J.Neuropsychiat. 1, 283-292 (1960).

LSD 809

JB 329*—A NEW PSYCHOTOMIMETIC. ITS ANTAGONISM BY TETRAHYDROAMINACRIN AND ITS COMPARISON WITH LSD, MESCALINE AND SERNYL

SAMUEL GERSHON M.B., B.S., D.P.M.,** and J. OLARIU, M.D.

ABSTRACT

A study of the general effects of Ditran, LSD, Mescaline and Sernyl on 31 mental hospital patients is presented. A comparative study of the use of saline, Mescaline, LSD, Sernyl and Ditran in 9 of the same patients, all of whom received all of these drugs at weekly intervals, is presented. The antidotal effects of tetrahydroaminacrin and of succinic acid upon the toxic effect of the four psychotomimetic drugs is described.

A number of chemical agents have been employed to produce "model psychosis" in an attempt to further understanding of psychotic states not induced by drugs. Mescaline [15, 39, 47] and LSD [36, 47] have been most frequently studied. Recently Abood, Ostfield and Biel [8] reported on a group of anticholinergic compounds with psychotomimetic properties. The most potent member of this series, Ditran, was considered by these authors [2] to produce effects simulating some aspects of psychosis more closely than do LSD and Mescaline. A related compound, Sernyl, has been reported to cause post-operative transient psychotic states [31] and what has been termed "schizophrenomimetic" effects.[29]

Perhaps one of the most important contributions to experimental psychiatry is the creation of chemical models derived from psychotomimetic agents and their antidotes. Schueler [39] seems to have been the first to use such a chemical model when, on the basis of *in vitro* experiments by Quastel and Wheatley,[35] he was able to antidote the effects of Mescaline in man with intravenous succinate. This antidotal effect of succinate has been confirmed by Gershon,[17] Stevenson,[41] and Fischer.[15] Succinate was also found to block the Mescaline induced behavioral responses of mice.[24] The behavioral changes induced by LSD in mice [19] as well as the mental symptoms induced in man,[5] are also blocked by succinate.

Pharmacological studies have shown that Ditran is weakly antihistaminic, has no antiserotonin activity and has marked anticholinergic properties. However the anticholinesterases eserine, neostigmine and DFP have been reported ineffective against the central effects of Ditran.[28]

In the present study tetrahydroaminacrin (T.H.A.) was employed to antidote the effects of Ditran. This compound was selected because it has been shown to have marked anticholinesterase activity [21] and to exert central effects in animals and man.[18, 40]

The purpose of the present study is to describe the central and peripheral effects produced by these four psychotomimetic

*JB 329 is a product of the Lakeside Laboratories, Milwaukee, Wisconsin, with the trade name Ditran, and is actually a mixture of two compounds: the N-ethyl piperidine and the N-ethylmethylpyrollidine derivatives.

**Pfizer Medical Research Fellow for 1959. Present Address: Department of Pharmacology, University of Melbourne, Victoria, Australia.

From the University of Michigan and Ypsilanti State Hospital Joint Research Project in Schizophrenia and Psychopharmacology. Supported by U.S. P.H.S. MY 1972 and MY 1971.

Acknowledgements: Thanks to Dr. A. Yuwiler for his valued discussion and help with preparation of the manuscript; also to Mrs. V. M. Reuell, R.N., and Mr. McFadden for their help with the clinical observations and ratings.

Received for publication: March 9, 1960.

agents in a group of mental hospital patients under controlled conditions. A previous study of the effect of Ditran on depressed patients was done by Abood and Meduna.[3a]

In this study the principal objective was to ascertain the nature and intensity of the psychotomimetic effects produced on patients; hence, dose regulation was designed to produce a psychosis and maintain it. The therapeutic effects were secondary. Dose schedules differed from the generally recommended levels. In the case of Ditran the repeated oral doses were selected for continued daily administration rather than occasional intramuscular injections, which were administered to some patients.

Thirty-one subjects were selected for this study and housed on our research ward. This group of mental hospital patients was made up of schizophrenics, alcoholics and sociopaths. Diagnosis was independently established by three psychiatrists. Of the 21 schizophrenics two were catatonics, three relatively recent admissions, and the remainder were chronic schizophrenics. The non-schizophrenics consisted of four sociopaths and six alcoholics. Neither subjects nor observers were aware of the agents used nor of any of the responses that might be expected. The effects of the different drugs were compared with each patient acting as his own control and the entire procedure was carried out under standardized experimental conditions.

