Research With Psychedelics

Some Biopsychological Concepts and Possible Clinical Applications

Julian Silverman, PhD, San Jose, Calif

Recent studies of the sensory effects of psychedelic drugs indicate drug-induced sensitivity to minimal and ordinary stimulation. This kind of laboratory observation accords with subjective reports that psychedelic-drugged subjects' sensory experiences are intensified and that they are aware of qualities of sensory experience which they never were before. Paradoxically, these individuals also evidence an increased tolerance for strong stimulation. The paradox is explained by an experimentally derived model of differential excitation which indicates how psychedelic drugs act differently on parts of the brain. The literature on various aspects of laboratory and clinical research with psychedelic drugs is reviewed on the basis of this formulation.

THIS PAPER is concerned with an evaluation of the effects of psychedelic drugs on sensory functioning. Two neurophysiological constructs, excitation-inhibition balance and stimulus intensity control, are utilized both to explain the paradoxical sensory effects of psychedelic drugs and to make them relevant to certain important psychiatric problems.

Drugs that act on the brain appear to do so through biochemicals involved in the transmission of electrical impulses from one part of the brain to another. Changes in the levels of two neurohumors, nonadrenaline, and serotonin, have been shown by Freedman[1] to be closely linked to lysergic acid diethylamide (LSD) ingestion. It has been suggested that LSD first acts at certain receptor sites where serotonin is concentrated, causing norepinephrine to be released or utilized. Subsequent shifts in the dynamic equilibrium and locations of serotonin are directly attributable to the influence of LSD.[2] Marazzi and Hart[3] have demonstrated that intracarotid injection of serotonin in cats, in doses as small as 1μg to 2μg, produced synaptic inhibition (reduced electrical activity) in the visual cortex. The fact that this highly potent substance occurs naturally in the brain suggests that it is part of a neurochemical synaptic inhibitory mechanism. LSD and mescaline also were found to produce synaptic inhibition in the visual cortex. A more complex electrophysiological effect was reported by Purpura[4] who worked with LSD-drugged cats. Consistent with the findings of other investigators, he observed decreased electrical activity, inhibition, from the primary sensory cortex to the association cortex and also in the nonspecific sensory system. Conversely, increases in electrical activity, excitation, were observed in discrete sensory pathways leading to the primary sensory cortex. The substantive evaluation of the effect had to wait for other facts and methods to become available. Thus, Evarts[5] reported results with differently prepared animals which, at first glance, were not totally consistent with Purpura's. Actually, Evarts' studies, some carried out with extraordinary large LSD dosages, also indicated a differential inhibitory effect of LSD. Further, a large number of experiments were not yet available to throw light on the effect. It appears now that Purpura's effect provides a parsimonious base for ordering the vast literature on behavorial and experiential effects of psychedelic drugs. Purpura anticipated this possibility as follows: "Without an adequate knowledge of the organization of excitatory and inhibitory components operating in any given evoked (electrical) response, further efforts to clarify the mode of action of pharmacological agents will of necessity remain basically unsatisfactory."[6(p375)]

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From the Department of Mental Hygiene, Agnews State Hospital, San Jose, Calif, and the Esalen Institute, Big Sur, Calif.

Reprint requests to Department of Mental Hygiene, Agnews State Hospital, San Jose, Calif 95114.

Excitation-Inhibition Balance

The behavorial significance of the neurophysiological effect is a straightforward one: There is a relationship between LSD-induced excitation in the specific projection pathways mediating incoming sensory signals and hypersensitivity to low-to-moderate intensity stimulation. There is a concomitant relationship between LSD-induced inhibition in the nonspecific sensory system and corticocortical association pathways and increased tolerance of high intensity stimulation (pain). This paradoxical association of hypersensitivity and hyposensitivity suggests a complex mechanism for effecting differential adjustment to low and high intensity sensory stimulation (Fig 1). Such differential responsiveness depends upon the actual intensity of stimulation at the receptor sites and also upon the complex pattern of excitation-inhibition in the nervous system—the momentary adapted state of the organism. Further:

> The inhibition by LSD of dendritic activity, synaptically induced via association and nonspecific mesodiencephalic pathways terminating on cortical dendrites, may in part explain the disorganization of behavioral activity described in man under the influence of this psychotogenic agent. This would support the hypothesis that much of the highly integrative process involving complex neuronal interrelations is carried on at the neuropil-like axodendritic level.[4(p140)]

(Incidentally, nowhere in this paper are assumptoms made regarding the character of events occurring at single synapses; conceivably these events could even turn out to be solely inhibitory events occurring at every synapse at which LSD and other psychedelic drugs act. Rather, the excitation-inhibition formulation is offered specifically as an interpretation of

