockade of its noradrenergic function, cause severe deficits in goal-directed behavior and the loss of consummatory reactions (*12*). There is some evidence that these findings in animals may be extrapolated to man (*13*). If so, one could speculate that the two primary symptoms of schizophrenia—both the deficit in goal-directed thinking and the deficit in the capacity to experience pleasure—may be due to a chronic and at least partially irreversible impairment of the noradrenergic reward system.

Genetic studies provide indirect support for the idea that an impairment of noradrenergic function may be involved in schizophrenia. The early impression that schizophrenia is inherited has been verified by systematic family studies and studies of adopted children (*14, 15*), which establish "the importance of genetic factors in the development of schizophrenia . . . beyond reasonable dispute" (*15*). Several modes of inheritance have been proposed, but many

Table 1. Acute suppressant action of 6-hydroxydopamine on feeding. Rats were trained to drink milk from a graduated tube in a 45-minute test until intakes stabilized. Tests were made 3 hours after injections of 6-hydroxydopamine or the vehicle solution. First and second tests were separated by 1 week. The suppressant effects of lower doses showed evidence of tolerance in the second test.

Rat No.	Dose (μg)	Milk intake (ml)				
		No drug		Ascorbic acid vehicle	6-Hydroxydopamine	
		1st test	2nd test		1st test	2nd test
W-31	6.3	13	14.5	16	6	17
W-36	12.5	24	21.5	23	18.5	22.5
W-35	25	17	13.5	13.5	12	17.5
W-34	50	17.5	19.5	19	6	20*
W-32	100	26	22.5	30	12	13.5

* Received 6.3 μg rather than 50 μg.

Table 2. Suppressant effect of 6-hydroxydopamine on self-stimulation. A single dose of 200 μg; was injected intraventricularly 23 hours before the start of a series of six daily tests.

Treatment	Rats (No.)	Mean self-stimulation rate (% of control before drug)					
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
6-Hydroxydopamine	5	41.1 ± 12.7	71.2 ± 8.8*	69.2 ± 14.3	71.0 ± 18.3	65.6 ± 21.1	65.7 ± 10.9
Ascorbic acid vehicle (10 μl)	3	96.5 ± 25.3	98.6 ± 11.5	99.4 ± 8.9			

* Differs from vehicle mean at $P = 0.5$ (t test, single-tailed).

authorities currently favor the idea that a main gene of large effect, modified either by a second gene (*16*) or by multiple factors (*15*), is responsible for schizophrenia and borderline schizoid disorders. In any case, the conclusion that schizophrenia is hereditary necessarily implies a biochemical aberration, since no other mechanism is known for the expression of genetic traits.

Several lines of biochemical evidence suggest that 6-hydroxydopamine (2,4,5-trihydroxyphenethylamine) is the aberrant metabolite that causes schizophrenia (*17*). This compound is an autoxidation product and metabolite of dopamine, and "its formation can occur to a significant extent in the intact animal" (*18*). 6-Hydroxydopamine induces a specific degeneration of peripheral sympathetic nerve terminals with a marked and long-lasting depletion of norepinephrine (*19*). When injected intraventricularly into the rat brain, 6-hydroxydopamine similarly causes a prolonged or permanent depletion of brain catecholamines. Only catecholamine-containing neurons are affected, and brain norepinephrine is more severely depleted than is dopamine (*20*). Electron microscopic evidence reveals that norepinephrine (but not dopamine) nerve terminals in the brain degenerate and eventually disappear after repeated doses of 6-hydroxydopamine (*21, 22*).

Surprisingly, despite the profound damage to central noradrenergic neurons, rats treated with 6-hydroxydopamine are reported to be "grossly indistinguishable" from controls "except for a slight decrease in body weight and a lack of self-grooming" (*23*). If sensitive behavioral tests are used, however, marked deficits are obtained after single or repeated doses of 6-hydroxydopamine (*24*). Behavioral tests in the unanesthetized rat also may be made more sensitive by use of permanently indwelling cannulas, which permit injection of solutions into the lateral ventricle with minimum disturbance.

