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Psychological Response to *d*-Lysergic Acid Diethylamide and Its Relationship to Adrenochrome Levels

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d-Lysergic acid diethylamide-25 (LSD) causes psychological changes in normal people that closely resemble the experiences described by some sufferers from schizophrenia. Those authorities who deny this have based their objection on a comparison of the first or second experience of volunteers for LSD with well-established schizophrenia where the symptoms have been present for months and years. It seems more logical to compare either the first LSD experience with the early stages of schizophrenia of rapid onset or the LSD experience of volunteers who have used it several times with schizophrenia of longer duration. When this is done the analogy is much closer.

Although it is rarely emphasized, the psychological study of this hallucinogen, as with that of mescaline, has far outdistanced our understanding of the meaning of the biochemical and physiological responses to taking it. These biochemical and physiological responses have still to be related to the psychological changes in some comprehensible manner. At least three biochemical hypotheses based upon some known in vitro and in vivo properties of LSD can be developed. First, because LSD is a potent antiserotonin, using uterine muscle as an indicator, it has been suggested that there is an analogous activity in the brain, which is known to contain serotonin. However, since other LSD isomers and brom-LSD, which are not hallucinogenic, are more strongly antiserotonin in the same test system, this suggestion seems implausible. Second, LSD, a potent acetylcholine esterase inhibitor, elevates brain acetylcholine levels. Other substances that are esterase poisons, such as diisopropyl fluorophosphonate and others, also produce remarkable psychological changes. Yet this in itself can not be a main factor because brom-LSD, which is not a hallucinogen, is equally strong as an esterase poison. Third, there may be some interference in the intermediary metabolism of the sympathomimetic amines, noradrenaline and adrenaline. A substantial quantity of data suggests that this may be the key factor. Of course, biochemical changes are not as a rule isolated from other changes. One disturbance in metabolism produces changes in all the allied areas. It is likely LSD has its unique action

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because it interferes in adrenaline utilization, poisons choline esterase, and is an antimetabolite of serotonin. Similar compounds, such as *d*-iso-LSD, might share two but fail in one of these attributes and would therefore not be hallucinogenic.

The psychological change in people who are mentally ill or who are given LSD is apparently more clearly associated with adrenaline metabolism than with the parasympathetic, which in turn is more heavily involved than serotonin. Anxiety, which is a function of adrenaline secretion, may become very intense, remain moderate, or disappear within the first hour after taking an adequate quantity of LSD. During this period, plasma adrenaline levels show substantial fluctuations. Physiologically, autonomic changes are marked. A very constant finding is pupillary dilatation. This in itself is a useful index of LSD activity. One of the major sites for the production of adrenaline, the adrenal medulla, shows an increase in metabolic activity, i.e., the radio phosphorus uptake is markedly increased. This is specific for the medulla since there is no comparable change in the cortex.

Adrenochrome and adrenolutin are readily formed from adrenaline in vitro[10] using either plasma or enzymes extracted from biological tissue. It would be surprising if similar activity did not occur in vivo. In fact, these substances have been extracted from human and animal tissues. Furthermore, it has long been suggested that there is a relationship between adrenaline and pigmentation. Pigment formation must be through some preliminary indole reaction followed by polymerization. Finally, they produce psychological changes in man and behavioral change in animals. The evidence is reviewed by Hoffer and Osmond,[8] where references for these statements are given.

Adrenolutin in normal volunteers produced changes in phosphate excretion similar to those induced by LSD.

We have examined further the possible relationship of LSD to adrenaline metabolism by: (1) measuring the effect of LSD on adrenaline oxidase,[10] (2) measuring the effect of LSD on in vitro conversion of adrenaline to adrenolutin, (3) measuring the in vivo plasma adrenochrome levels after administration of LSD, brom-LSD, and lysergic acid morpholide (LSM).

METHOD

The activity of adrenaline oxidase was determined by measuring the conversion of adrenaline into adrenolutin.[4] Adrenochrome was measured by converting adrenochrome in the plasma to adrenolutin and determining the fluorescence in the Farrand spectrofluorometer (excitation at 405 μ, emission maximum at 500 μ).[9] The ascorbic acid factor was measured in the manner described by Hoffer.[5] This factor is a measure of the bleaching of plasma by ascorbic acid after incubation with adrenaline. Adrenochrome was synthesized by Heacock et al.[3]

Our subjects were healthy normal volunteers, who received payment, and physically healthy alcoholics (character disorder and psychopathy), who received these compounds for therapy.[1, 11]

Blood was drawn in the morning, while fasting, into heparinized flasks. The subjects were then given 100 to 300 μg. of LSD, and blood samples were taken at intervals during

TABLE I

Effect of d-LSD-25 and of Various Diagnostic Groups on Conversion of Adrenaline into Adrenolutin and into AAF