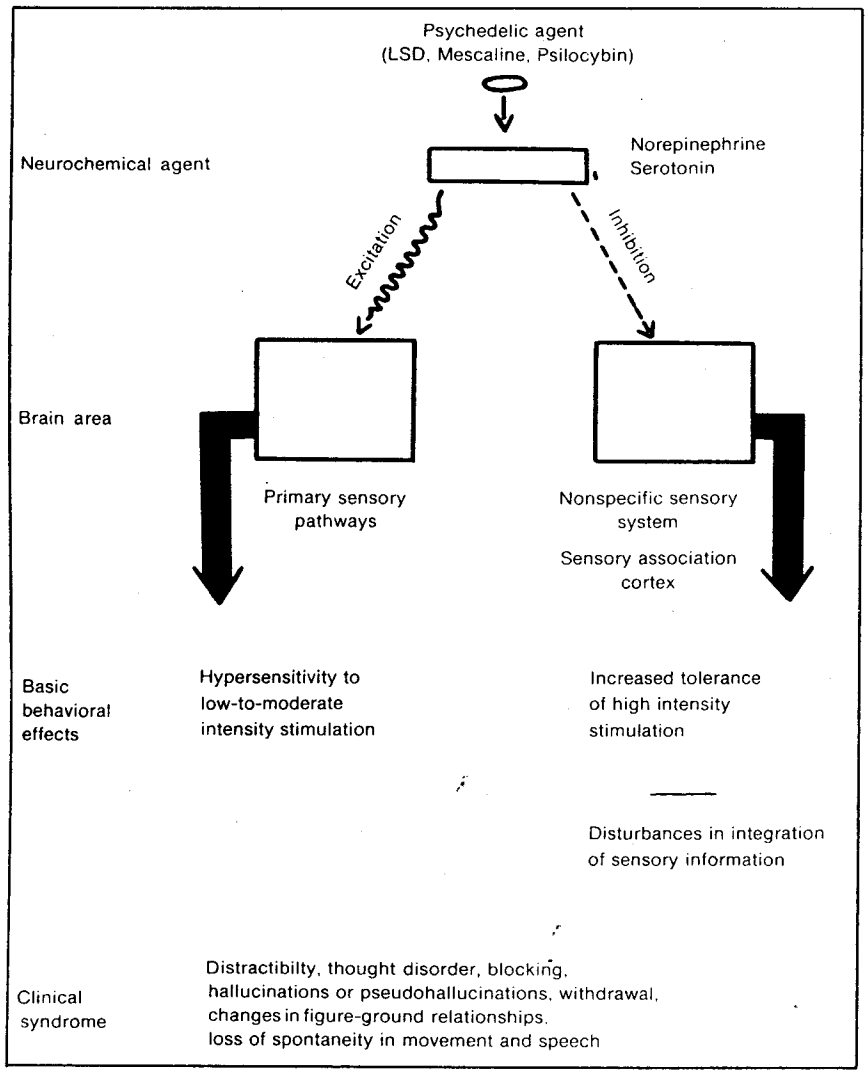

Fig 1.—*Model of psychobiological effects of psychedelic drugs.*

relationships between the complex events occurring in different locations of the brain [referred to earlier] and different characteristics of sensory and perceptual functioning.)

Hypersensitivity and Excitation in Discrete Sensory Pathways.—Ordinarily, performance accuracy on psychological tests is decreased under the effects of psychedelic drugs. This has been observed on tasks ranging from simple sensory discrimination, such as two-point threshold, to more complex perceptual and cognitive judgments, such as the rod-and-frame test and standard intelligence tests. On measures of absolute sensory threshold and on certain other measures from which sensitivity to minimal intensity stimulation can be inferred, the story is quite different. Thus, within the past several years, a number of researchers have reported psychedelic-drug-induced *hyper*sensitivity in humans. Using psilocybin (10 to 15 mg), Fischer and Kaelbling[7] found increased taste sensitivity in normal volunteers. Henkin and our group at the NIMH,[8] using 50μg LSD dosages, recorded lower thresholds to auditory stimuli. Our subjects, experienced users of psychedelic drugs, actually evidenced lower than normal auditory thresholds on admission to the experimental unit. Hill et al,[9] using psilocybin (160μg to 200μg per kilogram) reported that 12 to 15 subjects changed their brightness preferences to less bright at the peak of the drug experience. Four and one-half hours later brightness preferences returned to predrug levels. Delay et al[10] found a similar hyperaesthesia effect of psilocybin in eight of nine subjects. Caldwell and Domino[11] cited an unpublished study by Alpern indicating increased sensitivity to minimal differences between colors induced by LSD. Landis and Clausen[12] compared subjects' critical flicker fusion thresholds (CFF) under normal and LSD-drugged conditions. The frequency at which the flickering light increased, and finally appeared steady, was higher during the LSD-drugged state. In a much earlier report, Maloney (cited by Kluver[13]) observed that "nearly blind" tabetics increased visual acuity markedly following injections of mescaline. Indications of hypersensitivity to low-to-moderate intensity stimulation also are found in studies of animals. In a series of experiments by Bradley and his collaborators[14] LSD-drugged animals were found to have decreased thresholds for auditory and visual stimuli. In accord with these findings the increased response generalization to stimulation by LSD-drugged ani-

mals was interpreted as indicating distractibility and hyperreactivity to low-to-moderate intensity stimulation rather than insensitivity to differences between stimuli. Other animals' studies indicating hypersensitivity have been summarized by Key.[15] Studies of the effects of dosage levels of psychedelics on sensitivity have suggested that at high dosages animals may either fail to respond at all to the laboratory task (eg, Evarts[5]) or may be so disoriented by the drug that performance accuracy declines. Becker et al,[16] using a critical flicker frequency procedure with pigeons, found increased flicker frequency when the LSD dosage was 20μg/kg of body weight. At 80μg/kg dose levels, however, a decrement in CFF discrimination was observed. Incidentally, it appears that disruptive effects of psychedelic drugs are observed on visual performance tasks at lower dosage levels than on performance tasks employing other kinds of stimuli such as auditory or olfactory stimuli.[11] The apparent predilection of these drugs for the visual system is indicated by the results of a number of experiments. Snyder and Reivich[17] using monkeys found LSD to be highly concentrated, not in cortical centers, but in subcortical visual centers which have been implicated in the production of visual hallucinations. Apter and Pfeiffer,[18] using cats infused with 100μg LSD dosages, observed spontaneous action potentials in the electroretinogram, even under conditions of constant illumination. Spontaneous action potentials, "higher and sharper," also appeared over the visual cortex. Kluver's[13] work has suggested that the visual effects of mescaline, in many ways similar to those of LSD, are in part hypersensitized responses to the various structures within the eye. These studies would tend to explain the one published inconsistent finding in this area by Carlson[19(p350)] of an LSD-induced elevation of absolute visual threshold in man. Apparently, at absolute visual threshold, spontaneously occurring visual stimulation in the optical system interferes with detection of external minimal intensity visual signals.