In our experiments, 6-hydroxydopamine as a hydrochloride salt is dissolved in 10 μl of Ringer-Locke solution containing 0.1 percent ascorbic acid (*p*H 4.5). Control animals are injected intraventricularly with 10 μl of the vehicle solution. Under these conditions, large deficits in behavior are readily observed after administration of 6-hydroxydopamine, either in acute experiments with small doses (Table 1) or in chronic experiments with larger or repeated doses.

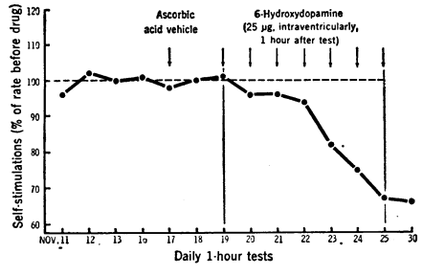

Fig. 1. Suppression of self-stimulation by repeated doses of 6-hydroxydopamine (averaged data of three rats.)

Most directly relevant to the present argument are studies of the chronic effects of 6-hydroxydopamine on "self-stimulation" (*8*) behavior maintained by rewarding electrical stimulation of the medial forebrain bundle (at the level of the ventromedial nucleus). A single 200-μg dose of 6-hydroxydopamine reduced the rate of self-stimulation by 58.9 percent on the first day after the injection; recovery of the rate before drug administration was incomplete over the next 5 days (Table 2). In a related experiment, seven daily doses of 25 μg caused progressive suppression of the self-stimulation rate to 67 percent of control. The suppression persisted for at least 5 days after dosing was discontinued (Fig. 1). In a third study, an intraperitoneal injection of the monoamine oxidase inhibitor pargyline potentiated the suppressive action of a series of 400-μg doses for several days; during most of this time, the rat displayed a catatonic-like syndrome of "waxy flexibility" (Fig. 2). It is evident from these results that 6-hydroxydopamine markedly impairs self-stimulation and other rewarded behaviors. Furthermore, because the drug-induced impair-

