covered with a cloth bag for 20 minutes each evening. A black bag was carefully placed over the topmost lateral branches of each tree. A wire supported the bag above the growing point. Any movement of the trunk was gentle. Without exception, every terminal section that was bagged made less growth than those not bagged. Putting the bag on and immediately removing it gave similar results.

Shoot growth was slowed regardless of whether the plants were shaken at 8:30 a.m. or at 8:30 p.m. P.D.T. (*1*).

More recently, daily shaking of corn, *Zea mays*, plants for 30 seconds resulted in reductions of 50 percent in height growth, 30 percent in leaf number, and 15 percent in leaf length (Fig. 1). However, when the shaken plants were no longer shaken each day, height-growth rate equal to that of the unshaken plants was evident within 3 days. It seems doubtful that cavitation would have been the main cause in growth reduction in these trials.

Leaf-size reduction has been noted in handling leaves during their measurement (*2*, *3*). Gentle stroking of leaves of *Bryonia dioica* resulted in smaller leaves and shorter internodes (*4*). Auxin concentrations in the touched plants were less than in the untouched. Growth rate was restored to normal by adding auxin. In addition, shaking for 30 seconds daily resulted in shorter corn leaves (note above) and *Cucurbita melopepo* petioles (*3*).

Such marked responses from short periods of handling or movement suggest that another factor in addition to those usually ascribed to slowing growth may be involved. A growth-influencing mechanism of a hormonal nature does seem to be indicated. Ethylene has been shown to reduce longitudinal growth accompanied by increased radial expansion in pea epicotyls (*5*). An ethylene-enriched atmosphere (5 to 20 parts per million) around the base of young Monterey pine and *Liquidambar* resulted in increased radial growth of xylem and phloem (*6*).

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6-Hydroxydopamine, Noradrenergic Reward, and Schizophrenia

Stein and Wise (*1*) propose "a novel physiological and chemical etiology for schizophrenia" which involves the endogenous buildup of 6-hydroxydopamine or its metabolites and a resultant deterioration of noradrenergic pathways that mediate reward. Data-related evidence rests principally on their finding that 6-hydroxydopamine hydrobromide impairs lever pressing for rewarding electrical stimulation (self-stimulation) of the brain. Our results do not fully support this finding. Rats were prepared with hypothalamic electrodes and indwelling lateral ventricular cannulas (*2*), were tested for self-stimulation, and were then given two, 200-μg intraventricular injections (72 hours apart) of 6-hydroxydopamine hydrobromide in a vehicle of 0.9 percent saline and 0.1 percent ascorbic acid. Although the temporary decrement in self-stimulation rates observed by Stein and Wise is replicable, priming (experimenter-delivered stimulation not contingent on lever pressing) during sessions on the first day after treatment with 6-hydroxydopamine can bring animals to the rates of self-stimulation prior to treatment. Priming becomes less necessary, then completely unnecessary within less than a week. Our data suggest that permanent impairment of most norepinephrine-containing terminals does not adversely affect significant aspects of the self-stimulation phenomenon, and that temporary behavioral changes are most likely related to depression of an adrenergic arousal mechanism, or to a complex of short-term changes or toxic reactions, or to both, rather than to selective interference with a positive reinforcement system.

To verify that our injections did indeed deplete brain norepinephrine (NE), we assayed for telencephalic NE in two animals (*3*). Telencephalic NE in both animals was found to be depleted 90 percent relative to control values, a greater depletion than Stein and Wise have reported.

It is our contention that Stein and Wise would not have obtained even a temporary decrement in the rate of self-stimulation after 6-hydroxydopamine had they given their animals priming stimulation, and that they are monitoring changes that do not involve any basic shift in responsiveness to reinforcement parameters. Roll (*4*) advanced a similar argument earlier against Wise and Stein (*5*) in experiments in which each utilized disulfiram for NE depletion. Roll found that animals treated with disulfiram became soporific, yet when aroused by the experimenter, their rates of self-stimulation were as high as those prior to the treatment.