Hyposensitivity and Integration Disturbances Associated With Electrophysiologic Inhibition.—Relevant to inhibition in the diffuse sensory system and from primary sensory cortex to association areas of the brain are two types of findings. One involves reduced responsiveness to intense sensory stimulation. The other involves disturbances of integration of sensory and perceptual *information* into organized or meaningful configurations. In regard to the former, a study of LSD-drugged male volunteers by Rodin and Luby[20] indicated reduction (inhibition) of the visual evoked response amplitudes to light flashes occurring at the rate of 3/second. No such effect was observed when the stimulus flash rate was 1/second. The LSD dosage was 1μg/kg of body weight. This finding is in accord with one by MacKavey[21] which indicated a relationship between flash rate and stimulus intensity. Caldwell and Domino[11] found longer response latencies in albino rats at higher stimulus intensities than at lower stimulus intensities under the effects of high LSD dosages (200μg and 400μg per kilogram). (Conditioned response to light was more affected than conditioned response to sound.) Henkin et al[8] reported increased tolerance for strong auditory stimulation following a 50μg dosage of LSD in eight experienced drug-users. Their tolerances also were significantly greater than those of normal nondrugged subjects. Kast and Collins[22] and Kast[23,24] reported increased tolerances for pain following 100μg dosages in 128 gravely ill medical patients. The action of LSD was observed to be more effective in comparison with two other well-known analgesic drugs, meperidine (Demerol) and hydromorphone (Dilaudid). Evarts[5] reported an interesting syndrome in monkeys following intravenously administered dosages of LSD up to 1 mg/kg. Whereas righting reflexes, vestibular eye movements, responsiveness to auditory stimuli, and, later, motor coordination, did not appear to be grossly impaired, there was abolition of response to painful stimuli (and to visual stimuli). As the syndrome receded, ataxia became slight and finally disappeared, while absence of responsiveness to painful and visual stimuli were among the last symptoms to disappear.

Thus, two kinds of research findings exist in the psychedelic drug literature. One indicates *hyper*sensitivity to low intensity stimulation; the other indicates *hypo*sensitivity to strong stimulation. Taken together these reports suggest the following mechanism for this paradoxical effect: LSD and other psychedelic drugs induce a state of hypersensitivity to stimulation by causing marked excitation in the primary sensory pathways of the brain. Neural inhibition in the diffuse sensory system and in corticocortical association pathways occurs as a compensatory adjustment to overexcitation in the primary pathways. In teleological terms, the inhibition is an automatic "attempt" by the sensory control apparatus of the nervous system to reduce the intensity of overloading stimulation. It is interesting to note that when LSD-drugged individuals are placed in so-called sensory deprivation situations, the degree of aberrant behavior and experience is less than in an ordinary environment.[25,26] This effect probably occurs because exaggerated sensory-input reduction responses in the nervous system are elicited to a lesser extent. In a normal sensory environment, exaggerated "reduction re-

sponsiveness" to overstimulation has disruptive effects on perceptual and cognitive functioning. (Extensive discussions of reduction responsiveness have been elaborated elsewhere.[27-29] A further consideration of its significance is presented in a later section of this paper.)

Hypersensitivity to stimulation and compensatory reduction responsiveness, which interferes with the integration of sensory stimuli, are also associated with performance deficiencies on a variety of phychological tasks. Numerous studies ranging from psychomotor functioning (eg, discrimination reaction time) to perceptual and cognitive differentiation (eg, Stroop Color Word Test, proverb meanings) indicate this to be so. Reviews of these studies have been presented elsewhere.[30] On the basis of all these studies, as well as ones conducted with normal nondrugged subjects and individuals in other altered states of consciousness, the following general principal can be stated: Individuals who evidence hypersensitivity to low-to-moderate intensity stimulation evidence, relative to others, less effective performances on many complex psychological tasks. These are tasks which require suppression of responses to immediately obvious stimulus attributes in favor of responses to other not immediately obvious attributes.[31-33] In effect, the sensory attributes of complex information exert a particularly strong influence on hypersensitive individuals. The term "stimulus bound" has been used to refer to this effect.[34] In psychedelic-drugged individuals the subjective experience of being stimulus bound is one of being "caught" or being "compelled to attend" to irrelevant and otherwise innocuous events. Consistent with such subjective reports, Key[15] has found alterations in cortical auditory evoked potentials in LSD-drugged animals indicative of increased responsiveness to previously irrelevant stimuli. It is especially difficult for a psychedelic-drugged subject to sustain attention on experimenter-designated relevant cues. The subjective consequences of this difficulty range from perplexity all the way to fragmentation of perceptual configurations, depersonalization, and derealization.[34] Other behavioral and experiential effects of psychedelics, such as withdrawal, thought blocking, and loss of spontaneity in movement and speech, may be thought of as psychobiological maneuvers aimed at restoring sensory control. In effect, what takes place in the nervous system during a psychedelic drug state is an increase in data content—increased neural excitation in primary sensory areas—without a corresponding increase in rate of data processing—increased neural inhibition in integrative areas.[35]

Individual Differences in Sensory Nervous System Functioning.—Individual differences in response to sensory stimulation are observable during the first days and months of life.[36-40] They are correlated with individual differences recorded several days later,[41] several months later,[42,43] from several months to a year later,[44,45] and from several months to several years later.[46] Taken together with other studies, they suggest that a rudimentary "style" of responding to stimulation is present at birth and that this style affects the manner in which the child organizes and makes meaningful sensory information. In turn, the way he "makes sense" out of his environment affects the manner in which he masters each developmental phase.[38,45,47-54] This inference is based on studies employing sensory habituation and discrimination techniques, measures of excitability and irritability, ocular photography and electrooculography, perceptual-autonomic indices of attention, and measures of cognitive organization.[32]

A relationship between degree of responsiveness to sensory stimulation and such cognitive variables as imaginativeness and depth of fantasy life is suggested by the results of a number of studies. Escalona and Heider[46] reported data on the relationship between overall sensory threshold level in a group of infants 1 to 8 months old and the degree of imagination which they manifested several years later. The play activities of children who as infants had higher sensory thresholds were found to center around concrete, nonimaginary play things. In no case did a child who was a high sensory threshold infant demonstrate a high degree of imaginativeness. In contrast, more than two-thirds of the children who as infants evidenced low sensory thresholds manifested obvious concern with imaginary play things, companions, and fantasy situations. Other studies have indicated that normal (nondrugged) adults, who differ in response to sensory stimulation and depth of fantasy life, also evidence different psychological adjustments.[55-58] Further, they tend to respond to psychedelic drugs in different ways.

