NICOTINIC ACID MODIFIED LYSERGIC ACID DIETHYLAMIDE PSYCHOSIS*

By

N. AGNEW, M.A.†

and

A. HOFFER, Ph.D., M.D.‡

Regina, Saskatchewan

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INTRODUCTION

THEORETICAL models ranging from neurological to analytical have been introduced in the hope of providing new insights into psychopathology. The flesh and blood model is of more recent origin in this field. The experimental or model psychosis results from giving "normals" drugs which bring about a psychotic-like experience for a few hours. As is the case with theoretical models, the flesh and blood models are not accurate representations of the naturally occurring psychosis. In fact, the variability manifest in most naturally occurring psychoses makes the existence of an accurate model impossible. A model, whether carefully planned and developed or accidentally discovered, is useful to the extent that it assists us in better understanding the naturally occurring process it approximates. It is useful if it enables us to set up and test hypotheses which contribute additional knowledge about disease aetiology, mechanisms, or treatment. The model psychosis to be studied in this paper is that produced by lysergic acid diethylamide (LSD).

When LSD became available for psychiatric study, it spurred anew correlative biochemical and psychological investigations. Many authors (1, 2, 3, 4) have reported using LSD to produce experimental psychoses, as an aid to psychotherapy, as an euphoriant and as a diagnostic adjunct. This amazing compound is effective in gamma (·001 mgm.) dosages compared to mescaline which is used in 0·3–0·5 gram dosages. The mescaline and LSD phenomenon have been compared with toxic and acute florid schizophrenic psychoses.

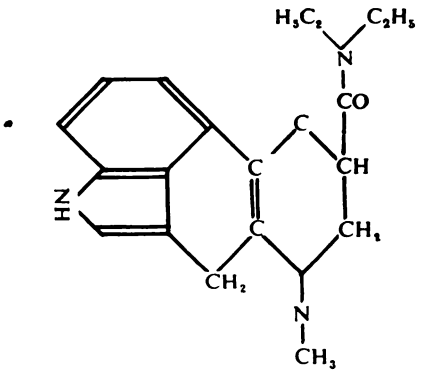
For the purpose of this study we assume this model psychosis in some ways approximates to the naturally occurring phenomena known as schizophrenia. To outline a systematic argument for the similarity between the model selected and schizophrenia will not be undertaken here for various reasons; one reason being that no generally acceptable systematic description of schizophrenia has been made and we doubt our own ability to do it. Another reason is that the value of the model will be judged initially by its ability to help develop testable hypotheses. Thus, knowing the pharmacology of LSD, the compound which produces the model psychosis, and knowing the symptoms that "normal"

* Saskatchewan Committee on Schizophrenic Research. Supported by the Department of National Health and Welfare, Canada.

† Research Psychologist, Munroe Wing, Psychiatric Services Branch, Department of Public Health, Regina, Saskatchewan.

‡ Director of Psychiatric Research, Munroe Wing, Psychiatric Services Branch, Department of Public Health, Regina, Saskatchewan.

subjects commonly develop when the compound is administered, our task is to develop a hypothesis about the modification of this model psychosis and to run a pilot project built around the hypothesis developed. The structure of LSD is as follows:

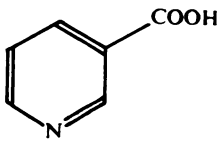


Lysergic Acid Diethylamide

In looking for a means of modifying its effects, we can think in terms of chemical modification through competitive inhibition by structural analogues. Thus, we should look for a chemical similar in structure to LSD as one criteria.

Further, some work has been done on the possible action of LSD which should be considered. Mayer-Gross (5, 6) has made the assumption, and presented some evidence in support of it, that LSD interferes with carbohydrate intermediary metabolism. Similarly, Schueler (7) reported that in four cases administrations of sodium succinate rapidly removed most of the effects of mescaline from their research subjects. Thus, another criterion in looking for a compound to modify the LSD action would be one that facilitates carbohydrate intermediary metabolism.

Finally, the LSD psychosis has been compared to both toxic and functional psychoses. In surveying compounds which have proven useful in the treatment of the above conditions, and which met the two requirements previously outlined, nicotinic acid emerged as an eligible candidate. Nicotinic acid has been used in the treatment of the following illnesses: pellagra psychoses (8), nicotinic acid deficiency encephalopathy (9), atypical psychotic states of senility without much evidence of pellagra (10), depressed states (11, 12), in confusional psychoses of alcoholism and drugs (13), and in cases of active psychoses without evidence of pellagra (14).



Thus, our hypothesis is that nicotinic acid will modify the LSD produced psychoses. The dosage of nicotinic acid to be used must be determined by trial and error methods. In clarifying the meaning of the word modify, we will assume that nicotinic acid could have a preventive action, that is modifying the effects of LSD when administered prior to it, and also that it could have a treatment effect, that is modifying the effects of LSD when given during the model psychotic experience.

Procedure

We selected 10 male subjects from a group of 14 volunteers. Our screening methods included a routine medical history and physical examination. Volunteers with a history of severe or recent liver damage were excluded.* A Rorschach was administered to all volunteers. Only those who were willing to participate in a related study† were included, only one of the 10 volunteers had any special knowledge of psychiatry and none reported any history of psychiatric treatment. The mean age of the group was 26 years, with a range of 19 to 31, and all were of average or above average intelligence. The group's mean years of education was 14 with a range of 10 to 18.