In addition, there is no evidence that durable changes occur in an animal's response to natural rewards after 6-hydroxydopamine. Stein and Wise cite a paper by Schoenfeld and Zigmond (*6*) as evidence that deficits occur, yet the behavior of animals in that study returned to normal levels within 3 days, and Schoenfeld and Zigmond make the telling point that a later injection of 6-hydroxydopamine had no further effect on NE amounts, but disrupted behavior to the same extent as earlier doses. We find food and water intake reduced as much as 75 percent after 6-hydroxyopamine, but complete recovery occurs in 2 to 3 days. The copulatory behavior of male rats is unaffected by our 6-hydroxydopamine regime, perhaps because priming is continually present in the form of a moving partner giving multisensory input.

Only one mechanism (receptor supersensitivity due to NE depletion) might enable the NE mediation of reward hypothesis to encompass such data. However, available evidence (*7*) suggests that changes in receptor sensitivity to NE (unlike the rapid sensitization to exogenous NE that follows denervation and is due to interference with NE reuptake by presynaptic terminals) do not occur quickly enough to explain these data. Also, we have given intraventricular injections of 50 and 100 μg of phentolamine, an alpha-adrenergic receptor blocking agent, to animals treated with 6-hydroxydopamine (their self-stimulation rate had

returned to previous levels). This treatment should counteract any effects of receptor supersensitivity and virtually eliminate functional utilization of the small amount of NE remaining in brain tissue. Nevertheless, we see a decrease in the self-stimulation rate of only 10 to 30 percent under these conditions, and even this deficit decreases over repeated tests with phentolamine or, in most animals, is reversed during the initial test if current levels are raised. We feel these and other data (*4, 8*) suggest that neurons directly mediating positive reward are not predominantly noradrenergic, though they may partly depend on and interact with NE-containing neurons that mediate arousal (*8*). In any event, Stein and Wise should not enlist denervation supersensitivity to rescue the NE mediation of reward hypothesis without considering its implications for their etiology of schizophrenia theory. If the mechanism were effective enough to permit rapid recovery of function after NE depletion, it should also protect against the severe and long-term changes which Stein and Wise predict are due to decreased availability of NE.

There are other important procedural and interpretational questions about the Stein and Wise report. To strengthen their hypothesis that 6-hydroxydopamine is involved in the etiology of schizophrenia, Stein and Wise present data and pictures on a single animal displaying "catatonic-like behavior . . . after seven intraventricular injections of 6-hydroxydopamine (400 μg) and a single interperitoneal injection of pargyline." Exception can be taken to this interpretative extrapolation of any one of several grounds. (i) A single, central 500-μg dose of 6-hydroxydopamine can produce effects such as torpor, convulsions, or even death (*9*), so the overall physical condition of their animal becomes an important consideration. (ii) Because pargyline potentiates the depleting effect of 6-hydroxydopamine on brain dopamine without either a depleting or saving effect on brain NE when given in conjunction with 6-hydroxydopamine (*10*), the catatonic-like syndrome more likely involves motor impairment due to an enhanced depletion of dopamine rather than to any effect of pargyline on brain NE (which would be maximally depleted by the 6-hydroxydopamine regime). In humans, akinesia and postural rigidity have been linked to dopamine deficiency in the corpus striatum (*11*). In animals, a similar syndrome consisting of rigidity, a lack of motor activity, and the maintenance of unnatural postures (catalepsy) has long been recognized, and may also be closely related to dopamine depletion (*12*). In any event, it has been strongly questioned whether terms such as catatonic should ever be used to describe such syndromes in animals, because no relationship to the catatonic state of schizophrenia is as yet evident (*12*). (iii) An additional cautionary note is necessary because of the strong hypotensive actions of pargyline. It seems likely that a combination of factors, including toxic reactions to an overdose of 6-hydroxydopamine, hypotension from treatment with pargyline, and maximized depletion of dopamine from the drug combination used, are responsible for the syndrome described, not a further NE depletion as implied by Stein and Wise.

The chlorpromazine and 6-hydroxydopamine data reported by Stein and Wise are both interesting and suggestive, but the tests for self-stimulation were delayed 5 days after treatment with 6-hydroxydopamine until in our hands the major effects of 6-hydroxydopamine on self-stimulation have disappeared. In addition, the pharmacological effects of chlorpromazine are complex and involve changes in a number of biogenic amine systems so that almost any theory can be supported by any outcome. It is surprising, however, that in the data by Stein and Wise [figure 4 in (*1*)], there appears to be evidence for maintenance and even potentiation of self-stimulation rates under chlorpromazine, although data in the literature (*13*), as well as the theory of Stein and Wise, should predict a suppressive effect, because one of the reported actions of chlorpromazine is to block adrenergic receptor sites (*14*).