Fischer and his colleagues[59,60] reported that taste-hypersensitive and also more perceptually variable subjects, under nondrugged conditions, evidenced the greatest range of behavioral and subjective changes following ingestion of psilocybin (160μg to 200μg per kilogram of body weight). Comparable findings were obtained by our NIMH research team using 50μg LSD dosages.[61] These findings are consistent with others which indicate that hypersensitive non-drug-users tend to evidence a number of personality traits which are used to describe psychedelic-drugged subjects. Thus, hypersensitive subjects are found to evidence greater receptivity to influence or suggestion, lesser suppression

of excitement, and lesser perceptual rigidity.[55,56] Studies of other personality variables accord with the above reports. Greater sensitivity to low intensity stimulation is reported in introverted than in extroverted individuals,[58,59] in leptosomatics more than in pyknics, and in schizothymics more than in cyclothymics.[62-64] Consistently, profound psychedelic drug reactions are reported among introverted subjects more than among extroverted subjects, among individuals with leptosome body types more than among individuals with pyknic body types, and among schizothymic-type individuals more than among cyclothymic-type individuals.[59,65,66] Still other investigations have suggested that greater changes in sensitivity and changes in sensory evoked responses under the effects of psychedelics are associated with more profound drug experiences.[9,59,67] Indeed, in the Fischer et al[59] study, subjects who evidenced the least subjective changes and drug-induced psychopathological disturbance evidenced sensory-perceptual responses which were contradictory to those usually observed. In our NIMH study a tendency also was found for lesser changes in sensitivity under LSD to be associated with fewer subjective and behavioral changes.[61] The unusual reaction to psychedelic drugs is one in which no impressive temporary impairment occurs in perceptual and cognitive functioning. On the basis of all the studies reviewed here, it is suggested that these individual differences in personality, perception, and intensity of psychedelic drug reaction are referrable to differences in the underlying neurophysiological balance of excitation-inhibition. Further research on this neurophysiological balance in various drugged and nondrugged states should contribute substantially to our understanding of differences in normal personality development and function.

Stimulus Intensity Control: Reduction-Augmentation

In the previous section of this paper, the results of a large number of studies of sensory perceptual and cognitive functioning under the effects of psychedelic drugs were interpreted in terms of a "differential excitation" hypothesis; this hypothesis was derived from a consideration of neurophysiological researches by Purpura and others. The section below is concerned with another hypothesis, "stimulus intensity control"; this hypothesis was proposed as an explanation of how different individuals modulate the intensity of sensory inputs. It was derived primarily from the results of perceptual studies by Aseneth Petrie[27] and from perceptual and EEG-average evoked response studies by a number of investigators.[29,68] The two hypotheses are complementary. The former emphasizes a neurophysiological basis for psychedelic drug reactions; the latter suggests a specific way to interpret individual differences in drug reactions and in abnormal sensory-perceptual functioning, in general.

Psychosis and "Model Psychosis."—The basic sensory and perceptual response characteristics of psychedelic drug states are also characteristics of the acute nonparanoid schizophrenic reaction.[29,34] Hypersensitivity is pronounced. Most short-term schizophrenic individuals experiencing these changes report that initially everything around them looks "fascinating, objects standing out vividly in contrast to the background"; "noises all seem to be louder . . . it's as if someone turned up the volume." Fischer et al reported taste hypersensitivities in a subgroup of short-term schizophrenics which "resemble those of healthy volunteers under psilocybin-induced arousal."[69(p215)] Paradoxically hyposensitivity is reported to strong stimulation; a review of the relevant literature indicates that tolerance for high intensity stimulation is greater in schizophrenic subjects than in nonschizophrenics.[28,29] In studies of childhood schizophrenics, Goldfarb[70] reports a remarkable unresponsiveness to painful stimulation associated with hypersensitivity. (It will always be noteworthy when hypersensitivity is demonstrated in any non-reality-oriented subject. More often, the laboratory procedures for inferring sensitivity are ill-suited to preoccupied or uncooperative subjects who are unable to sustain attention to the demands of the testing procedures.[28,71])

Recently an electrophysiological procedure has been developed which is especially designed to study reduced responsiveness to strong stimulation. This technique employs computer averaging of EEG evoked potentials.[67,68,72-75] By averaging electrical potentials, recorded from the scalp, for long series of stimuli, such as light flashes, an averaged evoked response (AER) waveform is produced. For a given individual, the amplitudes of certain peaks of the waveform change systematically with changes in stimulus intensity. In the moderate-to-high range of stimulus intensities, amplitudes of one particular segment of the waveform are found to change in different ways for individuals with different perceptual judgment characteristics. (This waveform segment is the peak-to-trough amplitude from a positive peak at 80 to 90 msec to a negative peak at 120 to 140 msec. For brevity's sake, this segment is referred to as peak 4.) In brief, subjects who *reduce* the sizes of tactile judgments of width, following a period of tactile stimulation, evidence quite different peak 4 AER patterns than subjects who *augment* the sizes of tactile judgments following stimulation. Size-judgment