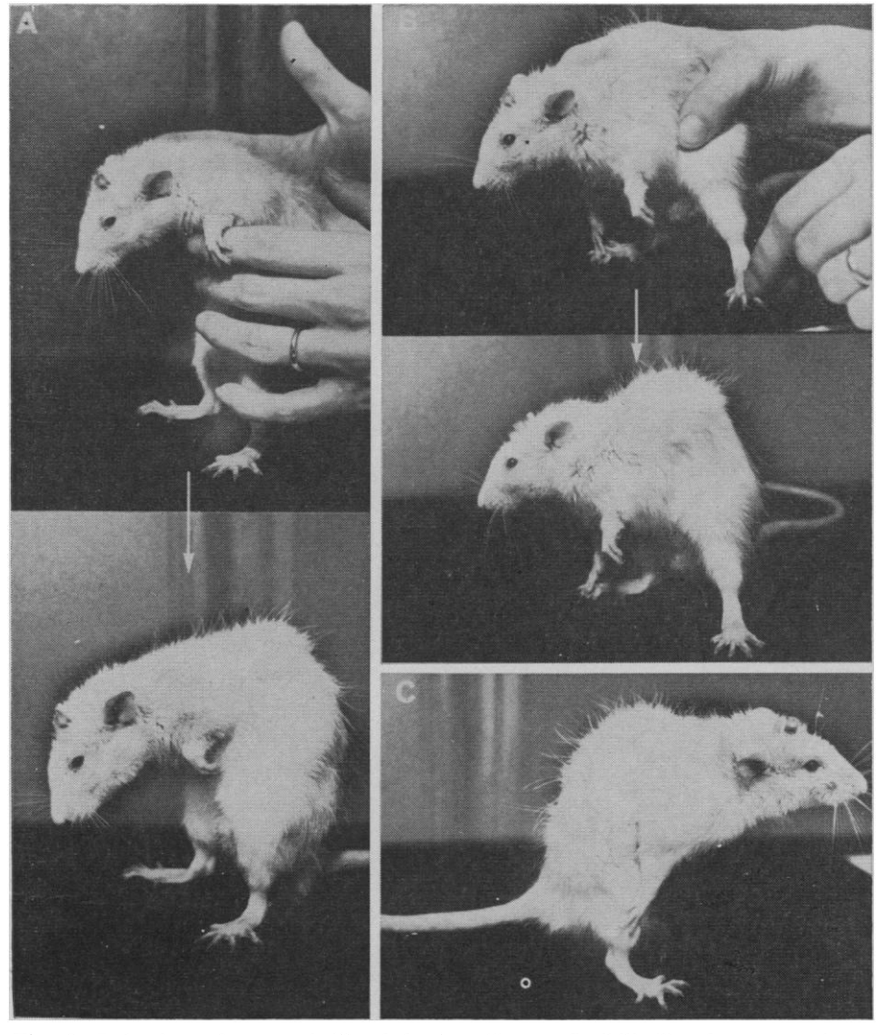

Fig. 2. Induction of catatonic-like behavior ("waxy flexibility") after seven intraventricular injections of 6-hydroxydopamine (400 μg) and a single intraperitoneal injection of pargyline (100 mg/kg). In the upper portions of parts A and B, the animal was molded in the indicated postures, which were retained for at least several minutes.

ment is long-lasting, it probably is caused at least in part by a selective destruction of the noradrenergic binding sites and, eventually, of the terminals of the medial forebrain bundle. It thus seems reasonable to assume that, if 6-hydroxydopamine were formed endogenously in sufficient amounts in the immediate vicinity of noradrenergic nerve endings, it would cause progressive and at least partially irreversible damage to the reward mechanism. As noted, such damage could produce the primary symptoms of schizophrenia.

The isolation and identification of a specific odorous substance [*trans*-3-methyl-2-hexenoic acid (*25*)] in the sweat of schizophrenics provides a second thread of evidence that links 6-hydroxydopamine to schizophrenia. H. Smith of Wyeth Laboratories has suggested hypothetical pathways for the formation of this substance by known biochemical reactions from 6-hydroxydopamine or 2-hydroxydopamine (Fig. 3).

A third line of evidence is suggested by recent studies of Shulgin and his associates (*3*) on mescaline-like psychotomimetics. This work reveals that phenethylamine derivatives with the same 2,4,5-substitution pattern as 6-hydroxydopamine have consistently high hallucinogenic activity in man. Indeed, Shulgin *et al.* postulate that 6-hydroxydopamine may be an intermediate metabolite in the formation of a possible endogenous psychotogen, 2-hydroxy-4,5-dimethoxyphenethanolamine. Although it is not inconceivable that metabolites of 6-hydroxydopamine are hallucinogenic and therefore may contribute to the accessory symptomatology, our theory emphasizes the role of 6-hydroxydopamine itself as the agent that causes the fundamental symptoms of schizophrenia (*26*).

The fourth line of biochemical evidence derives from the observation that chlorpromazine, the drug of choice in the treatment of schizophrenia (*27*), antagonizes the norepinephrine-depleting action of 6-hydroxydopamine (*28*). Chlorpromazine is an inhibitor of the neural norepinephrine uptake process [see (*29*)]; hence, it has been assumed that chlorpromazine prevents the depletion of peripheral norepinephrine by limiting the access of 6-hydroxydopamine to the noradrenergic nerve terminal (*28*). The drug may exert its central antipsychotic effect by the same mechanism. According to this idea, chlorpromazine protects the reward system of the schizophrenic by blocking the uptake of endogenously formed 6-hydroxydopamine into the noradrenergic nerve ending. Hence, although formation of 6-hydroxydopamine may continue in the chlorpromazine-treated schizophrenic, the toxic substance no longer would have entry to the vulnerable site.