In the initial study subjects were given Ditran either intramuscularly or orally and these observations will be recorded separately.

In the final comparative study, nine patients were employed and all of the psychotomimetic substances were given orally in 50 ml. aqueous solution. The dosages were: Ditran (Lakeside) 0.2 mgm./kg., Sernyl (Parke-Davis) 0.25 mgm./kg., Mescaline I (Mann) and II (California Corporation) 5 mgm./kg., and LSD-25 (Sandoz) 5γ/kg. and normal saline. Tetrahydroaminacrin or T.H.A. (Figure 1) was given intravenously in a dose of 60 mgm. in 20 cc. of sterile distilled water. It was administered over a five minute period. Sodium succinate (Brewer) was given intravenously in a dose of 12 g. in 50 cc. of sterile distilled water over a five minute period.

The two patients studied each day were put to bed one hour before administration of the drug and observed throughout the day. This was carried out in a small ward under conditions of normal illumination.

All observations were recorded on a specially compiled check list containing all the observations reported in the literature for each of these compounds. This included both the central and peripheral effects of each including blood pressure, heart rate, respiration and neurological checks. Patients were under careful observation throughout their entire stay on the research ward and day and night reports were kept.

A polygraphic study of the effects of Ditran on autonomic nervous system function of some patients was carried out by Dr. Gunnar Holmberg.

EXPERIMENTS AND RESULTS

I. GENERAL STUDY

DITRAN

Ditran was given to a total of 30 subjects intramuscularly, 14 orally, and, for comparison, six received it both orally and intramuscularly.

1. Typical Sequence of Symptoms following I.M. Injection:

0 minutes	Inject 10-15 mgm.
20-30 minutes	Autonomic reactions: Dryness of the mouth, slight tachycardia, flushing of the face and muscle relaxation.
45-60 minutes	Central Effects: Some confusion, speech difficulty and disturbed concentration, slight disorientation, occasional vertigo, and hallucinatory activity.
2-4 hours	The central effects become maximal; hyperreflexia and ataxia appear.
5-8 hours	Symptoms decrease.

A similar but slower sequence occurs after oral administration.

2. Autonomic Reactions:

Autonomic reactions occurred about 30-40 minutes after the ingestion of Ditran. These uniformly consisted of dry mouth, mydriasis, facial flushing, nausea (in four cases) and vomiting (in one). While the blood pressure was not appreciably affected in most cases, occasionally there was a slight rise which would either fluctuate or return to baseline in about two hours. A minor degree of tachycardia was occasionally noted. Autonomic effects preceded the onset of psychic phenomena and outlasted them in every case.

3. Psychological Reactions:

a. *Disorganization of Thought*

Disorganization of thought was observed in nearly all subjects. They showed an inability to maintain a logical thought sequence and a loss of goal directed thoughts. Some subjects had completely incoherent verbal productions, some blocking and a few, echolalia. While all patients had great difficulty in describing feeling states this condition was most marked with chronic schizophrenics. Patients had difficulty in elaborating on their general statements of feeling "funny," "strange" or "peculiar." About half the subjects seemed to have difficulty in understanding questions and were unable to interpret proverbs. Response to proverbs displayed either lack of understanding, or looseness of concepts to a severe degree. Repetition of part of the quotation sometimes occurred. Poor critical judgment and the inability to recognize absurd statements was seen in 50-60% of cases.

b. *Mood*

In most cases there was a change in mood, some becoming hostile, aggressive or combative, and others, quiet, cooperative and even somewhat euphoric. In some cases the mood change was affected by the nature of the patient's hallucinations and some subjects would be amused and laugh and giggle, while others became anxious and expressed fears of becoming insane. The mood would occasionally change and the subject shift from elation to sadness and depression.

c. *Confusion and Drowsiness*

Varying degrees of drowsiness were usually observed although most subjects were still responsive to stimuli. Four subjects exhibited a stupor-like state and two a mussitant delirium. Confusion was frequently found and occurred either as a steady state or in waves. Contact with reality and insight were completely disrupted in some subjects. Other effects observed were impairment of attention, of concentration, and of reaction to orders or questions. Time and space orientation were only infrequently impaired, time orientation being impaired to a greater degree. One patient when asked where he was said "Spain" and another said "at a baseball game." Also one subject when asked to read the words "Readers' Digest" said "Receiving Hospital."