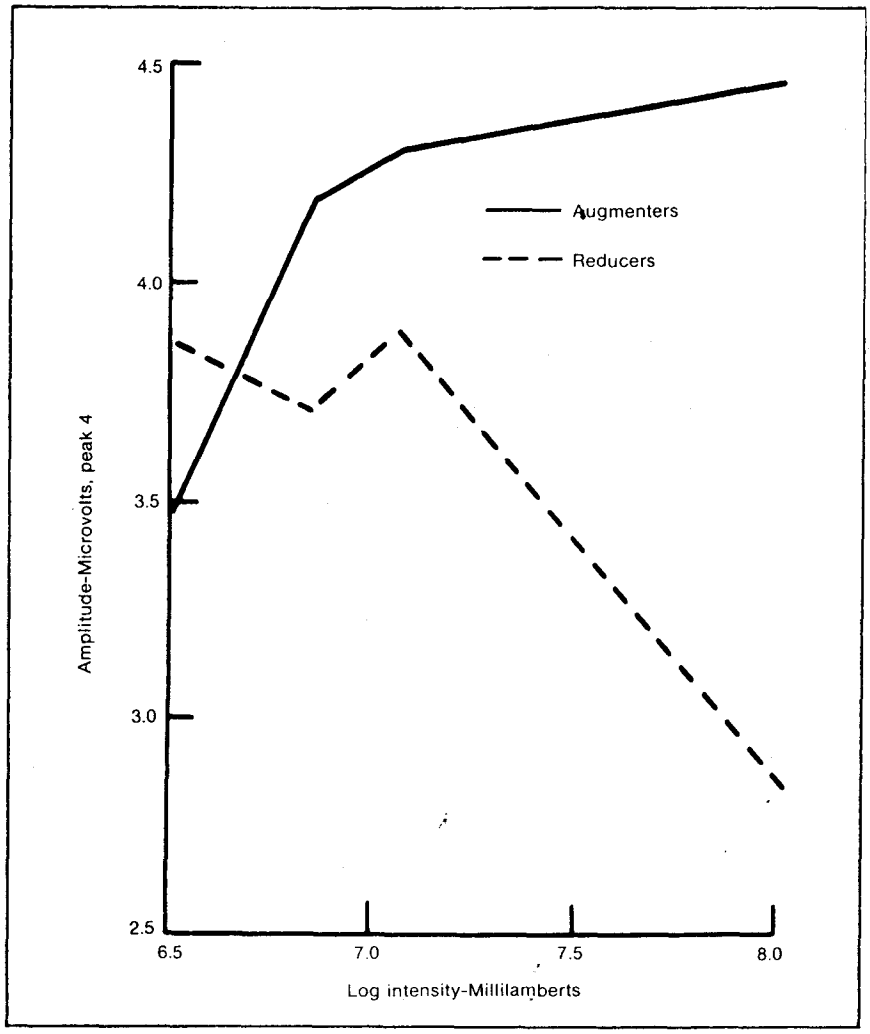

Fig 2.—*Amplitudes of AER to four intensities of photic stimulation for normal size-judgment augmenters and normal size-judgment reducers (from Buchsbaum and Silverman[68]). Peak 4 designation is based on the numbering system of Kooi and Bagchi.[106] Light values in lumen seconds range from 32 to 980 lumen seconds.*

"reducers" evidence relatively decreased AER amplitudes at the higher stimulus intensities. Size-judgment "augmenters" evidence increases in AER amplitudes with increases in stimulus intensity (Fig 2). This effect is found in normal subjects and in various psychiatric patients and medical patient groups.

The AER reduction curve was found to be pronounced in a small group of college-age, unmedicated, nonparanoid schizophrenic men[68] (Fig 3). A comparable AER reduction curve was reported by Blacker and his colleagues[72] for habitual LSD-users who had not ingested LSD within 48 hours of the EEG recording (Fig 4). The differences in amplitudes are intriguing; they probably reflect differences in degree of orientation to external stimuli.[71,76] Comparable results had been obtained in earlier studies of schizophrenic and LSD-drugged subjects using perceptual tests related to the stimulus intensity modulation construct.[29]

In AER studies of LSD-drugged subjects employing only one stimulus intensity, results are found which also are consistent with the stimulus intensity modulation construct. Chapman and Walter[77] reported dramatically reduced amplitudes on the various AER waveform components in eight of nine subjects following ingestion of 115μg of LSD. Light flashes were presented at the rate of 1/2 seconds. Rodin and Luby[20] using a lower dosage (1μg/kg) reported this effect when the light flash rate was 3/second but not when the light flash rate was 1/second. Shagass,[78] using larger dosages (2.5μg/kg to a total dose of 200μg) and a flash rate of 1/2 seconds, also found reduced visual evoked response amplitudes. Somatosensory evoked response amplitudes also were reduced. (Shagass commented on the marked effects of LSD observed using EEG averaging techniques, in comparison with the minimal effects observed in a number of earlier studies which relied on simpler inspection of EEG tracings.)

It is important to note on the basis of these studies that the interaction of dosage level and intensity of stimulation is a critical determinant of the reduction effect. In studies employing lower dosages or low flash rates, or both, AER amplitude reduction may not be observed. Furthermore, unpublished studies have suggested that

an absence of reduction responsiveness may be found in psychedelic-drugged individuals who are not overwhelmed by the experience but rather "go along with it." At very high dosages, however, the reduction effect appears to occur automatically. This point is especially relevant to studies of schizophrenic reactions. Petrie, on the basis of her studies of perceptual augmentation/reduction in schizophrenic patients, described the reduction effect (observed in 82% of her subjects) as "defensive reduction following upon sensory bombardment."[27(p61)] Her suggestion is certainly consistent with other evidence regarding hypersensitivity in early schizophrenia. "When the schizophrenic goes into what may be called his spasm of reduction, it is not a carefully modulated procedure in which he reduces just enough for his own convenience. Rather, he is seemingly forced by his own sensibility to go to an extreme."[27(p66)] Consistent with this are studies which indicate that abnormal perceptual responses are not as marked in schizophrenic subjects following a period in a sensory deprivation chamber.[79,80]

Other AER studies by our NIMH group and the work of Fischer and Kaelbling[7] have provided further information on the relationship of sensitivity and reduction responsiveness. Silverman et al[74] observed reduction on the AER procedure in a subgroup of normal male subjects evidencing the greatest sensitivity to auditory, visual, and thermal stimuli. Male subjects with augmenter AER curves tended to be not as sensitive to low intensity stimulation. In other studies sensitivity to low intensity stimulation was found to be attenuated by phenothiazine medication[7] which, when administered to schizophrenic subjects, changes baseline AER reduction to AER augmentation.[81] Finally, a study by Inderbitzen et