All things considered, the extrapolation by Stein and Wise that a complex of disorders, such as the schizophrenias, may be related to selective, 6-hydroxydopamine-mediated damage to a noradrenergic (reward) system is as tenuous as it is intriguing, but well worth further investigation. It links to a long history of attempts to relate biogenic amines and their metabolism to mental disorders (*15*), yet data that Stein and Wise have presented thus far would not appear to bear crucially or directly on such a proposition.

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One significant aspect of the hypothesis of Stein and Wise (*1*) should be seen in an historical context. Biological research directed toward those syndromes called schizophrenia has been evolving a certain sophistication over the past quarter of a century. From nonspecific components of blood, to urinary excretion products of the peripheral autonomic nervous system, to possible toxic derivatives of central neurotransmitter substances, the conceptual strategy of investigators in this field has related the biology to increasingly credible neuroanatomical substrata. The current hypothesis of Stein and Wise sug-

gests yet another conceptual advance—the idea that impairment in certain psychotic syndromes might exist in a specific neurochemical system that subserves a basic psychological response potential. Questions such as whether the reward system is the right one, whether genetic vulnerability necessarily means the formation of toxins, and whether the mechanism that Stein and Wise propose is operative in man, remain.

With the dosages of 6-hydroxydopamine they used, Stein and Wise did not find a decrease in brain dopamine in their animals, in contrast to the findings of others (*2*). For instance, Ungerstedt showed that intracerebral injection of 6-hydroxydopamine into the substantia nigra of rats produced "anterograde degeneration of the whole nigrostriatal dopamine neuron system." Burkard and co-workers found that an intraventricular dose of 6-hydroxydopamine in rats lowered brain norepinephrine and dopamine to 74 and 57 percent of control values, respectively. According to Uretsky and Iversen, higher doses of 6-hydroxydopamine given to rats intraventricularly produced depletion of both norepinephrine and dopamine. Breese and Traylor found that preliminary treatment with pargyline enhanced the dopamine-depleting effects of intracisternal 6-hydroxydopamine in rats. Thus, as Bloom and co-workers have pointed out, "the dosage schedule and route of administration are important variables for the selectiveness of 6-hydroxydopamine effects." Therefore, unless fortuitously a selective low-dose effect of 6-hydroxydopamine, which affects only norepinephrine neurons, were operative in the Stein and Wise proposal for schizophrenia, we would expect damage to dopamine-containing neurons as well. In Parkinsonism, a syndrome characterized in part by degeneration of nigrostriatal dopaminergic pathways and decreased brain dopamine, the accumulation of homovanillic acid (HVA), the major dopamine metabolite, is decreased in cerebrospinal fluid (*3*). A similar finding might be expected in schizophrenics if they were autointoxicated by the long-term presence of 6-hydroxydopamine. In studies of central monoamine metabolism in psychiatric and neurological disorders, we measured the levels of HVA in the cerebrospinal fluid of several patient types, including acute schizophrenics (not on psychotropic drugs), after partial blockade of the egress of this metabolite by probenecid (*4*). Compared to a group of inmate controls and a group of depressives, the amount of HVA in the cerebrospinal fluid of schizophrenics was not significantly different (Table 1). However, HVA values for those schizophrenics were significantly higher than those for the Parkinsonians ($P < .001$). These results suggest that the central dopaminergic system in these schizophrenics was not impaired.

Table 1. The amount of homovanillic acid (HVA) in the cerebrospinal fluid of schizophrenics, depressives, inmates, and Parkinsonians after probenecid; S.E.M., standard error of mean.

Subjects		HVA (ng ± S.E.M.)
Type	No.	
Schizophrenics	23	108 ± 9
Inmates	15	92 ± 7
Depressives	11	135 ± 17
Parkinsonians	10	43 ± 8