In order to study possible modification of LSD psychosis by nicotinic acid both from a "preventive" and "treatment" point of view, the 10 subjects were divided, at random, into 2 sub-groups of 5 members each. Sub-group A received 200 mgm. (i.v.) of nicotinic acid‡ at the height of the LSD experience. The time of the administration of nicotinic acid was not standardized since from our experience, and from the literature (16), the time at which individuals reach the height of the LSD experience varies. Sub-group B received, orally, 3 grams of nicotinic acid per day for the 3 days prior to the experimental day. Subject #5 of this sub-group also received a 200 mgm. injection (i.v.) of nicotinic acid 15 minutes after drinking the LSD. On the experimental day each volunteer received, on an empty stomach, 100 gamma of LSD.§ We decided to use this dose because our own experience shows that 80 gamma or more is needed for any sure reaction to the drug. Also, our own experience and that of Stefaniuk‖ shows that dosages of 200 gamma make it virtually impossible for the subject to give any coherent report of his experiences or for investigators to carry out any comprehensive testing programme during the experience. The decision to use a standard dosage of LSD for all subjects rather than determine dosage on the basis of body weight is based on our observations that variability of response does not appear to be particularly related to body weight.

Each subject was under constant observation by one of the investigators for at least the first 4 hours following the administration of LSD and comprehensive tape recordings were made. The experimental situation was one of relatively constant questioning and testing. On the day following the experiment each subject submitted a report of what he recalled of the experience.

Results

Table I¶ summarizes the effects of nicotinic acid on LSD-produced disturbances (listed under 5 categories—proprioceptive, perceptual, etc.) for each subject of sub-group A, the group which received nicotinic acid at the height

* It has been reported by Fischer *et al.* (15) that subjects in whom only a slight modification of hepatic function is present have a marked and prolonged reaction to LSD.

† These subjects participated in a study in which the relationship between personality structure and reaction to drugs was investigated. This study will be reported at a later date.

‡ We are using nicotinic acid as a pharmacologic agent rather than as a vitamin. It is non-toxic in much larger concentrations.

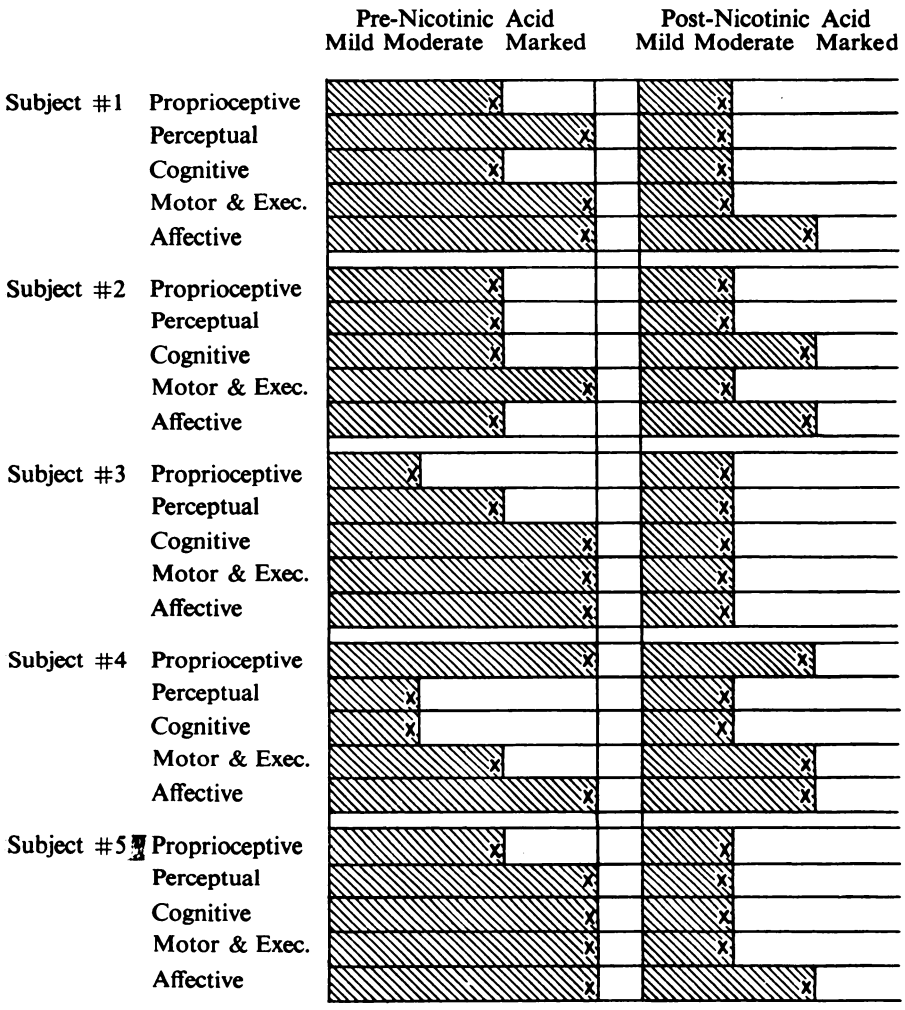
§ The LSD used in this study was provided through the courtesy of Professor E. Rothlin, Director of the Pharmacological Laboratories of Sandoz Chemical Company, Inc., Basel, Switzerland.

‖ Research Psychologist, Saskatchewan Hospital, Weyburn, Saskatchewan, carried out investigations with over 20 volunteers, each of whom received 200 gamma LSD.