d. *Feelings of Inebriation*

Some of the early effects of Ditran were likened to those obtained from alcohol. This was particularly true among the non-psychotic group. Chronic alcoholics who had previously experienced episodes of delirium tremens, however, reproduced the classic picture of this syndrome. This was a consistent finding restricted to this diagnostic group.

e. *Disturbances of Perception*

Tactile, visual and auditory hallucinations were observed. Visual hallucinations consisted of objects, people, animals, landscapes, and even scenes, like a group of men playing pinochle. Often the people in these scenes were familiar to the subject: parents, girl friends or other patients. The subjects often reacted to these visual hallucinations as if they were real. Patients picked up invisible objects from clothes, sheets and bed, sometimes continuously plucked at bed clothes, drank from imaginary cups (accompanied by sipping noises), ate imaginary food, danced, and sometimes exhibited violent behavior.

Auditory hallucinations of human voices

sometimes elicited laughter or hostility. Other hallucinations consisted of indistinct voices or sounds and, rarely, music. Some subjects stated that people were talking about them behind their backs. Patients frequently talked or muttered continuously to themselves. Behavioral responses to auditory hallucinations were also observed. One subject jumped out of bed saying "Get out, the barn is burning down." Another stated that the voices told him the attendant would write in the records that he is insane. Questioning as to how the patient felt, elicited such replies as "The man got on the bus," and "They clean up on Saturday." Other responses such as "There's a crowd of them over there," and "Another mouse ran across my elbow," were recorded.

f. *Other Observations*

Echopraxia, echolalia and repeated motor acts like touching all the beds were noted. The inability of the subject to recognize his own image in a mirror was observed in five cases. One subject had difficulty in sexual identification and when asked his sex held his genitals and then expressed doubt as to his sex.

g. *Response Differences*

Two catatonic schizophrenics received Ditran intramuscularly and neither showed any marked psychic responses. Neither blood pressure nor heart rate altered significantly but tended to fluctuate above and below the baseline. Dilation of the pupils, yawning, tremor, and some restlessness occurred and one patient frequently raised his head from the pillow while the other made rocking movements. Both patients remained mute and during their stay in bed they voided urine and lay therein without comment.

Of the six alcoholics, four with previous experience of delirium tremens reproduced the classical picture of this condition. These subjects exhibited restlessness, tremor, picking at objects in bed and in the air, and delirium with hallucinations. Patients asked for various types of alcoholic beverages, searched for bottles, and drank from imaginary glasses. On the following day all six cases were amnesic for the preceding day's events and all were somewhat euphoric, alert, and energetic. All the subjects in this group appeared to show some improvement in their general clinical condition after intramuscular administration of Ditran. This improvement was characterized by a change from inactivity, disinterest and disinclination for work to improved mood, alertness and level of interest and activity.

Sociopaths did not seem to respond in any specific manner and could not be differentiated in responses from normals [2] or from our schizophrenics.

All schizophrenics given oral or intramuscular Ditran showed marked central effects. In some cases this appeared to constitute a reactivation of the basic psychotic process and the endogenous psychotic picture could not be distinguished in these individuals from that produced by the drug. Reactivation was less marked or absent in very deteriorated chronic schizophrenics. For example, one chronic schizophrenic admitting to hallucinations and bizarre delusions but disinclined to discuss them, became actively disturbed after Ditran, and shouted about fire coming from his eyes, and turtles, mice and rats crawling under his bed. Another subject after Ditran saw his girl friend in the room and searched about the bed for some of her letters. The girl friend and the lost letters figured prominently in his incoherent productions prior to the drug. In many cases, except in those where confusion or drowsiness precluded it, there was an elucidation and clarification of material that could be found in the subjects' previous history and in some a reproduction of the acute phase of the illness.

Schizophrenic subjects on daily oral medication initially produced the usual autonomic and psychic effects observed with intramuscular administration. Under these conditions some tolerance develops, first to autonomic effects, and later to central effects. Termination of medication did not result in a return to the "baseline" condition but rather all cases were temporarily worsened. An increase in withdrawal, apathy, asocial behavior and

inactivity was noted the first few days following cessation of medication. Patients previously on work assignments were unable to resume them. This deterioration was particularly marked in a paranoid schizophrenic. Before medication he admitted to auditory hallucinations of paranoid type but tried to dismiss them and had a degree of insight into their nature. He did not talk back to these voices and was pleasant, cooperative, sociable and willingly helped with ward work. His condition deteriorated while on Ditran and remained so after its cessation. He was withdrawn, uncooperative, hostile, completely asocial, and lounged about actively talking to his hallucinatory voices. After a week or two all these patients returned to their pre-treatment status.