As a first test of this idea, we attempted to protect self-stimulating rats from the toxic action of 6-hydroxydopamine by prior treatment with chlorpromazine. One week before the start of a 6-hydroxydopamine test series, four rats received daily intraperitoneal injections of chlorpromazine hydrochloride (3 mg/kg) immediately after the self-stimulation test. Three controls were given injections of saline solution. During the next 7 days, 6-hydroxydopamine (25 μg) was administered intraventricularly to all rats 1 hour after injection of chlorpromazine or saline solution. Injections and self-stimulation tests were discontinued for a 5-day interval and were then reinstated during a second 3-day test period. Self-stimulation rates in the chlorpromazine group were not significantly reduced in either test period, whereas the rates of unprotected control animals declined progressively with successive doses of 6-hydroxydopamine (Fig. 4). We assume that the behavioral deficit in the unprotected group is due to depletion of brain norepinephrine after administra-

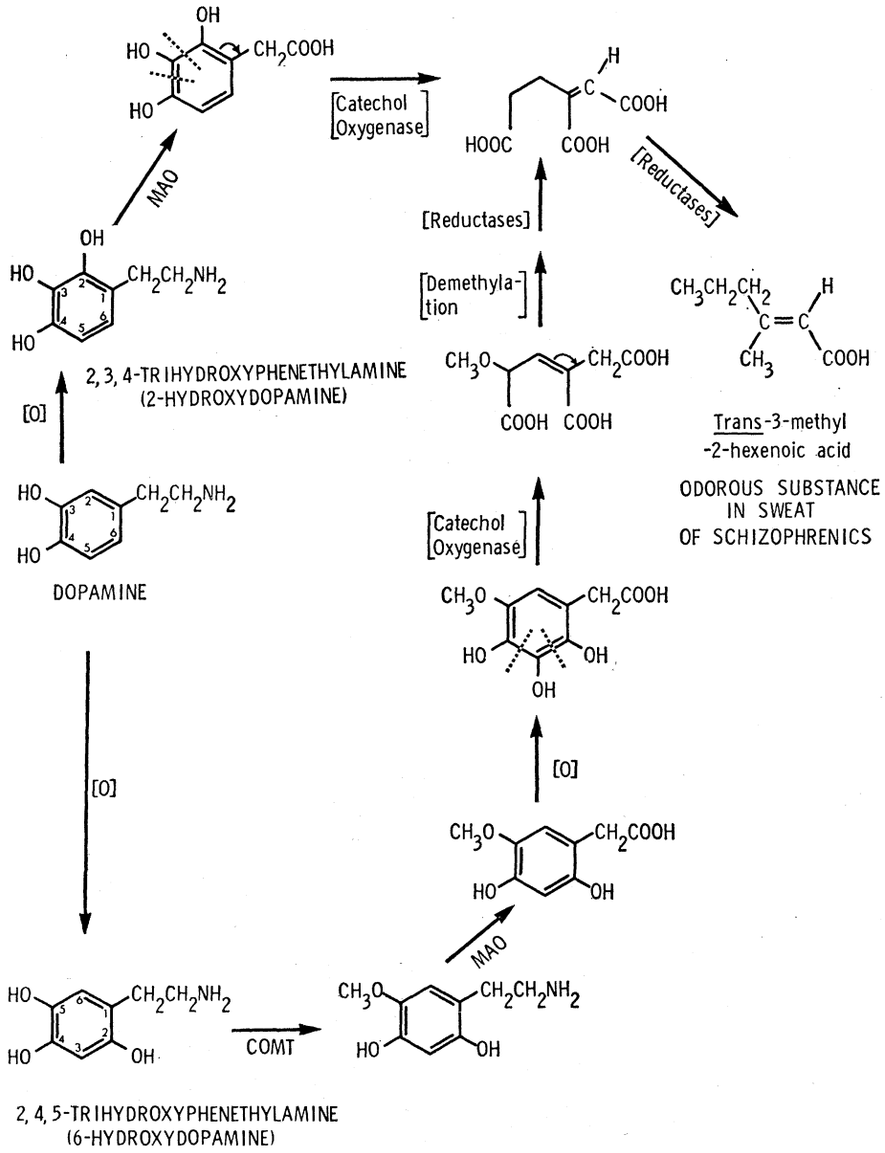

Fig. 3. Hypothetical pathways for the formation of *trans*-3-methyl-2-hexenoic acid from either 6- or 2-hydroxydopamine. The postulated steps involving reductases are unlikely to occur in man but may be mediated by bacteria in the skin. *MAO*, monoamine oxidase; *COMT*, catechol-*O*-methyl transferase.