¶ We realize the presentation of data in this form involves gross over-simplification. The criteria for differentiating qualitative and quantitative reactions of the kind with which we are dealing are vague. However, for those who have had little or no experience with LSD reaction in "normals" the table provides a rough guide. The only baseline we have for making the judgments we did is that established by the collective experience of members of our research unit with over 70 volunteers who received dosages of LSD ranging from 20 to 200 gamma.

TABLE I

Degree of LSD Disturbances Prior to and Following Nicotinic Acid (Sub-Group A)



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of the LSD experience. For a more detailed presentation of data on which this table is based, see Appendix A.

The variation between subjects, both as to category and degree of response to LSD, is apparent upon examining pre-nicotinic acid disturbances listed on the left half of Table I. Furthermore, the qualitative differences between subjects within any one category, for example perceptual, become clear upon examination of the left half of Appendix A. Subject #4 experienced only mild time misperception, whereas subject #5 experienced a wide-range of marked perceptual disturbances.

Table I demonstrates a clear shift of the degree of disturbance toward the left (mild) in all categories following nicotinic acid. Disturbance in the affective category, while shifting in the same direction, proved to be the most resistant to modification.

Modification in disturbances were recorded on the basis of changes which appeared within 15 minutes of the nicotinic acid injection and which were maintained at that level or decreased. If a marked reduction in disturbance was noted within 10 or 15 minutes of the nicotinic acid injection and yet 30 minutes later due to reappearance of symptoms it appeared to be only a moderate reduction of disturbance, it is recorded in Table I as a moderate disturbance under the post-nicotinic acid heading. For example, subject #4 reported a marked reduction of affective disturbances immediately following nicotinic acid, but some time later reported a return of some anxiety.

Table II summarizes the disturbances experienced by each subject of sub-group B, the group which received nicotinic acid for 3 days prior to the administration of LSD. For a more detailed presentation of the data on which this table is based, see Appendix B.

Once again reference to Table II or Appendix B points to a strong factor of inter-subject variability in response to this particular drug-combination.

Within the framework of variability there are some striking features to be noted about sub-group B results. First, difficulties in power of expression and concentration were mild compared to those found in sub-group A prior to nicotinic acid. Second, visual disturbances, which are usually the most striking feature of the LSD experience for our subjects, appeared as the major symptom in only one subject, subject #2. Finally, there were marked disturbances experienced by 3 of the 5 subjects in this series (subjects 1, 3 and 5) centering around confusion about self-identity, and unreality problems. The following are excerpts of verbatim material from the subjects:

Subject 1

"I have the feeling of trying to hang on to real things and I'm being pulled away . . . I'm localized up here and six inches to the left (points to place over his head) and it's as though I had an ear down here and an ear up there and they don't blend together . . . words seem to be very reassuring—seem to be solid, they brought me back to something that was real . . . it's as if I'm soaring around some mean little point (he was referring to the microphone which symbolized reality for him) from which I can't get free . . . This mike is my contact with reality—but this other part I feel I could almost get lost in it . . . if I break away from this (mike) I won't have to come back . . . nothing terrifying about it except the thought of losing my reference point, that would be true sensation. I feel sometimes I come right on the edge of that where I wouldn't be sensing things but rather sensations themselves . . . I see myself sitting here—stodgy kind of me and then these flights into a dimension of another world completely free of limitations I know are inherent in this world, tremendous expanded time and speed—not speed of things—just scope . . . I'm bored with real world things, ink blots and microphones . . . my experience is far more real to me than Rorschach cards . . . my experience is the real world . . . you are an individual now with a body and located in space a while ago you were merely a voice—the rest had no part." (Draws a diagram in which he depicts himself soaring around a small core of reality—at times he comes close to it and at other times he almost loses touch with it.) "This is like a conspiracy . . . you're part way

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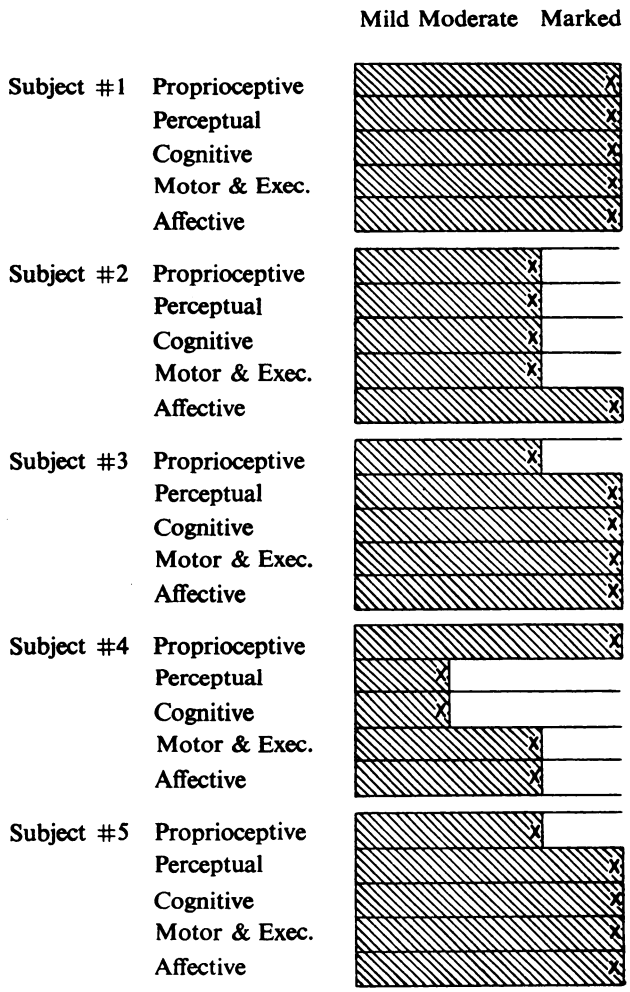
TABLE II

Degree of Disturbance when Nicotinic Acid Administered Prior to LSD (Sub-Group B)



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in it with me . . . we're sharing a secret that those bastards in the other room don't know anything about . . . you talk about Gardner Murphy and Morton Prince, I feel that they're little spots down there—they don't really know what the hell's going on—we're on out where we've seen it—experienced it—it's tremendous their writing about something in distant words that they don't understand at all."