h. *Toxic Effects*

The only toxic effects encountered on routine administration were nausea on five occasions and vomiting on three. Unusual responses were noted in three subjects who had received 10-15 mgm. Ditran orally for a two to three week period and after an interval of three weeks were given 10 mgm. Ditran intramuscularly. The first such case, involving a patient who had a history of hypertension, was the most alarming. Six minutes after injection the patient's speech became slurred and incoherent, he appeared rather stuporose, and 10 minutes after injection, his blood pressure was 234/120 mm. Hg. and heart rate 124 beats/min. Fifteen minutes after injection these values had risen to 240/120 mm. Hg. and 160 beats/min. and the patient showed symptoms of acute cardiac failure. The other two patients, who also had histories of hypertension, reacted similarly but to a much lesser degree. In both within 5-8 minutes after injection there was a very rapid onset of the central effects. The order of increase of blood pressure and heart rate was 40 mm. Hg. and 50/beats/min. respectively. This rapid onset of central effects and this marked cardiovascular response was only observed in these three cases distinguished by this particular sequence of Ditran medication.

LSD AND MESCALINE

The responses of 13 subjects to LSD and Mescaline was qualitatively similar to that reported in the literature but quantitatively smaller. This is shown in Table I.

SERNYL

Sernyl was orally administered to nine subjects in a dose of 0.25 mgm./kg. Higher doses of Sernyl produced stupor. Patients were unable to speak and completely lost contact. In lower doses Sernyl elicited no significant responses. We did not observe many of the psychological effects reported by Luby *et al.*[29] under these conditions of dosage and administration. In general the responses produced by Sernyl fell into two groups depending on the previous condition of the patient. Quiet, and generally underactive patients became stuporose and some showed catatonic features after Sernyl. More reactive patients became extremely overactive and disturbed with violent restlessness. Our findings are essentially the same as those of another study in this hospital with Sernyl.[12]

II. COMPARATIVE STUDY

Nine subjects, composed of five schizophrenics, two sociopaths and two alcoholics, were given saline, Mescaline, LSD, Sernyl and Ditran at weekly intervals.

AUTONOMIC AND NEUROLOGICAL EFFECTS

No significant autonomic or neurological effects were seen with saline. Two Mescaline preparations produced some increase in tendon reflexes, some diminution of the cremasteric reflex, depression in respiration, and occasionally nausea (three subjects), vomiting (two subjects) and dilatation of the pupil (five subjects).

LSD produced pupillary dilatation and lachrymation and occasional nausea (three cases) vomiting (one case). Neither LSD nor Mescaline produced significant differences in the mean blood pressure, pulse rate or rate of respiration.

Sernyl produced lachrymation in four,

vomiting in two and nausea in three subjects. Generally there was an initial rise in blood pressure falling to or below baseline after one to two hours. One subject developed a marked pulse irregularity due to multiple premature ventricular beats as evidenced by EKG recordings. Pupil size was either not altered or it was reduced. Nystagmus, ataxia, Romberg-Phenomenon, muscle weakness and slurred speech were seen in all cases.

Ditran caused mydriasis, dryness of the mouth, ataxia, Romberg-Phenomenon, muscle weakness, slurred speech, facial flush and, in one case, nausea. Skin sensitivity to pain was not impaired by saline or Mescaline in two cases but Ditran decreased sensitivity in two cases, Sernyl in four, and LSD in three. In two of the LSD cases, this decreased sensitivity was so marked that needles could be pushed through folds of the skin on arms and legs without complaint.

PSYCHOLOGICAL EFFECTS

The psychological effects of these compounds are shown on Table I. Mescaline exerted very little psychological effect. LSD led to a slightly higher incidence of psychological effects than did Mescaline but these effects were limited to "strange feelings" and the usual type visual disturbances. In no case were there true hallucinations. Sernyl produced drowsiness or stupor in some subjects and wild restlessness in others, but, again, there were no hallucinations Ditran produced both the greatest incidence and severity of effects. The duration of drug effects with all compounds generally lasted about 12-24 hours. However, the effects of Sernyl on two subjects continued for 48 hours.