tion of 6-hydroxydopamine and that the absence of a deficit in the chlorpromazine group is evidence that norepinephrine levels remained substantially unchanged. These conclusions are supported by biochemical experiments, which demonstrate that chlorpromazine largely prevents the depletion of brain norepinephrine by 6-hydroxydopamine (Table 3).

The present hypothesis of the mode of action of chlorpromazine may explain why the antipsychotic effect of the drug usually takes weeks to develop and why its abrupt withdrawal usually does not cause immediate deterioration (*30*). In animal studies, after electrolytic lesions of the medial forebrain bundle (*12*) or after chemical damage by 6-hydroxydopamine (Fig. 1 and Table 2), recovery of feeding and goal-directed behavior takes place gradually over days or weeks. By analogy, recovery of normal behavior in schizophrenic patients may take weeks to develop after the toxic action of endogenous 6-hydroxydopamine has been blocked by chlorpromazine; in this regard, it is of interest to note that several days may be required for the synthesis and transport down into the terminals of new noradrenergic vesicles (*31*). Furthermore, after chlorpromazine is discontinued, deterioration should become manifest only gradually as the 6-hydroxydopamine regains entry to the noradrenergic storage sites. Finally, the hypothesis explains why chlorpromazine has reduced efficacy in "burnt-out" schizophrenics (*30*), if it is correct to assume that in these cases the noradrenergic reward terminals have suffered irreversible damage.

Taken together, the foregoing lines of evidence provide reasonable support for the theory that chemical damage to the noradrenergic reward system by endogenous 6-hydroxydopamine causes schizophrenia. If this hypothesis is correct, it would be logical to ask (i) how 6-hydroxydopamine gains access to the noradrenergic nerve endings of the reward system, and (ii) why toxic quantities of the substance are formed only in the schizophrenic and not in the normal individual.

Although one can only speculate in the absence of data, the answer to the first question may be relatively straightforward: 6-Hydroxydopamine has access to the noradrenergic reward terminal because it is formed from dopamine in the noradrenergic nerve. After its release into the synaptic cleft, dopamine could be converted (by autoxidation or by an enzymatic reaction) to 6-hydroxydopamine, which could then be taken up by the norepinephrine uptake mechanism. In the normal brain, only negligible amounts of 6-hydroxydopamine would be formed in this way. The conversion of dopamine to norepinephrine by dopamine-β-hydroxylase normally is not the rate-limiting step in the synthesis of norepinephrine (*32*); hence, only a negligible amount of dopamine would be stored in noradrenergic binding sites under ordinary physiological conditions. In the schizophrenic brain, however, the step from dopamine to norepinephrine could be rate-limiting if dopamine-β-hydroxylase activity, or the capacity to induce the enzyme under stress, were drastically reduced by a pathological gene. In such a case, dopamine would be released from noradrenergic nerve endings into the synaptic cleft and converted into 6-hydroxydopamine. Continuous uptake of this substance over a long period of time could damage the binding capacity and, eventually, the structural integrity of the noradrenergic terminal (*33*) (Fig. 5).