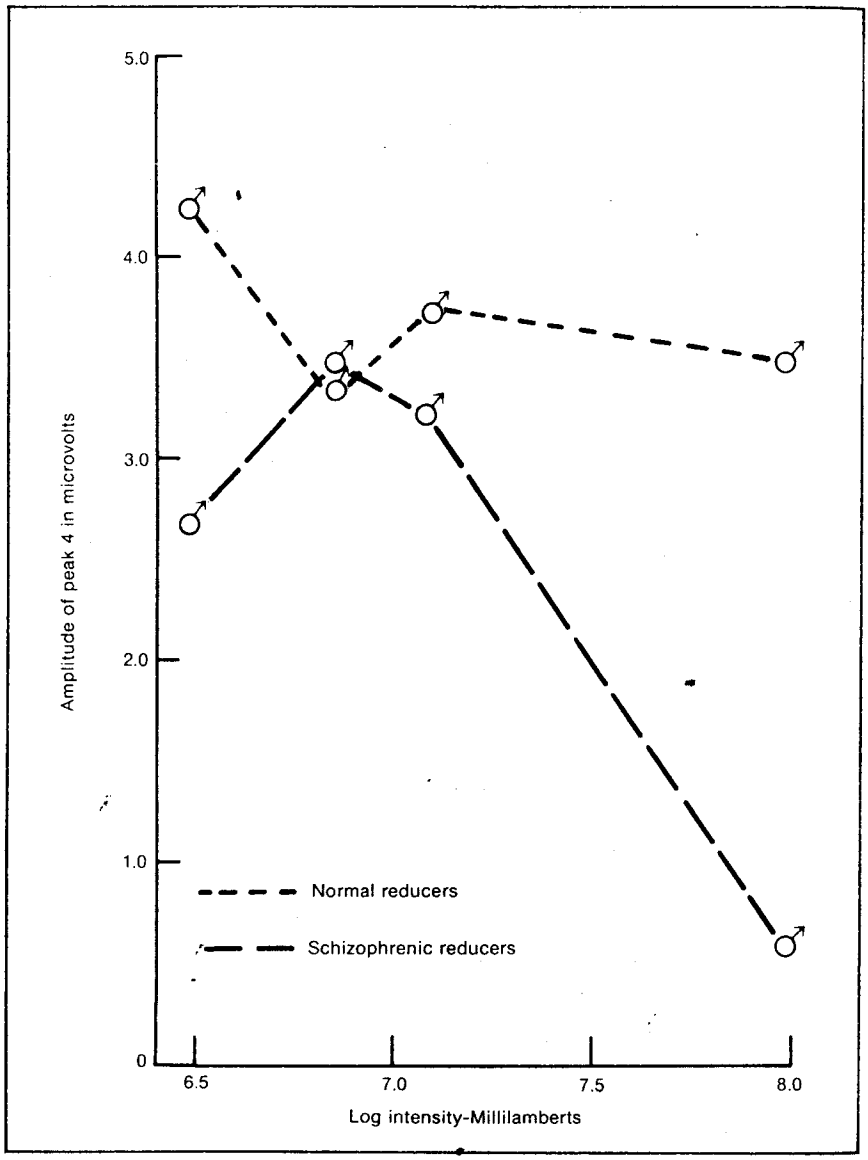

Fig 3.—*Amplitudes of AER to four intensities of photic stimulation for normal size-judgment reducers and schizophrenic size-judgment reducers.*

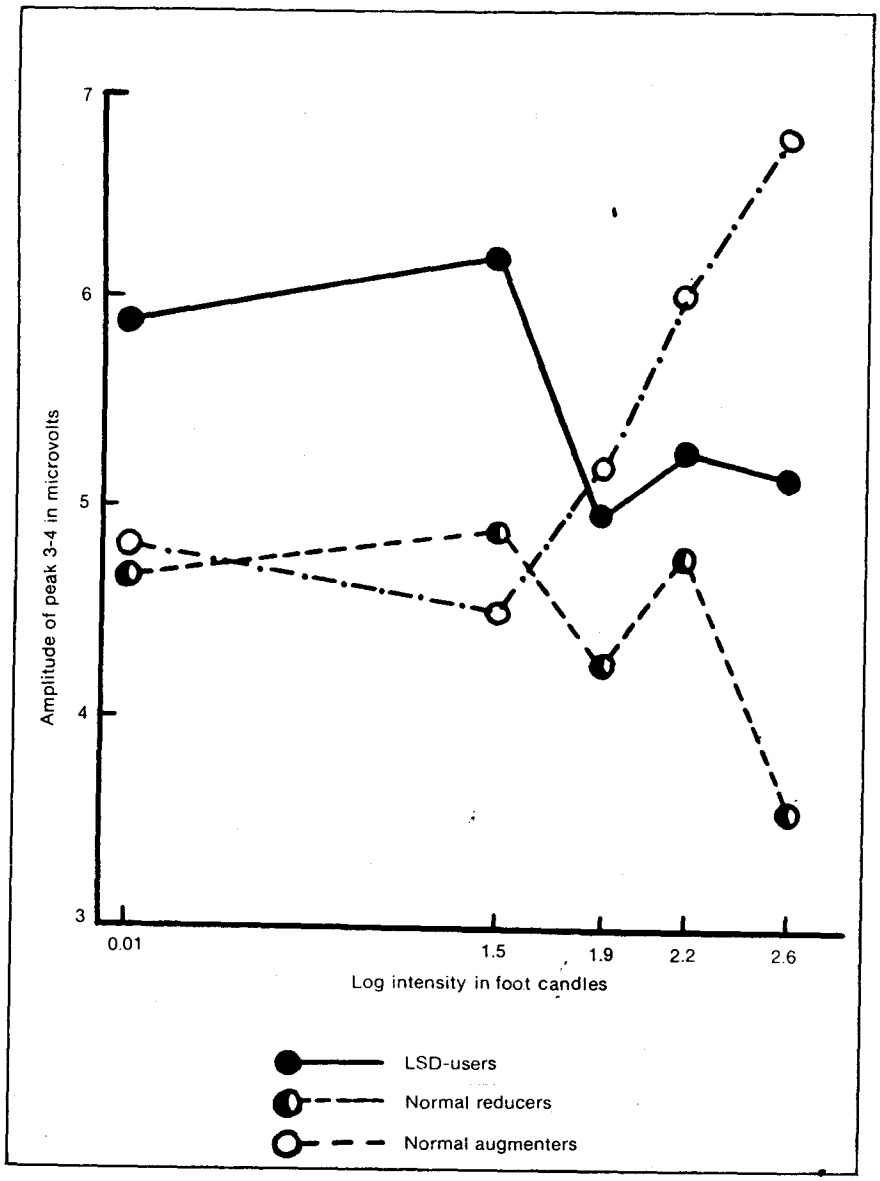

Fig 4.—*Amplitudes of AER to five intensities of stimulation for three groups of subjects (from Blacker et al[72]). Light intensities 1.5 to 2.6 in foot candles are similar to the light intensities employed by Buchsbaum and Silverman,[68] measured in millilamberts.*

al[82] has suggested that individual differences in AER are related to differences in adjustment to the hypersensitive schizophrenic state. Paranoid schizophrenics, who do not evidence hypersensitivity to low intensity sensory stimulation, tended to evidence lesser AER reduction, lesser AER variability, and lesser trial-to-trial perceptual variability than nonparanoid schizophrenics. Sullivan[83] has said of the paranoid resolution of the essential schizophrenic state:

> A paranoid systematization is, therefore, markedly beneficial to the peace of mind of the person chiefly concerned, and its achievement in the course of a schizophrenic disorder is so great an improvement in security . . . [Unfortunately,] these conditions are of relatively much less favorable outcome.[83(p157)]

The implication of this last statement for the treatment of adverse LSD reactions will be considered in the following section.