III. ANTIDOTES

Succinic acid was perhaps one of the first compounds to be used as an antagonist against chemically induced changes in behavior.[5, 6, 7, 9, 15, 37, 39] It has been shown to be effective against the psychotomimetic effects of Mescaline and LSD.[5,39] In this study succinate was found to antidote both the central and peripheral effects of Sernyl but not of Ditran. As an illustration, Mr. A. W. became very quiet, sleepy and drowsy after Sernyl. Nystagmus, ataxia, Romberg-Phenomenon were present, his speech was very slurred, he felt dizzy and drowsy and said his head was all "fogged up." The patient was disoriented, occasionally laughed out loud and when asked to write his name started with the first four letters and then followed with a crooked line. His blood pressure prior to Sernyl was 114/62 mm. Hg. and his pulse was 76 beats/minute. After two hours his blood pressure reached 142/74 mm. Hg. and pulse rate was 120 beats/minute. At the time of the succinate injection (3½ hours after ingestion of Sernyl) blood pressure was 96/44 mm. Hg. and pulse was 88 beats/minute. Six grams of sodium succinate in 50 cc. of water was given intravenously over five minutes and the patient immediately became mentally clearer, blood pressure rose to 128/74 mm. Hg. and pulse rate was 78 beats/minute. The patient's speech became perfectly clear, he could converse rationally, answer questions correctly and write his name without fault. He said his head was now clear and he could "think straight." He was able to stand and walk without ataxia but nystagmus was still present. There was no recurrence of Sernyl symptoms. Two other cases also exhibiting a similar clinical picture after Sernyl reacted to succinate in much the same manner.

The peripheral and central effects of Ditran given to 21 subjects were completely reversed by T.H.A., which was effective whether the subject was in a mussitant delirium, was restless, combative, stuporose, active, or alert and able to verbalize his delusions and hallucinations. For example, Mr. H. W. was given Ditran (10 mgm. I. M.) and 1½ hours later he was stuporose with eyes staring fixedly ahead, unable to articulate any sound or word, and his limbs were markedly hypotonic. Sixty mgm. T.H.A. in 20 ml. of water was then given intravenously over five minutes. Two minutes after beginning the injection he could speak and reply to questions clearly and rationally, was alert and in good contact. After completion of the injection he could move his limbs and 10 minutes later

could get out of bed and walk.

Mr. A. F., the subject who developed the hypertensive crisis and acute cardiac failure after Ditran (See I. 3. h.), was given 60 mgm. T.H.A. intravenously during this crisis and by the time the injection was completed his blood pressure and heart rate dropped almost to his baseline levels. Concomitantly he became mentally clear and alert.

Mr. H. G. received 12 mgm. Ditran in aqueous solution orally. One hour later he became restless, had visual and auditory hallucinations, and was grasping for non-existent objects. His speech was rambling, incoherent and inconsequential and he mumbled intermittently in apparent response to his hallucinations. Some muscle hypotonia and a slightly staggering walk were also present. Intravenous T.H.A. (60 mgm.) was given and his speech became clear, he could respond as well as before the experiment, and his restlessness, mumbling, and hallucinations stopped. Muscle tone was also restored and he could walk without assistance.

The antidotal effect of T.H.A. was very rapid in onset in all cases and in the majority of cases was lasting. There was, however, a slight recurrence of Ditran effects three to four hours later in some patients. The blood pressure and heart rate changes induced by Ditran were also restored to baseline in all cases. Pupillary dilatation remained substantially uneffected by T.H.A. while dryness of the mouth was reduced in some subjects.

TABLE I

RESPONSE OF 9 PATIENTS TO THE DRUGS

	Saline	Mesc. I	Mesc. II	LSD	Sernyl	JB 329
Drowsiness	3	1	3	5	5	5
Confusion	0	0	2	6	6	6
Contact Impaired	0	1	2	4	7	5
Disorientation (time, space, person)	0	1	2	5	4	3
Strange Feelings	0	2	2	3	2	3
Illusions	0	1	2	2	2	2
Hallucinations						
Visual	0	0	0	4	0	6
Auditory	0	0	0	0	0	3
Tactile	0	0	0	1	0	2
Mixed (as pecking at objects)	0	0	0	1	0	6
Mood Change	1	2	2	6	2	4
Overtalkative	0	0	0	3	3	2
Repetition Words	0	0	0	3	2	2
Inappropriate Laughter	0	2	1	4	1	2
Talking to himself or hallucinations	0	0	0	1	2	7

EPICRISIS

Induced "model psychosis" has frequently been employed to test hypotheses relevant to the causes, correlates and treatment of schizophrenia. In this context psychotomimetic effects of Ditran were observed in 31 subjects of different diagnostic groups. This compound closely simulates schizophrenic symptomatology, the indole nucleus is not necessary for hallucinogenic action and further, is an inhibitor of acetylcholine and thus involves a neurohumor other than epinephrine, norepinephrine or serotonin.