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Stein and Wise (*1*) make several awkward connections between a promising biochemical finding and the problem of schizophrenia. Because the concept of schizophrenia is so complex, and because this term is used in such diverse ways, it is not possible to consider schizophrenia without specifying one of the commonly accepted operational definitions. Stein and Wise use only a part of E. Bleuler's (*2*) concept of schizophrenia, incompletely quoting him as saying, "The fundamental symptoms consist of disturbances of association and affectivity." In fact, Bleuler gives four, not two, fundamental symptoms of schizophrenia in that sentence. The other two symptoms are "the predilection for fantasy as against reality, and the inclination to divorce oneself from reality (autism)" (*2*, p. 14). Stein and Wise mentioned Rado's view that pleasure resources are inherently deficient in schizophrenia. This concept, which was elaborated by Meehl (*3*) and termed anhedonia, appears to be most germane to the hypothesis of Stein and Wise. As their second criterion of schizophrenia, the authors quote M. Bleuler's 1911 monograph regarding the course of this disorder "which can stop or retrograde at any stage, but does not permit a full *restitutio ad integrum*." They omit entirely any reference to the generally accepted work of Bleuler, Stephens, and others performed since 1911, which established the favorable outcome and complete remission in a considerable percentage of schizophrenic patients (*4*). Stein and Wise propose a biochemical explanation for "the fundamental symptoms of schizophrenia and its long-term downhill course." In relating their findings to schizophrenia they might better have limited themselves to trying to explain some of the characteristics of that disorder, such as anhedonia, rather than to explain the entire disorder, which includes other characteristics their findings do not explain.

Stein and Wise use unaccepted theories about schizophrenia to support their point. For example, they state that "schizophrenia is inherited" and that the importance of the genetic factor is established. What, in fact, is established is the presence of a genetic factor, but not the importance of it. There is no evidence that schizophrenia per se is inherited, and it appears more reasonable from the work of Rosenthal, Kringlen, Kety, and others to hypothesize that genetic endowment contributes to vulnerability to schizophrenia rather than fully accounting for the disorder (*5*). Genetic findings certainly establish the plausibility of some kind of biochemical mechanisms in schizophrenia, but Stein and Wise are not entirely justified in claiming that "genetic studies provide indirect support for the idea that an impairment of nonadrenergic function may be involved in schizophrenia."

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29 March 1971

In view of the controversy that surrounds schizophrenia, it is not surprising that the initial, necessarily brief, description of our neurochemical model of the disease (*1*) has raised questions in the minds of some readers. Although the model is speculative, we chose to publish it for two reasons. First, we felt that it provided a consistent and reasonably detailed concept of schizophrenia, which is compatible with a considerable body of information obtained from many different fields. Second, because the model is testable, it may open up fruitful new approaches for research on the disease. For this reason, the results of experiments, and not debate, will determine whether the model is generally correct and capable of modification without losing its parsimonious qualities, or whether it is wrong and must be scrapped. Nevertheless, we reply here to the foregoing commentaries in the hope of clarifying our hypothesis and maintaining its credibility as a plan for research.

Fisher and his colleagues (*2*) find most disturbing the observation that 6-hydroxydopamine induces a relatively permanent depletion of brain norepinephrine (NE) but often only temporary deficits in hypothalamic self-stimulation and other behaviors. Recognizing that function often is recovered after permanent brain damage, these investigators conclude, "Only one mechanism (receptor supersensitivity due to NE depletion) might enable the NE mediation of reward hypothesis to encompass such data." Direct evidence of supersensitivity to NE after 6-hydroxydopamine in the self-stimulation test is shown in Fig. 1; similar evidence has been reported by Mandell and co-workers (*3*) in tests of exploratory behavior. The increased responsivity to NE in our tests cannot be attributed to an artifact of the intraventricular injection procedure, since control rats injected with the ascorbate vehicle exhibited unchanged or slightly diminished responses to repeated doses of NE. Neurohormonal specificity is suggested since self-stimulation was not facilitated by *d*-norepinephrine or dopamine. Although a full account of these experiments is not possible here, the data leave little room for doubt that supersensitivity to NE is an important factor in the recovery of self-stimulation after 6-hydroxydopamine treatment.