Subject 3

"What is the self the essential I and how does one know the I? I felt as if the 'real I' was trying hard to look after the 'drugged I' I was disturbed that there appeared to be no boundary between the two . . . the lack of control and responsibility experienced while 'drugged I' was uppermost could at any time overlap with the 'real I'. Standing by the canteen door I was aware of being different to the man behind the counter—not being able to control the difference and not particularly caring to—after all this was not a permanent state."

Subject 5

"Wait a minute—what happened . . . something happened just then. (Expt. what do you mean) . . . well now let's see the reason I came here was to take some tests and we're in the General Hospital. When you stood up and opened the door something lifts off my face—things clear up and then it's gone and Jesus you'd give anything to have it cleared up again . . . you see for a while you seemed kind of pudgy—sort of round at the edges—for a while there all of a sudden I took my glasses off—wiped my face and things seemed to clear up—you seem to just peel off the pudgyness and for a while you were clear and normal and things got smaller and I just felt relieved—for a while I seemed to come out of a dream but now I'm back in the dream. (Expt. how do you feel now) Scared—when you started to peel off you started to get real again—things were clear-cut again and now this." (This is the subject who ran down hallways in an effort to get back to reality—see Subject 5, Appendix B.)

Discussion

The results will be considered under the following headings:

I. The variability of response to LSD and LSD–Nicotinic acid combinations.
II. Sub-Group A—the apparent or real antidotal action of nicotinic acid.
III. Sub-Group B—a different kind of model psychosis.

I. Variability

Since we are preparing a report of a study of the relation between personality structure and reaction to drugs in which variability is dealt with at length, we will comment here only briefly. First, the variability of response within both our sub-groups is almost as striking as the similarities perceived. Second, on the basis of the collective experience of workers in our research unit, variability of response to LSD, whether the dosage be small or large, has made it exceedingly difficult to make generalizations. Third, on the basis of the literature (1, 16, 17) most authors make reference to variability of response. However, since in the case of LSD the reactions observed are difficult to define, and space permits only limited examples in reports, it poses the problem of whether similar kinds and extent of variability are found by most investigators. A further factor adding to the complexity of the problem is that the various investigators approach the data with markedly different frames of reference which determines, to a large extent, the selection of reactions to the drug which are noted. For example, some investigators conclude that various subjects' reactions are different with respect to both quality and quantity (1), others note differences in the quality and quantity of reaction but note similar patterns of response (17), still others report essentially uniform responses on the part of their subjects (16). Thus, inter-subject and inter-investigator variability make generalizing exceedingly difficult. In this one respect at least the model psychosis resembles a naturally occurring illness called schizophrenia.

II. Antidotal Action of Niacin

The administration of nicotinic acid at the height of the LSD experience appeared to result in a striking reduction of all LSD-induced disturbances.

except affective, in all subjects but one. The reduction of the disturbances occurred within a few minutes of the nicotinic acid injection, and was maintained.

The first question that demands consideration is to what extent the modification of symptoms was due primarily to the lapse of time during which detoxication was taking place. The only adequate way to answer this question is to move the time of the administration of nicotinic acid progressively closer to the time at which LSD is taken. The effects of administering the nicotinic acid prior to LSD will be discussed in the next section. Due to individual differences and lack of criteria, it is difficult to determine the time at which volunteers taking this dosage should be expected to pass from the florid state or show definite signs of modification. On the basis of our experience, with this dosage level and using the criteria outlined by DeShon *et al.* (1), the height of the reaction lay within a period of from one to six hours after administration of the drug. This is based on a sample of only 6 subjects, none of whom passed from the florid state, as far as we could judge, prior to 3 hours and one-half, after taking the drug. DeShon *et al.* (1), using dosage levels below ours, report the height of the reaction occurring within a span of from one to five hours after administration. They do not indicate the minimum time encountered but, in the three representative cases listed, none passed from phase II (height of the reaction) prior to four and one-half hours after administration. In our subjects the nicotinic acid was injected two and one-half hours after LSD, except in one case (Subject 5) who didn't appear to enter the height of the reaction phase until two and one-half hours after administration.

A second complicating factor to be considered in attempting to assess the part played by nicotinic acid in producing the modification of LSD disturbances perceived, is the fact that ordinarily the intensity of disturbances during an LSD experience follows a wave-like rise and fall. As best we could judge, however, where modifications did appear, they were maintained.

A third question arises as to the mode of action of nicotinic acid in producing modifications of LSD disturbances. It seems clear that the action of the nicotinic acid is not that of direct biological antagonism. If it were, we should expect the modification of the LSD experience to be at least as pronounced in those subjects receiving nicotinic acid prior to the LSD which was not the case. It may be that it is acting in an indirect way, for instance, by interaction with one or more compounds produced by the introduction of LSD in the organism. It should be noted, in considering the possible mode of action, that an intravenous injection of 200 mgm. of nicotinic acid is quite unpleasant.* Therefore, apart from any specific biochemical action, it was experienced as a stressor by all subjects.