The results of these researches indicate that the "pattern hypothesis"—hypersensitivity to minimal intensity stimulation, hyporesponsiveness to strong stimulation, and failures of integration of complex information—is equally applicable to acute schizophrenic and psychedelic drugged states. In regard to integration defects, suffice it to state that it has been demonstrated again and again that schizophrenic and psychedelic-drugged subjects do worse than "normal" subjects on tests of sensory-motor, perceptual, and cognitive integration. Unfortunately, such laboratory demonstrations have led to few insights about the psychological and physiological processes underlying behavior, for it is usually impossible to specify to what extent poorer test performances reflect defects in psychophysiological response mechanisms *or* preoccupation *or* disinterest *or* a different subjective criterion for evaluating stimuli.[29]

Clinical Disturbances With Known Sensory Abnormalities.—

Infantile autism is a disorder which which occurs at the beginning of life. The symptom picture centers around: (1) preoccupation with and stereotyped manipulation of objects; (2) isolation, minimal contact with people, including minimal eye contact; (3) failure to acquire general social behaviors (eg, the use of the word "I"); and (4) bizarre self-stimulation behavors which are rhythmic and repetitive (eg, headbanging). Rimland,[84] in his review of this syndrome, has noted a pattern of sensory response characteristics which is similar to the one induced by LSD. These children evidence a hypersensitivity to minute changes in the visual environment, an unusual insensitivity to pain, and severe disturbances of integration of sensory information. The integration disturbances which occur in children with infantile autism are, however, unlike those that occur in normal psychedelic-drugged individuals and in short-term schizophrenic individuals. Rather than the fluidity of perceptual and ideational responsiveness which characterizes the two latter types, children with infantile autism evidence an abnormal rigidity or overfocused responsiveness to fragments of perceptual and ideational stimuli.

In a number of early studies, Bender[85] reported favorable results using psychedelic drugs in the treatment of autistic and schizophrenic children. The children did not evidence the psychotomimetic responses typically observed; rather they exhibited an increased awareness of the world about them, a heightening of mood, and a lessening of stereotyped, rhythmic behavior. "There seemed to be more comprehension of speech and attempts to communicate, though minimal. Disturbed behavior such as headbanging and self-mutilation diminished markedly, although this behavior in these children had not responded to other forms of medication, which was entirely discontinued before and during the use of LSD."[85(p1)] Although quite provocative, Bender's findings could be criticized on several methodological points.[84] In an effort to delineate more clearly the effects of LSD in cases of infantile autism, Simmons et al[86] devised a carefully controlled experiment with two autistic children, identical twins, who presented a reasonably homogeneous symptom picture. An intrasubject replication design was used in which 50μg LSD dosages were presented on certain days interspersed with control and placebo observations. The subjects were tested during two periods of time, once for six daily sessions at the age of 4 years 9 months, and again beginning five months later in a series of nine sessions carried out over a two-month period. Behavioral measurements were made by an observer in an adjoining observation room using a pushbutton console connected to a 12-pen recorder (Esterline Angus). The reliability of this procedure had been established previously. Extraordinary care was used in regard to the circumstances under which the drug and placebo were given and to the definition and measurement of the dependent variables. Significant changes in all primary symptom behaviors were obtained which were attributable to the effects of LSD. They noted:

> In the usual state it is often difficult to intrude upon the child because of a general lack of responsiveness coupled with the random character of responses when they are obtained. The barrier to external stimuli is further increased by self-stimulatory behavior with a high percent time appearance both in the resting state and when stimuli are presented from the external environment. The results of our experiments clearly demonstrate changes in exactly these areas with increased attendance to physical and face contact with an attending adult and concomitant reduction of competing self-stimulatory behavior.[86(p1207)]

Noteworthy also was the positive emotional tone which the children evidence during these significant behavior changes. Most important was that the effect of LSD on these children was not merely to replace self-produced stimulation with pharmacologically produced stimulation, for rather than blocking interaction with the environment, LSD served to facilitate it.

The *psychopathic personality* presents a psychiatric problem which is of a much different kind than that of infantile autism. The nonsocialized behaviors of the inaccessible autistic individual contrast with the antisocial behaviors of the adolescent or adult psychopath. Psychotherapists who have attempted to work with these anxiety-free, guilt-free individuals are well acquainted with the feelings of frustration which this work so often entails. Recent papers have presented convincing evidence that the characteristic lack of motivation in psychotherapy of psychopathic personalities is physiologically determined.[87,88] Compared with nonpsychiatric subjects and neurotic subjects, the psychopath is reponsive to "fewer cues which have the capacity to elicit the autonomic components of fear and anxiety."[87] In their sensory responsiveness, these individuals are found to evidence higher detection thresholds for stimuli in general, that is hyposensitivity to low intensity stimulation.[89,90] In a subgroup of primary psychopaths this hyposensitivity was found to be correlated significantly with a minimal tolerance for pain stimulation; in secondary psychopaths the correlation was reversed. (This distinction between primary and secondary syndromes is based upon clinical and experimental studies suggesting that the diagnosis of psychopathic personality consists of at least two relatively distinct subtypes. The primary, also termed the ideopathic or "true psychopath," is the anxiety-free, guilt-free individual. The