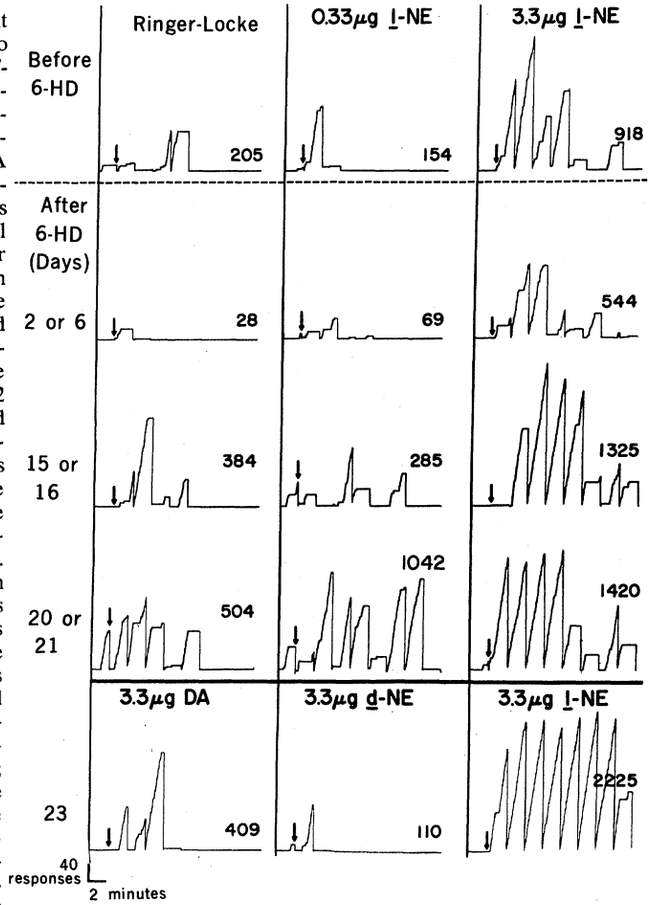

Fig. 1. Development of supersensitivity to *l*-norepinephrine (*l*-NE) in a representative rat after 6-hydroxydopamine (6-HD) treatment. A 100-μg dose of 6-hydroxydopamine was injected in the lateral ventricle 2 hours after the self-stimulation test for two successive days. Each record represents an 18-minute test and shows the response output 2 minutes before and 16 minutes after intraventricular injections of *l*-NE, Ringer-Locke solution, dopamine (DA), or *d*-norepinephrine (*d*-NE). Ringer-Locke solution and the 0.33-μg doses of *l*-NE were always injected on the same day; the 3.3-μg doses of *l*-NE were injected 1 or 4 days later. Self-stimulations are cumulated over time; the slope of the curve is proportional to the response rate. Pen resets automatically every 2 minutes. Numbers give total number of self-stimulations in the 16-minute periods after injections (indicated by arrows). Note especially dose-related facilitation of self-stimulation by *l*-NE before 6-hydroxydopamine decreased responsivity to *l*-NE 2 or 6 days after 6-hydroxydopamine, increased responsivity in the Ringer-Locke test and supersensitivity to *l*-NE 20 or 21 days after 6-hydroxydropamine, and selective effect of *l*-NE 23 days after 6-hydroxydopamine. Prior to 6-hydroxydopamine treatment, the rate of self-stimulation was stabilized at a low level by reduction of current intensity. [From unpublished experiments performed with B. D. Berger]

Pursuing this point, Fisher's group advises, "In any event, Stein and Wise should not enlist denervation supersensitivity to rescue the NE . . . reward hypothesis" because the supersensitivity mechanism "should also protect against the severe and long-term changes [in schizophrenia] which Stein and Wise predict are due to decreased availability of NE." This admonition is puzzling and misleading. In the first place, we suggest explicitly that supersensitivity to NE probably develops in the earliest stages of schizophrenia and may account for the otherwise paradoxical observations of euphoria, manic and agitated states, delusions of grandeur, and so on [reference 33 in (*1*)]. Furthermore, the same mechanism is implicitly invoked in our use of a recovery of function model to explain the antipsychotic action of chlorpromazine. In any case, our critics confuse these instances of (apparent) behavioral recovery after administration of 6-hydroxydopamine has ceased with our proposed etiology of schizophrenia. According to the model, "episodic or continuous formation of endogenous 6-hydroxydopamine" occurs throughout the course of the disease. In early stages, the deficits in reward function often are largely reversible; hence, in our view, remissions are observed if the formation of 6-hydroxydopamine spontaneously ceases for an extended period, or after

the chronic administration of chlorpromazine has blocked the uptake or production (*4*) of the endogenous toxin. In advanced stages, complete recovery of normal behavior is quite rare, presumably because repeated exposure to 6-hydroxydopamine eventually causes irreversible damage to the reward mechanism. On this point it may be noted that residual deficits probably are much harder to detect in animals than in man; hence, sensitive and demanding tests should be used to measure permanent deterioration in the adaptive behavior of animals after 6-hydroxydopamine.