As to why the affective disturbances were more resistant to modification, no adequate explanation can be offered at this time. However, in our work with volunteer subjects it appears that certain kinds of LSD-produced disturbances are more specific and predictable than others. The proprioceptive disturbances initially experienced have been noted by all investigators and an explanation has been offered by Liddell and Weil-Malherbe (18). Perceptual disturbances, particularly time misperception and changes in size and shape of objects perceived, are common. Also, disturbances in concentration and power of expression, as well as in motor and executive functions, are noted in most subjects. It is in the spheres of affect and mood that variability appears to be

* One of the authors (N.A.) had the injection at the height of an LSD experience and does not feel the results are so unpleasant as to discourage the use of the dosage.

the greatest. Variability in affective disturbances from our own experience, like that reported in the literature (1, 2, 16, 17, 19, 20), ranges from marked euphoria through to deep depression, from blunting through to intense anxiety. Some authors (19, 20) maintain that LSD exaggerates the previous affective state whether of a "constitutional" or temporary nature. Thus, it appears that certain reactions are more or less specific to LSD while others are more dependent upon situational and personality factors. Hyde (21) is investigating the effects of situational factors on the LSD experience and, as indicated previously, we are attempting to investigate the relationship between personality structure and LSD reaction. It is possible that nicotinic acid modifies those disturbances more or less specific to LSD but is not so effective in normalizing reactions related to the organism under general stress. For example, we have noted marked shifts in mood in some subjects when we unwittingly changed their milieu. We have been struck by the effects of leaving the subject alone for a few moments or directing our attention to a task or third person. Three of our subjects reported a marked shift in attitude toward us, we changed from friend to foe in a few seconds, or they informed us that if we were putting on an act for their benefit, it wasn't being appreciated. With respect to the possible effects of personality structure, we have some indication, for example, that subjects presenting symptoms of free floating anxiety and high blood pressure have a markedly atypical reaction to LSD.

In summarizing the effects of nicotinic acid given at the height of the LSD reaction, the most obvious result is the clear-cut modification of disturbances. It seems clear that the mode of action is not that of direct biological antagonism as hypothesized initially. These results are of theoretical and practical interest with respect to the role of certain drugs in helping the organism manifesting disturbances on many levels to "normalize" (22).

III. A Different Kind of Psychosis

Within the framework of variability there appeared in the majority of Sub-group B subjects, the group that received nicotinic acid for 3 days prior to the experimental day, some uniformities of response that we have not encountered so clearly or consistently to date. First, all subjects showed much less difficulty in expressing themselves and concentrating than we have usually encountered with this dose. While it is true that in each case subjects would not shift their attention on request as readily as they did during the screening procedures, they were able to give much more coherent descriptions of their experiences for extended time periods than subjects in Sub-group A prior to nicotinic acid. In this respect one of the major difficulties we have encountered in using LSD as a "model" psychosis has been that the disturbances in expression and concentration have made it exceedingly difficult to get a coherent report of the subjects' experiences. We are not suggesting that a subject in a "model psychosis" should be able to outline his experience with textbook-like clarity. Difficulties in power of expression are to be expected when the experience to be described is different from anything previously encountered. These subjects had difficulty describing what was happening to them. Like other LSD subjects, the words, concepts and experiences in their repertoire were, for the most part, inadequate to describe the state in which they found themselves. Nevertheless, the subjects in Sub-group B did not seem to be hampered by spans of attention and concentration limited to seconds. Therefore, though their descriptions were vague, they were longer and better organized than, for example, the pre-nicotinic acid reports given by subjects in Sub-group A.

A second apparent difference in reaction on the part of this group was that the visual distortions, involving motion and change of size and shape of objects, which our subjects usually find to be the most striking feature of the LSD experience, were unusually mild in four out of five cases (subjects 1, 3, 4 and 5). Subject number two did experience the above-mentioned disturbances but, much to our surprise, proceeded to attempt to explain them, though on an over-simplified level, by working out the laws of perspective involved on numerous sheets of paper. The usual preoccupation with visual changes, like the much reduced concentration span mentioned above, has been a disconcerting factor in the LSD-produced "model psychosis". Such symptoms make it difficult to decide of what naturally-occurring psychosis it is a model.

Finally, disturbances of self-identity and reality appeared as major symptoms in three of our five subjects in Sub-group B. One subject in Sub-group A reported similar disturbances (subject #5). Stefaniuk (23), using 200 gamma dosages, found that approximately one-quarter of his subjects reported disturbances of this kind. Fischer (15) using dosages ranging from 60 to 130 gamma encountered such disturbances in less than one-quarter of the subjects. Rinkel *et al.* (2), whose subjects received from 20 to 90 gamma, found such disturbances but stated they were of minor magnitude, while Savage (4) reports depersonalization and derealization upon the administration of 20 gamma. Once again it is difficult to compare results with other investigators. The concepts involved, depersonalization and derealization, are complex and often a classification is made on the basis of a statement like "my legs feel funny" or "things look funny". We have found that the usual disturbances of concentration and expression have made it difficult for us to assign these classifications to our data except in a few cases. Thus, we were impressed by the relatively clear descriptions of these disturbances on the part of three of the five subjects in Sub-group B. It should be pointed out that vagueness, affective disturbances, and lack of co-operation when pushed were also evident in these subjects.