secondary, also termed symptomatic, neurotic, or pseudopsychopath, evidences many of the same types of antisocial behavior but is not anxiety-free or guilt-free.) For both subgroups the data suggested that cues which are ordinarily salient for other individuals are not sufficiently salient to capture the attention of psychopaths. Apparently, these individuals simply are not as accessible as others during regular psychotherapeutic interviews. Of considerable interest in this connection are two clinical reports on the treatment of psychopathic personalities with LSD. Eggert and Shagass[91] and Shagass and Bittle[92] studied the effects of a single LSD treatment (2.5μg/kg of body weight) on 20 psychiatric patients, nine of whom were diagnosed as having psychopathic personalities. Each patient treated with LSD was closely matched with a patient treated by some other means on age, sex, marital status, years of education, psychiatric diagnosis, and for his pattern of symptoms and deviant behavior. Patients in the LSD therapy group also were differentiated into so-called responder and nonresponder groups. Responders were designated on the basis of criteria for an "insightful" response" to LSD therapy—if during an LSD session, the patient experienced early memories and altered his perception of his relationships to the world, if he related these memories and fresh perceptions to his present problems, and if he made a convincing resolution to change his future behavior as a consequence of his new understanding. It was found that seven of the eight individuals who were rated as responders on the basis of ratings of the tape-recorded sessions carried diagnoses of psychopathic personality. In the follow-up study, subsequent changes in symptoms and deviant behavior at 6 and 12 months were evaluated for all patients on the basis of interview ratings made by each patient and closest relative. The greatest overall improvement ratings, both at 6 months and at 12 months, were found in the LSD responder group. The improvement ratings of the responder group were not, however, as marked at one year as they were at six months. Indeed, a few LSD patients indicated that they had recently begun to relapse. It was suggested that a series of LSD sessions might yield results superior to those obtained with single treatments.

Another clinical problem area in which psychedelic drug research appears to be of significance is in the treatment of pain, particularly in cases of terminal illness. As was noted earlier, increased tolerance of strong sensory stimulation has been found to be associated with ingestion of LSD. To a considerable extent, awareness becomes focused on the immediate, awesome sensory life, causing heightened sensitivity to ordinary stimulation and also diminished sensitivity to very strong stimulation. This analgesic effect is of major significance for severely ill terminal patients.[22,23,93] Kast[93] has suggested several effects of LSD on the experience of pain: (1) it temporarily interferes with a patient's concentration on one specific sensory input; (2) minor sensations make a claim on the patient's attention; (3) it diminishes cortical control of thoughts, concepts, or ideas and thus reduces their significance in relation to vegetative function; and (4) it diffuses body boundaries and this diffuses painful sensations in the body. In two large-scale clinical studies of terminal patients, Kast reported significant reductions in their experienced intensity of pain for a ten-day period. Parallel to this change, sleep patterns improved for approximately 12 to 14 days and a definite lifting of mood also was noted during the same period.

It should be noted that in both studies, a minority of the patients did not want a repeat of the LSD administration. This is not at all surprising since profoundly unpleasant reactions to psychedelic drugs occur even under controlled research conditions. The existing research on individual differences in reactions to psychedelic drugs suggests that it may soon be possible to predict prolonged negative reactions on the basis of specific personality and perceptual response characteristics.[34,94,95] It appears that those individuals who place strong emphasis on structure and control generally have no taste for an intense experience in which depth of feeling is enhanced without a conceptual structuring of the increased feeling. In this connection, the Food and Drug Administration and the Public Health Service have authorized a study which will examine psychophysiologic response patterns of different types of LSD reactors (Silverman et al, unpublished research protocol).

Among individuals who evidence *adverse reactions to psychedelic* drugs sensitivity to ordinary range stimulation initially is increased. Both neurophysiological studies and studies of the subjective reports of psychedelic-drugged subjects suggest the metaphor of a "filter" or "stimulus barrier" which has ceased to function in a normal way.[34] The individual is acutely aware that he has stepped beyond the bounds of his usual state of consciousness. Sensory impressions are awesome and attention is directed, in large measure, *by them.* This openness to stimulation may be associated with a fear of being swamped by sensations and images. Laing[96] terms this the "implosion" of reality—the danger of losing all control, of being hurt, of being obliterated. Under these conditions, the sensorily overloaded individual engages in various psychologi-

cal and physical maneuvers which are associated with reducing sensory excitation. Classical psychotic symptoms observed in adverse drug reactions, such as withdrawal, blocking, and constriction of movement and speech, do serve to reduce the amount of sensory stimulation experienced. Even the development of delusional ideas characteristic of the paranoid person may have a sensory modulation function. The construction of a delusional system may be thought of as an attempt to make nonsense out of an intense sense experience.[61] (Most noteworthy in this regard is a recent study by Hall et al[97] who observed in animals a relationship between degree of withdrawal behavior and reduction responsiveness on the EEG evoked response procedure developed by Buchsbaum and Silverman.[68])

Whether or not a drug reaction is adverse or positive, the overall effect of a substantial psychedelic drug dosage is to disorganize habitual response patterns that have protective, defensive, and reality-oriented functions. When these response patterns no longer operate as they formerly did, unconscious emotions and images surge into the individual's field of attention. In terms of the differential neural excitation model elaborated upon here, this is the result of marked inhibition occurring in cortico-cortical association brain areas as a compensatory adjustment to a drug-induced increase in excitation in primary sensory pathways. This pattern of neural activity is suggested as a model for what occurs in the brain when an individual "loses his mind."

It is certainly understandable that chlorpromazine, which significantly decreases sensitivity to ordinary stimulation, has been used widely in the treatment of adverse psychedelic drug reactions. Recently, however, disturbing effects of chlorpromazine on adverse LSD and amphetamine reactions have been reported.[98] Animal studies have corroborated these clinical impressions.[99,100] Halsaz et al concluded:

> The accumulated data show that a tranquilizer (chlorpromazine) acts as a weak psychotogen protecting against a stronger one by substituting for it at receptor sites, but in large enough doses adding to it or even producing the effect it was intended to correct.[99(p571)]

It appears that although hypersensitivity is reduced by chlorpromazine, no changes or even negative changes may occur in perceptual accuracy and problem-solving behavior. Helper et al[101] reported that chlorpromazine interfered with effective information-processing on performance measures requiring active attention to novel and significant details. In animals, phenothiazines have been found to interfere with sensory discrimination[102] and to cause a more intense stimulus to be given in order to produce behavioral arousal.[15] Normal individuals attempting to solve complex problems experience chlorpromazine as most disruptive. Studies conducted with short-term schizophrenic patients indicate that, in certain individuals chlorpromazine exaggerates rather than reduces the extent of thought disorder.[103] Comparable exacerbations of symptoms have been reported in individuals with psychedelic drug reactions treated with chlorpromazine. Such exaggerated disturbances usually are readily handled without tranquilizing medications by experienced psychedelic drug "guides" working in quiet, sensorily subdued surroundings.[104,105]

Figure 4 is reproduced from the *American Journal of Psychiatry* (125:341-351, 1968) with permission.

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