Our results with 6-hydroxydopamine differ in other important ways from those reported by Fisher's laboratory (*2*). For example, in their experiments the deficits in self-stimulation directly induced by 6-hydroxydopamine seem to be much smaller and shorter in duration than the deficits obtained in our experiments (*1*) or those of Breese and co-workers (*5*). The discrepancy probably is due to differences in methods, but we cannot be sure since certain details of their procedure are not given. For example, we find that the suppressive action of 6-hydroxydopamine is decreased if injections of the drug closely precede or follow self-stimulation tests. Although direct evidence is not yet available, it seems likely that the strong activation of noradrenergic fibers and the release of NE induced by self-stimulation (*6*) interferes with the uptake and retention of the toxic substance. Furthermore, since nerve fibers in the field of stimulation would be selectively protected by self-stimulation, total amounts of brain NE could be greatly reduced with little effect on the neurons that are directly involved in the self-stimulation test. Finally, with regard to the effects of priming, we and others (*7*) find that such "free" reinforcements facilitate self-stimulation even if response rates have been lowered by reduction of current intensity—a manipulation that clearly affects the rewarding value of the stimulation. Hence, Fisher's demonstration that priming facilitates self-stimulation in animals treated with 6-hydroxydopamine is not inconsistent with the idea that the drug suppresses self-stimulation by an action on the NE reward mechanism.

Other points raised by Fisher require only brief reply. We are reproved for the use of "terms such as catatonic," although we in fact used the more neutral term "catatonic-like"; and nowhere did we imply that the catatonic-like state induced by 6-hydroxydopamine and pargyline was caused by NE depletion. The comments on the chlorpromazine-protection experiment suggest misunderstanding of the experimental design. As we described in the text, chlorpromazine- or saline-pretreated rats received seven daily injections of 6-hydroxydopamine in a first series of tests, and then, after a rest period of 5 days, three more daily injections in a second test series. The protective effect of chlorpromazine was obtained throughout the course of 6-hydroxydopamine administration in both series of tests, and not, as Fisher suggests, only after the 5-day rest period. In any event, our results could hardly be explained by dissipation of the effects of 6-hydroxydopamine, since the performance of the chlorpromazine-treated rats was evaluated against that of the saline-treated controls, which received the same number and sequence of 6-hydroxydopamine injections. Finally, the erroneous suggestion that our findings conflict with data in the literature with regard to the direct action of chlorpromazine on self-stimulation apparently arises from a failure on Fisher's part to distinguish between the short-term and 24-hour delayed effects of the drug.

Bowers and Van Woert (*8*) incorrectly interpret our model to predict damage to dopamine-containing neurons in the brains of schizophrenic patients. Indeed, the observation that schizophrenics ordinarily do not exhibit Parkinsonism influenced our thinking from the start. Together with other considerations, this fact led us to the idea that 6-hydroxydopamine may have selective "access to the noradrenergic reward terminal because it is formed from dopamine in the noradrenergic nerve." Also interesting in this regard is the occurrence of Parkinson-like symptoms in schizophrenics after overdoses of chlorpromazine and related antipsychotic drugs. Although direct blockade of dopamine receptors must be involved here, it is also intriguing to speculate that dopamine terminals may be damaged by 6-hydroxydopamine if the uptake of the endogenous toxin into NE terminals is blocked by chloropromazine.

Strauss and Carpenter (*9*) fail to recognize that "the predilection for fantasy as against reality" and "the inclination to divorce oneself from reality" represent one and the same symptom (autism). This error leads them to assert mistakenly that "Bleuler gives four, not two, fundamental symptoms of schizophrenia in that sentence," whereas actually the quotation contains only three. According to Bleuler (*10*) and Meehl (*11*), the fourth fundamental symptom, ambivalence, like autism, may be derived from disturbances in the "elementary" or "simple" functions of association and affectivity. Hence, we felt it would be consistent with Bleuler's concept of schizophrenia to focus attention on these functions. Strauss and Carpenter also take us to task for assuming with Kraepelin and E. Bleuler that schizophrenia is a chronic and progressive disease, and for omitting reference to the more recent views of M. Bleuler and others. No doubt there are instances of favorable outcome and complete remission in schizophrenia as there are in cancer, but in neither case do these exceptions invalidate the general view that both diseases are progressive.

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