Several questions arise with respect to the above discussion. The sample is small. Since, as yet, we do not know what personality and situational factors are operative in accounting for the variability of response to LSD, it is conceivable that such uncontrolled factors are essentially responsible for the symptoms we attribute to the particular drug combination used. One of the five subjects (subject #4) had an unusually mild experience. Was this due to the nicotinic acid or, as we tend to feel, to personality structure factors? However, even with such limitations inherent in our results, reporting our observations appeared to be important for several reasons. The LSD psychosis has been most readily compared, to date, with schizophrenic symptoms (1, 2, 16). In making such comparisons all investigators add a note of caution with respect to obvious differences between the two. For us the unusually short spans of concentration and the more or less constant visual distortions have been primary symptoms of the LSD experience. From what little we know of the inner world of schizophrenia, this does not appear to be the case. Apart from the relatively rare hallucinations, as differentiated from illusions, and the extremely variable affective disturbances, it is in the area of depersonalization and derealization that similarity between schizophrenic conditions and the LSD experience becomes most striking. Thus, in observing three out of five cases in which depersonalization and derealization emerged with relative clarity; in which unusually short spans of concentration and more or less constant visual distortions were not major symptoms; yet in which affective disturbances, vagueness and lack of co-operation were evident, it appeared to us that

here was a "model" psychosis more in keeping with the schizophrenic prototype.

If nicotinic acid was to modify the LSD reaction through direct biological antagonism, it is with this group, the one receiving nicotinic acid prior to LSD, that the most clear-cut evidence of reduced disturbance should exist. This was not the case. Fischer (24), investigating some of the factors involved in drug-produced model psychoses, postulated that compounds structurally related to LSD, and displaying higher affinity for wool-protein, should block out by competitive inhibition the LSD experience. Based on this hypothesis Fischer and Agnew (25), using the same subject, ran three experiments. In the first 80 gamma of LSD was given, in the second methylene blue followed by 80 gamma LSD, and in the third diparcol followed by LSD. Largacile, which also meets the above criteria, has also been used (26). The data to date support Fischer's hypothesis.

Summary

Nicotinic acid was administered to one group of subjects at the height of the LSD experience and to another for three days prior to the administration of LSD. Tentative findings are presented which indicate that nicotinic acid, when administered at the height of the LSD experience, has a markedly normalizing effect. The lack of modification of affective disturbances is noted and discussed. The administration of nicotinic acid prior to LSD reduced disturbances in concentration and vision. However, in some subjects it produced a psychosis, the primary symptoms of which more closely resemble the primary symptoms of schizophrenia than those most commonly found when LSD alone is administered.

The mode of action of nicotinic acid does not appear to be that of direct biological antagonism as initially hypothesized.

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APPENDIX A

		LSD Symptomatology	Nicotinic Acid Symptomatology
Subject 1 24 years 130 pounds		12.20 100 gamma LSD (orally).	2.50 200 mgm. nicotinic acid (i.v.). Flush, intense warmth.
	Proprioceptive	1.00 tense, nausea, fatigue, anorexia, shaky.	3.00 no evidence of LSD symptoms.
	Perceptual	1.15–2.50 After images, rippling motion and variation of size and shape of objects; light, colour, touch and noise sensitive; size of hand changed upon suggestion.	3.02 slight "rippling" effect and sensitivity to noise.
	Cognitive	1.20–2.50 "running away" of ideas, pre-occupation, difficulty in power of concentration. Comprehension of question poor, could not organize replies.	3.04 mild difficulty in concentration, much improved grasp of questions and organization of replies.
	Executive and Motor	1.30–2.50 poor co-ordination; uncontrolled smiling; anti-social comments and uncooperative. Power of expression disturbed.	3.10 intensified effort to communicate; "I feel a much greater sense of responsibility".
	Affective	1.15 Initial euphoria followed by periodic suspiciousness.	3.50 periodic moderate suspiciousness continues. Evening: (at home) not hungry but ate supper, "felt hilarious, really enjoyed baby". "Slept well, felt like hangover next day."
Subject 2		12.10 100 gamma LSD (orally).	2.35 200 mgm. nicotinic acid (i.v.) Flush and intense heat.
23 years 156 pounds	Proprioceptive	Initial dizziness and nausea. 12.40–2.35 Persistent "pressure at the back of my neck"; "cigarettes taste flat".	2.40 no evidence of LSD symptoms other than cigarettes continue to taste flat.
	Perceptual	12.55–2.35 Colour sensitive; objects appear "rubbery" changing shape in time with breathing; distance and time misperception; size of hand changed upon suggestion.	2.38 "The floor's stopped moving!" Some change of size and colour of objects continues—"Nothing like it was before".
	Cognitive	Confusion and some disorientation.	2.40 some confusion remains "are you quizzing me?"