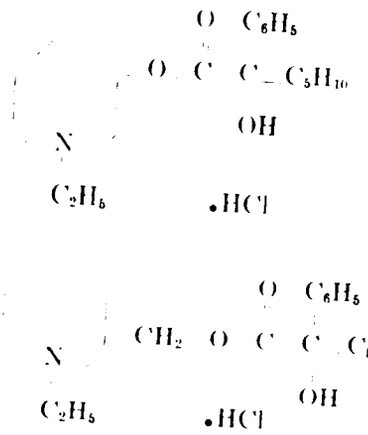
The structure of this hallucinogen is shown in Figure 1. Replacement of the cyclopentyl group of this compound by a phenyl group considerably decreases the intensity and duration of the induced toxic psychosis.[3]

Substitution of H for OH in the benzilic acid nearly abolishes psychotomimetic properties and greatly reduces anticholinergic potency. Although substitution of a quaternary nitrogen in the piperidyl ring also abolishes psychotomimetic properties there is little affect on anticholinergic properties. In pharmacological studies the anticholinergic effect of Ditran on guinea pig ileum is comparable to and may exceed that of atropine.[2,5] It also has a weak antihistaminic but no known antiserotonin activity.

Very small cerebral concentration of Ditran is required to produce behavioral disturbances in rats. Extrapolation from these data on rats to man would imply that cerebral level of 100γ is sufficient to exert psychotomimetic effects. Only LSD is effective at lower levels.

Tritium labelled studies in rats[1] have shown that over 90% of ingested Ditran is excreted within two hours of administration. Only about 0.1% of the dose is present in the central nervous system; the caudate nucleus and hypothalamus having the largest concentrations. The original investigators were of the opinion that the psychotomimetic effects of Ditran simulate some aspects of psychosis much more closely than LSD or Mescaline.

FIGURE 1



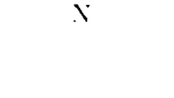
JB 329* N-ethyl-3-piperidyl-phenyl-cyclopentyl glycolate hydrochloride

and

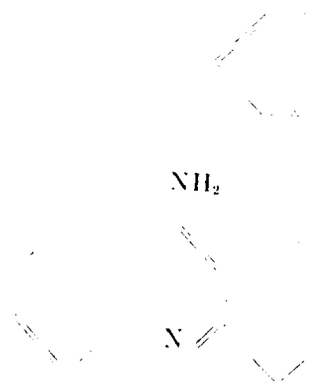
N-ethyl-2-pyrrolidylmethyl-phenylcyclopentyl glycolate hydrochloride

*JB 329 (Ditran) is actually a mixture of two compounds: the N-ethyl piperidine and the N-ethylmethylpyrollidine derivatives.

SERNYL



1-(1-Phenylcyclohexyl) Piperidine Monohydrochloride



1, 2, 3, 4-Tetrahydro-5-Aminoacridine. (Tetrahydroaminacrin)

This was unambiguously demonstrated in our comparative study of psychoactive drugs with nine subjects. The kaleidoscopic, visual hallucinatory phenomena so characteristic of LSD-25 and Mescaline were not observed with Ditran.[27, 39]

Both schizophrenic and non-schizophrenic subjects reacted to the same dosage of Ditran with equally florid symptoms but some of the schizophrenic subjects produced an intensification of the primary symptoms and a reactivation of the psychotic picture. Patients with chronic schizophrenia are resistant to LSD and Mescaline and also are able to discriminate between the drug effect and the normal manifestations of their illness.[11, 34, 42] In contrast, schizophrenics given Ditran are unable to distinguish the drug induced psychosis from the endogenous disease. The intensity of effects produced by LSD and Mescaline was far less than is generally reported in the literature, as observed in this compara-

tive study of these drugs in the same nine subjects. This is of considerable interest and similar diverse responses have been considered in Wikler's review of the subject.[47] Many variables may contribute to this difference in response: dosage, setting, type of subjects, and the heterogeneity of the groups. The effects of suggestion and placebo have been pointed out by Abramson,[4] Savage,[38] Van den Berg,[46] and may be considerable. The intensity of hallucinations is most marked in subjects with marked "eidetic" tendencies.[26] Stoll [42] in his LSD studies and Marshall [30] using Mescaline, stress that a quiet and darkened room is essential for the production of hallucinations. Such conditions plus suggestibility may lead to an exaggeration of drug induced changes or perhaps it may produce changes independent of drug effect.