Needless to say, other enzymatic er-

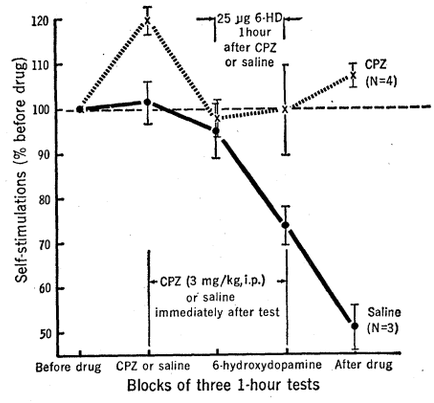

Fig. 4. Prevention by chlorpromazine (*CPZ*) of suppression of self-stimulation induced by 6-hydroxydopamine (*6-HD*). The means of the chlorpromazine and saline groups after drug administration differ significantly at $P = .005$. (*i.p.*, intraperitoneal)

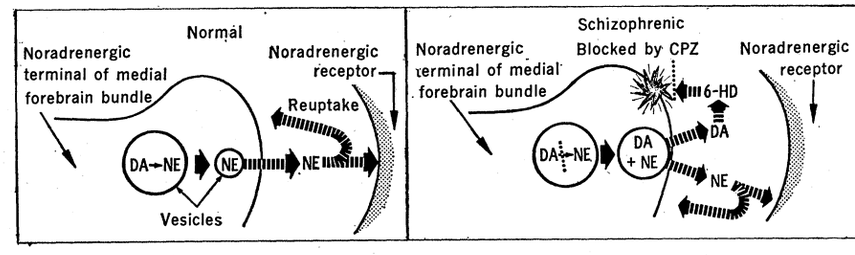

Fig. 5. Postulated etiology of schizophrenia—diagram of noradrenergic transmission in normal and schizophrenic brain based on the assumption that a pathological gene for schizophrenia causes reduced activity, or synthesis, of dopamine-β-hydroxylase (*34*). Normal: Virtually all dopamine (DA) is converted to norepinephrine (NE) by dopamine-β-hydroxylase. Schizophrenic: Dopamine is only partially converted to norepinephrine. After release into synapse, some of the dopamine is autoxidized to 6-hydroxydopamine. When this toxic substance is taken up by the nerve terminals, it gradually destroys the vesicles and eventually the nerve endings.

Table 3. Prevention by chlorpromazine of 6-hydroxydopamine-induced depletion of brain norepinephrine. Chlorpromazine was injected intraperitoneally in two doses (15 and 30 mg/kg, respectively) 24 hours and 1 hour before intraventricular injection of 6-hydroxydopamine (200 μg). Control animals received two injections of saline solution before the injection of 6-hydroxydopamine. Animals were killed 5 days later.

Treatment	Rats (No.)	Mean concentration in diencephalon and forebrain			
		Norepinephrine		Dopamine	
		μg/g	% of control	μg/g	% of control
Control (no drug)	3	0.314 ± 0.024		0.923 ± 0.066	
Chlorpromazine + vehicle	3	0.329 ± 0.013	104	0.938 ± 0.183	101
Chlorpromazine + 6-hydroxydopamine (200 μg)	3	0.251 ± 0.048	80	0.812 ± 0.314	88
Saline + 6-hydroxydopamine (200 μg)	4	0.093 ± 0.007	29	1.550 ± 0.127	168
*Saline + 6-hydroxydopamine (100 μg)	4	0.103 ± 0.001	33	0.982 ± 0.025	106

* Animals received 100 μg of 6-hydroxydopamine and were killed 2 days later.

rors also could lead to the formation of 6-hydroxydopamine in the schizophrenic brain (*34*). Some support for the dopamine-β-hydroxylase assumption is provided by the observation of psychosis in alcoholics after overdoses of the dopamine-β-hydroxylase inhibitor disulfiram. According to Angst (*35*), disulfiram psychosis can be symptomatically indistinguishable from schizophrenia.