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		LSD Symptomatology	Nicotinic Acid Symptomatology
		2.27 "I can't get to the bottom of it", "this is an experiment isn't it?" Marked difficulty in concentration and comprehension. Replies to questions are disorganized.	Concentration improved; replies to questions much more coherently.
	Executive and Motor	1.00–2.35 Unusually talkative and aggressive in manner; resists tests—"don't feel I'm doing what I should but it's too much bother."	2.45 less talkative and more subdued; makes greater effort to report experience; still slightly aggressive. 3.20 feels LSD experience may return.
	Mood	1.10 Euphoria—persists in modified form throughout experiment.	2.57—slight tendency to smile periodically—some suspiciousness. 4.00 returns to work, feels restless—some euphoria and aggresiveness remains. Evening: ate a large supper—went for a drive, slept well.
Subject 3		9.40 100 gamma LSD (orally).	12.00 200 mgm. nicotinic acid (i.v.).
29 years 150 pounds	Proprioceptive	10.00 Initial tenseness. 10.20 Metallic taste, nausea. 10.30 hands perspiring, flush. 10.00–12.00 restlessness—anorexia.	Marked flush and heat sensation. 12.07 no sign of LSD symptoms, feels relaxed. Reports hunger. 12.30 enjoys hearty lunch.
	Perceptual	10.20 fingers feel thick. 10.30–12.00 colour, light sensitive, and objects change size and shape taking rippling motion in time with breathing. Finds certain colours very distasteful. Complains of figure-ground disturbance, time and distance and touch misperception.	12.06 no evidence of perceptual disturbances. 12.15 reports periodic return of slight motion on flat surfaces, but figure-ground disturbance no longer evident.
	Cognitive	10.30 preoccupied with Rorschach cards. 10.40 ideational perseveration. 11.00–12.00 Flow of clang, distant, loose associations and perseveration of theme, "silly" replies to questions.	12.10 pays attention to questions and gives coherent well organized replies. "I feel the way I normally do." Some tendency toward preoccupation.
	Executive and Motor	9.50 mildly aggressive. 10.30 reports difficulty in speaking. 10.45–12.00 unsteady, uncontrolled laughing, "no sense of responsibility", unable to cooperate in testing situation.	12.08 "all of a sudden I'm steady on my feet"; cooperative in answering questions and completing tests; slight tendency to smiling remains.
	Mood	10.30 mild euphoria. 11.00–12.00 marked euphoria.	12.05 euphoria markedly reduced. 1.30 returns to work—becomes preoccupied with piece of work he had been avoiding. Reports that his overcoat looked shabby and dirty. Evening: enjoyed supper; slept well.
Subject 4* 29 years 210 pounds	Proprioceptive	12.20 100 gamma LSD (orally). 12.10 (prior to LSD). Reports strong anxiety.	2.55 200 mgm. nicotinic acid (i.v.). Flush and spreading warmth.

* This subject appeared to the examiners to have no apparent reaction to the drug—most of the material presented is based on the report of the experiences he handed in the following day.

		LSD Symptomatology	Nicotinic Acid Symptomatology
		12.30–3.00 tenseness at back of neck, anxiety becomes more and more intense. (Compares it to waiting to take off for bombing operation); shaky.	3.00 "nervousness has disappeared for first time." 3.30 "felt rather agitated and restless."
	Perceptual	2.30–2.55 time misperception.	3.05–4.00 nothing unusual noted.
	Cognitive	1.10–2.55 "couldn't follow questions which required other than stock answers; concentration impaired; "unusual slowness in thought".	3.05–4.30 "less difficulty in following and participating in conversation, still didn't feel exceptionally conversational."
	Executive and Motor	2.00–2.55 "Felt I might make ridiculous statements—so tried to discourage conversation." 2.45 Felt shaky standing, refused to walk to test steadiness.	3.05 still somewhat unsteady.
	Affective	12.10–2.55 mounting anxiety. 2.45 suspicious.	3.07 anxiety markedly reduced. "feel good for the first time." 3.40 "feel pretty tense again." 4.30 "felt relief at leaving hospital for home." 5.30 anorexia—euphoria. Enjoyed (more than usual) playing with children—pupils dilated. 7.30 noticed slight visual disturbance (rippling) for a few seconds. Had good nights sleep.
Subject 5 31 years 153 pounds	Proprioceptive	10.00 100 gamma LSD (orally). 11.30 Floating sensation and tension; nausea and neck pressure. 12.30–2.10 metallic taste, floating sensation, heightened awareness of parts of body.	2.10 mgm. nicotinic acid (i.v.). 2.15 LSD symptoms not in evidence.
	Perceptual	11.45 light and noise sensitive. 12.30–2.10 light, noise and colour sensitive; objects and person change size and shape; shifts of mood were immediately reflected in perception—warm colours, relaxed movements, soft sounds or cold colours, jerking movement, harsh noises; gross time misperception, depersonalization "Detached feeling as though I wasn't part of myself."	2.17 slight, periodic return of motion.
	Cognitive	11.00 difficulty in concentration. 12.30–2.10 preoccupation; transient and interchanging feelings of heightened reasoning capacity (actually gross oversimplification) and unreality; reporting "everything is there but it's unreal"; confused disorganized.	2.20 much less confused and reporting well organized; periodic return of mild unreality feelings.

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		LSD Symptomatology	Nicotinic Acid Symptomatology
	Executive and Motor	11.00 unsteadiness. 12.35–2.10 feels he can differentiate unreality feelings with effort—but disturbed over lack of control of constant mood changes which are reflected in proprioceptive and perceptual spheres, "I feel rejected, the room is cold, your face is stern and foreboding, my hands are cold." Non-co-operative.	2.20 "feel in control of myself for the first time." Co-operation much improved.
	Affective	12.00–2.10 continual shifts from feelings of security, sympathy and warmth to feelings of rejection, suspiciousness and hostility.	1.50–2.45 shifts in mood greatly reduced; suspiciousness evidenced periodically. 3.15 no effects of LSD in evidence. Evening: ate a good supper and wrote rough draft of experience. 10.30 bed—slept well. Next day felt somewhat foggy mentally.