Our subjects were observed in a normally illuminated ward although there was no extraneous activity at the time of testing. No prior information as to either the nature of the compounds or the expected effects was given. Suggestion therefore was minimal or absent. The subjects had not developed sophistication from any previous experiments. The response to Ditran was quite marked and consistent and the visual hallucinations consisted of animals, objects, faces and people, in distinction to the complete absence of such productions with LSD and Mescaline. Furthermore the verbal productions were not significantly disturbed with any compound other than Ditran.

Although Sernyl has been grouped with the piperidyl benzilate esters, including Ditran, it does not produce inhibition of acetylcholine and differs in other pharmacological aspects. Luby *et al.*[29] have reported on the psychotomimetic effects of Sernyl on nine psychiatric patients and nine normal subjects with medical and/or psychiatric training. Although Sernyl produced behavioral changes in our subjects which differed from those attained with any of the other compounds studied, the term "schizophrenomimetic" could not be justifiably applied to these changes. In some cases a stuporous-like state with catatonic features occurred and in others a wildly disturbed restless delirium resulted. In these studies the oral administration was employed and the dosage modified accordingly.

The study of compounds inhibiting or reversing drug induced behavioral changes are of considerable interest to experimental psychiatrists and pharmacologists because they may give insight into the mechanism of similar clinical disorders.

Succinic acid, one of the first compounds studied in this context [39] was given to three patients showing a stuporous-type response to Sernyl. Succinate effectively reverses both peripheral and central effects of Sernyl and the patients were restored to their pre-drug conditions. However, nystagmus persisted in every case. Succinate did not counteract Ditran. Succinate has also been reported to antidote other psychotomimetics and various types of drug induced and endogenous depressions.[5, 6, 7, 8, 9, 15, 17, 19, 20, 22, 23, 39, 41, 44, 45, 49]

The anticholinesterase, T.H.A. was found to antidote both the central and peripheral effects of Ditran in man but was ineffective against Sernyl. T.H.A. is also an effective decurarising agent,[14] reverses morphine depression in dogs,[10] and also significantly reduces the central effects of morphine in man. Preliminary screening employing the activity cage technique showed that T.H.A. counteracted the increased activtiy produced in mice by Ditran.[19]

The antidotal effects of T.H.A. are especially interesting because other cholinesterase inhibitors such as eserine, neostigmine and DFP do not modify the central effects of Ditran. Pfeiffer *et al.*[33] have reported that the "Mescarinic" effects produced by agents such as eserine and arecoline are of value in the treatment of catatonic schizophrenia. The possible efficacy of T.H.A. in schizophrenia is of considerable importance and studies are now underway. Acetylcholine concentrations and alterations in these concentrations do seem to influence psychic phenomena [10, 13, 14, 16, 25, 32, 33, 37, 43, 48] and may be of importance in the study of mental disease.

References

1. Abood, L. G.: *Personal Communication.*
2. Abood, L. G., Ostfield, A. M., and Biel, J. H.: *Proc. Soc. Exp. Biol. & Med.*, 97:483-486, 1958.
3. Abood, L. G., Ostfield, A. M., and Biel, J. H.: *Arch. Int. Pharmacodyn.*, 70:186-200, 1959.

3a. Abood, L. G., and Meduna, L. J.: *J. of Nerv. & Ment. Dis.*, 127:No.6, 546-49, 1958.