A similar process of neural damage by 6-hydroxydopamine also may be operative in endogenous depressions and Parkinson's disease. Manic-depressive psychosis has a close similarity to schizophrenia with many overlapping symptoms (*16*). Recent histochemical studies suggest that central noradrenergic neurons form two important ascending systems: a dorsal pathway, which mainly innervates the cerebral cortex and the hippocampus; and a ventral pathway, which mainly innervates the hypothalamus and the ventral parts of the limbic system (*36*). It is possible that primary damage to the dorsal system leads to thought disorders (schizophrenia), whereas primary damage to the ventral system produces affective disorders (manias and depressions). In any case, the therapeutic use of tricyclic antidepressants in endogenous depression parallels the use of phenothiazine antipsychotics in schizophrenia, and their mechanism of therapeutic action might similarly depend in part on a capacity to block the uptake of 6-hydroxydopamine into noradrenergic terminals (*28*). Moreover, as in the case of phenothiazines, the well-established delay in the onset of the therapeutic action may be explained by the time that would be required to synthesize new vesicles and transport them to active sites (*37*). Finally, in Parkinson's disease, the normal resistance of dopamine neurons to the toxic action of 6-hydroxydopamine may be weakened after viral infection or as a result of a pathological gene.

LARRY STEIN
C. DAVID WISE
Wyeth Laboratories, Inc.,
Philadelphia, Pennsylvania 19101

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33. Early in the process, reward function may be paradoxically augmented by various mechanisms: 6-Hydroxydopamine may displace norepinephrine from its storage sites, it may potentiate the release of norepinephrine by nerve impulses, or it may promote the development of receptor supersensitivity. In this phase, one might see manic and agitated states, euphoria, paranoid delusions of grandeur, and so forth. This phase would not necessarily occur in all cases. However, in all cases, the lesioning process would progressively destroy reward capacity—sometimes intermittently, as the formation of 6-hydroxydopamine waxes and wanes depending on stress and other factors. In the end, goal-directed thinking and behavior would become increasingly impaired and the mood would flatten, resulting in apathy or depression.
34. The theory as a whole obviously does not rest on the validity of the assumption that dopamine-β-hydroxylase is deficient. The theory merely requires that the schizophrenic, by some genetic aberration, either produces excessive 6-hydroxydopamine or is hypersensitive to amounts that normally are produced. Proof of the dopamine-β-hydroxylase assumption would require the demonstration of reduced activity (or reduced induction) of this enzyme in the schizophrenic brain relative to that of other enzymes involved in the metabolism of norepinephine.
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36. K. Fuxe, T. Hökfelt, U. Ungerstedt, *Int. Rev. Neurobiol.* **13**, 93 (1970).
37. These considerations suggest that antipsychotics and antidepressants could be used interchangeably or in combination in schizophrenia and manic-depressive psychosis. In certain types of depression, such combinations (for instance, perphenazine and amitriptyline) have in fact become the treatment of choice. Tricyclic antidepressant drugs are used in schizoaffective and cyclophrenic psychoses and in the depressive hypochondriacal states of chronic paranoid schizophrenic patients [T. A. Ban, *Psychopharmacology* (Williams & Wilkins, Baltimore, 1969)]. In general, however, imipramine-like drugs are not regarded as useful in the treatment of schizophrenia, possibly for the following reasons: (i) by a noradrenergic-facilitating action, imipramine may potentiate the manic or agitated early phases of some schizophrenias [see (*33*)] and (ii) the recommended imipramine dose of 75 to 250 mg per day for depression is well below the effective antipsychotic dose of chlorpromazine of 400 to 1000 mg per day (*27*), although the median effective dose (ED_{50}) for blockade of norepinephrine depletion by 6-hydroxydopamine in mouse heart is 2.8 mg/kg for imipramine versus 1.8 for chlorpromazine (*28*). In this regard, it is interesting to note that the norepinephrine uptake inhibitor cocaine fails to antagonize the norepinephrine-depleting action of 6-hydroxydopamine (*28*).
38. We thank Herchel Smith for suggesting a pathway from a catecholamine to *trans*-3-methyl-2-hexenoic acid. His suggestion of a trihydroxydopamine intermediate helped to stimulate the idea that 6-hydroxydopamine may be the chemical cause of schizophrenia. We also thank R. P. Stein for useful discussions and the preparation of trihydroxydopamines, E. Buckley for editorial assistance, and A. T. Shropshire, N. S. Buonato, W. J. Carmint, H. C. Goldman, H. Morris, J. D. Noblitt, and L. E. Wehren for expert technical assistance.

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