Appendix B

Group B. Each of the following subjects received 3 gm. of nicotinic acid (orally for 3 days preceding the experimental day

Subject 1*		12.25 100 gamma LSD (orally).
31 years	Proprioceptive	1.00 tenseness builds up, slight nausea; shaky.
155 pounds		1.30 "I feel a tremendous tenseness as though I'm waiting for something, just right on the edge of an emotional experience . . . like I'm going to blow apart."
	Perceptual	1.15 slight sensitivity to light and colour; mild touch misperception.
		1.45–4.00 marked time misperception and depersonalization; "my voice and body don't seem to belong to me, the real me is in space somewhere".
	Cognitive	1.50–4.00 marked feeling of unreality "drifting away from reality . . . experiencing different levels of reality all at once"; dissociation, hyperactive.
	Motor and Executive	1.50–4.00 rejected tests, "feel obligated to return part way to experimenter's world to report". "Your world can't begin to compete with mine."
	Mood	1.50–4.00 pleasure and excitement when not pressed to participate in testing procedures—if pressed, became hostile, . . . "like to piss on those ink blots".
		Dissociation and cognative hyperactivity continuous in modified form until approximately 2 a.m. when subject slept.
		Next day: No after effects evidenced.
Subject 2		12.35 100 gamma LSD (orally).
30 years	Proprioceptive	1.30 some tension and fatigue.
185 pounds	Perceptual	1.43 light, dark and colour sensitive.
		1.45–4.00 motion; distortion of perspective, shape, size; time and sound misperception. At one point reported "X-ray vision" (microphone did not obscure part of experimenter's arm on other side).
	Cognitive	1.55–4.15 preoccupied with visual distortions—made consistent effort with aid of drawings to explain phenomena—markedly over-simplified approach to problem.
	Motor and Executive	2.05–4.30 motor skill reduced (artist), negativistic; uncontrolled laughing; feels he is speaking with an accent (not apparent).
	Affective	1.40–4.00 Euphoria.
		4.00–4.30 insecure and suspicious.
		5.30 reluctant to go home for fear wife and family reject him in his present condition (Germanic accent).

* Kepner reference.

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		5.45 home—great feeling of relief—ate good supper, took family to band concert—bed at 11.30—slept soundly—felt fine next morning.
Subject 3		10.25 100 gamma LSD (orally).
30 years	Proprioceptive	11.00 tense, light-headed, mild nausea.
	Perceptual	12.15–1.30 mild colour sensitivity, slight motion; enjoyed for 5 minutes illusion of 6 inches of water on floor with tiny fish swimming around.
		1.15–3.30 depersonalization "real me and drugged me, which is which?"
	Cognitive	11.30 difficulty in concentration followed by preoccupation with ink blots.
		1.00–3.00 feelings of unreality and spoke of different aspects of reality and unreality, of blending—"can't distinguish".
	Motor and Executive	11.00 hyperactive—restless.
		11.30–1.00 uncontrolled laughing; irresponsible.
		1.30–3.00 feels he is weak, dependent and inadequate.
	Affective	10.45 anxious.
		11.30–1.00 Euphoria.
		1.30–3.00 depression.
		4.00–6.00 friend's home—philosophical, purpose of life; attempts to write about experience, can't concentrate, self-conscious, inadequate.
		6.00–8.00 home—room appears dismal—philosophizing continues—slept well—some carryover next day.
Subject 4		12.03 100 gamma LSD (orally).
22 years	Proprioceptive	12.30–2.00 extreme tension, nausea and fatigue.
		2.00 vomits—tension and nausea vanish; "feel full of spunk".
	Perceptual	12.40–2.00 slight light, dark, colour and noise sensitivity.
		2.00 slight motion, "reports that the ink blots look menacing".
	Cognitive	12.30–2.00 concentration difficult due to extreme nausea and fatigue.
	Motor and Executive	12.30–2.30 unsteady; poor co-ordination; restless; prior to 2.00 reluctant to participate in testing procedures—after 2.00 volunteers to do any tests we have to offer.
	Mood	12.30–2.00 anxious.
		2.00–3.30 moderate euphoria.
		4.00 returns to work—restlessness returns—lasts until 8.30; ate supper; retired at 10.00 and slept well. No after effects following day.
Subject 5		12.45 100 gamma LSD (orally).
19 years	Proprioceptive	1.04 200 mgm. nicotinic acid (i.v.).
		1.07 no feeling of flush or heat from niacin (he did flush).
		1.25 tenseness; dizzyness; slight nausea.
		2.00–4.30 periodic tenseness.
	Perceptual	1.40 "blurring sensation"; size of hands change on suggestion; "seem to be in a second story room" (basement room actually); depersonalization; "nothing's real, everything's blurry, I'm blurry".
		1.50–4.15 "blurriness" in all perceptual spheres; some disorientation.
		3.00 reports "everything became normal for a few seconds—then I was back in this dream world again". "Can't tell what's real."
	Cognitive	2.15–4.15 "dream world—Alice in wonderland world"; dissociation; "what I see and hear and think doesn't fit together, doesn't make sense"; loses "experimental" frame of reference for a short time.
	Motor and Executive	1.25 shaking.
		2.30 asocial—anti-social tells doctor he had never seen that he was a "funny looking duck"; feels loss of control; runs down corridor to get back to "real" world.
	Affective	1.40 very mild euphoria.
		2.15–4.15 shifts in mood from "dreamy relaxation", to panic and anxiety.
		4.15–8.00 gradual decrease in disorientation and confusion —becomes philosophical—purpose of life—not hungry—bed at 9.00 slept well—some "blurriness" next morning—normal by noon.