4. Abramson, H. A., Jarvik, M. E., Levine A., Kaufman, M. R., and Hirsch, M. W.: *J. Psychol.*, 40:367-383, 1955.
5. Arnold, O. H., and Hofmann, G.: *Wien. Z. Nervenheild.*, 11:92-104, 1955.
6. Barrett, R. H.: *Curr. Res. Anesth.*, 27:326, 1948.
7. Barrett, R. H.: *Curr. Res. Anesth.*, 26:74, 1947.
8. Boisson, P.: *Acta Chir. Belg.*, 49:953, 1950.
9. Burrell, R. H.: *New Zealand Med. J.*, 45:565, 1955.
10. Cohen, L. H., Thal, T., and Tissenbaum, M. J.: *Arch. Neurol. Psychiat.*, 51:171, 1944.
11. Condrau, G.: *Acta Psychiat. Kbh.*, 24:9-32, 1949.
12. Dukay, A. P.: *Personal Communication.*
13. Feldberg, W. S.: *Physiol. Rev.*, 25:596, 1945.
14. Feldberg, W. S.: *Lancet*, 2:900, 1955.
15. Fischer, R.: *Rev. Canad. Biol.*, 17:389, 1958.
16. Funderburk, W. H., and Case, T. J.: *J. Neurophysiol.*, 10:179-188, 1947.
17. Gershon, S.: *A Physiological and Pharmacological Study of Succinate and Lithium Salts*, Melb. Univ., 1957.
18. Gershon, S.: *The Blocking Effect of Tetrahydroaminacrin on a New Psychotomimetic agent.* (in press).
19. Gershon, S., and Altman, F.: *Unpublished.*
20. Gershon, S., and Shaw, F. H.: *J. Pharm. & Pharmacol.*, 10:22, 1958.
21. Gershon, S., and Shaw F. H.: *J. Pharm. & Pharmacol.*, 10:638, 1958.
22. Gershon, S., and Trautner, E. M.: *Med. J. Aust.*, 1:783, 1956.
23. Gershon, S., and Trautner, E. M.: *Med. J. Aust.*, 2:291, 1954.
24. Gershon, S., and Trautner, E. M.: *Unpublished.*
25. Grob, D., Harvey, A. M., Langworthy, D. R., and Lilienthal, J. L.: *Bull. Johns Hopkins Hosp.*, 81:257, 1947.
26. Jaensch.: Quoted from Wikler, A., p. 79, *The Relation of Psychiatry to Pharmacology.*
27. Kluever, H.: *Studies in Personality*, p. 175-207. McGraw-Hill, New York, 1942.
28. Lakeside Laboratories. Research Division of Chemistry and Pharmacology.
29. Luby, E. D., Cohen, B. D., Rosenbaum, G., Gottlieb, J. S., and Kelly, R.: *Arch. Neurol. Psych.*, 81:363-369, 1959.
30. Marshall, C. R.: *J. Neurol. Psychopath.*, 17: 289-304, 1937.
31. Meyer, J. S., Griefenstein, F. E., and De Vault, M.: (in press). Quoted from Luby, E. D. *et al.*
32. McKail, R. A. S., Obrador, S., and Wilson, W. J.: *J. Physiol.*, 99:312-328, 1941.
33. Pfeiffer, C. C., and Jenney, E. H.: *Ann. New York Acad. Sc.*, 66:753, 1957.
34. Phillips, D.: *Psychopharmacology.* National Academy of Sciences, p. 526, 1959.
35. Quastel, J. H., and Wheatley, A. H. M.: *Biochem. J.*, 27:1609, 1933.
36. Rothlin, E.: *J. Pharm. Pharmacol.*, 9:569, 1957.
37. Rowntree, D. W., Nevin, S., and Wilson, A.: *J. Neurol. Neurosurg. & Psychiat.*, 13:47, 1950.
38. Savage, C.: *Amer. J. Psychiat.*, 108:896-899, 1952.
39. Schueler, F. W.: *J. Lab. Clin. Med.*, 33:1297, 1948.
40. Shaw, F. H., Gershon, S., and Bentley, G. A.: *J. Pharm. & Pharmacol.*, 9:666, 1957.
41. Stevenson, I., and Sanchez, A. J.: *Amer. J. Psych.*, 114:328-332, 1957.
42. Stoll, W.: *Schweiz. Arch. Neurol. Psychiat.*, 60:1-45, 1947.
43. Suttel, R., and Ratsimiala-Ratandra, S.: *Presse Med.*, 63:1073, 1955.
44. Trautner, E. M., Gershon, S., and Duerrheim, G. E.: *Med. J. Aust.*, 2:181, 1954.
45. Trautner, E. M., Trethewie, E. R., and Gershon, S.: *Med. J. Aust.*, 2:848, 1953.
46. Van den Berg, J. H.: *Folia Psychiat. (Aust.)*, 54:385-406, 1951.
47. Wikler, A.: *The relation of Psychiatry to Pharmacology*, Williams and Wilkins, Baltimore, 1957.
48. Woolley, D. W., and Shaw, E.: *Brit. Med. J.*, 2:122, 1954.
49. Yamada, T., and Takumi, A.: *Fol. Psych. Neurol. Jap.*, 10:163-171, 1956.