Group	Number	Adrenolutin O.D.* at 395		Ascorbic acid factor bleaching at 420	
		Mean	Range	Mean	Range
Alcoholics, LSD					
0 time	5	0.36	(0.24-0.62)	0.17	(0.01-0.41)
2 hours	5	0.48	(0.21-0.94)	0.27	(0.05-0.54)
5 hours	5	0.40	(0.39-0.62)	0.24	(0.10-0.53)
7 hours	5	0.36	(0.25-0.49)	0.24	(0.12-0.34)
Normal	18	0.30	(0.17-0.45)	0.10	(0.01-0.29)
Nonschizophrenic	15	0.31	(0.15-0.42)	0.07	(0.02-0.24)
Schizophrenic					
Before treatment	13	0.35	(0.08-0.54)	0.21	(0.05-0.36)
After treatment	11	0.35	(0.17-0.49)	0.06	(0.02-0.11)
Surgical					
Before operation	28	0.36	(0.24-0.69)	0.13	(0.03-0.35)
During operation	12	0.43	(0.26-0.61)	0.22	(0.02-0.50)

* Optical density measured in spectrophotometer.[4]

and after the experience. In some instances, normal volunteers were treated before and/or during the experience with large quantities of ascorbic acid. During the whole experience every subject was carefully observed by a trained psychiatrist.

RESULTS

Effect of LSD upon Adrenaline Oxidase. The effect of LSD upon adrenaline oxidase activity (conversion of adrenaline into adrenolutin) is shown in table I. LSD increased the ability of plasma to convert adrenaline to adrenolutin. The ascorbic acid bleaching factor was also increased from 0.17 to 0.27 at two hours. The same table shows adrenaline conversion values and ascorbic acid factor for volunteers, psychiatric patients, and non-psychiatric patients before and during surgical operation. Schizophrenic and surgical patients before operation had a little more adrenaline oxidase than normal and nonschizophrenic controls. The highest concentration was found when blood was drawn during operation. These high values are probably due to slight hemolysis of the erythrocytes due to surgical trauma. Small quantities of freshly liberated hemoglobin catalyzes the conversion of adrenaline to adrenolutin.[5, 10]

Patients about to undergo surgery are usually apprehensive. This might account for the increases in their adrenaline oxidase. These values were comparable to the initial values in the 5 alcoholics before receiving LSD. The two hour LSD values are higher than those found in patients undergoing surgery. This cannot be entirely due to stress, for many patients who have been given LSD are quite relaxed and at ease two hours after

it has been administered. It is probably due to a direct effect of LSD on adrenaline oxidase concentrations in blood.

There is a good relationship between the ascorbic acid factor (AAF), diagnosis, stress,

TABLE II

Effect of d-LSD-25 on Adrenochrome and on Experience

	Adrenochrome			Experience				
	Init.	Max.						
Subject	μg./liter		Change, %	Anxiety	Perception	Paranoid	Affect	Withdrawal
Mrs. Y.A.								
First	92	84	−9	Intense	Slight	−	−	−
Second*	84	135	+61	Slight	Moderate	−	−	−
Third	78	171	+119	Moderate	Moderate	+	−	−
Mr. M.A.	194	190	−2	Intense	Slight	−	−	+
Mr. K.A.	62	131	+111	Moderate	Moderate	+	−	+
Miss J.E.	22	71	+223	Moderate	Moderate	+	−	+
Miss D.O.								
First	61	30	−50	Intense	Slight	−	−	+
Second*	44	122	+177	Slight	Moderate	−	−	−
Mr. R.O.	45	81	+80	Moderate	Moderate	+	−	+
Mr. N.O.								
First	48	91	+89	Intense	Slight	−	−	−
Second*	47	125	+163	Moderate	Moderate	−	−	−
Miss H.A.	62	212	+242	Moderate	Moderate	+	+	+
Miss N.E.	66	106	+61	Moderate	Slight	−	−	−
Miss W.I.	88	166	+89	Intense	Intense	+	+	−
Mr. C.H.	54	346	+540	Slight	Slight	−	+	−
Mr. D.I.	76	185	+143	Moderate	Intense	−	−	−
Mr. R.Y.								
First	54	166	+208	Moderate	Moderate	−	−	−
Second	61	239	+292	Slight	Slight	−	−	−
Ascorbic acid given during or before experience								
Miss D.A.	78	105	+35	Intense	Moderate	−	+	+
Miss H.O.	83	72	−13	Slight	Intense	−	+	−
Miss E.L.	64	83	+30	Slight	Moderate	−	+	−
Miss G.A.	51	87	+70	Slight	Moderate	−	+	−
Miss O.L.†	90	236	+162	Slight	Intense	−	−	−
Adrenochrome levels in urine								
Mr. B.L.	152	231	+52	Slight	Intense	−	+	+
Mr. B.O.	220	500	+127	Slight	Moderate	−	−	−

* 10 mg. of adrenochrome given intravenously.

† Ascorbic acid only before LSD.

and LSD. Normal subjects, nonschizophrenic psychiatric patients, and schizophrenics who had been improved by treatment had the lowest quantity of AAF. Schizophrenic patients, before treatment, had AAF values comparable to patients undergoing surgery and alcoholics before receiving LSD. The highest AAF values were reached two hours after receiving LSD and then remained high up to seven hours. AAF is probably a combination of some adrenaline derivative and some plasma constituent, perhaps with hemoglobin. AAF can be increased by hemoglobin, adrenochrome, adrenolutin, or by incubating plasma with adrenaline. It is a factor that is bleached by ascorbic acid, as is adrenochrome or hemoglobin.

The Effect of LSD, 2-Bromolysergic Acid Diethylamide and LSM on Psychological State and Adrenochrome Levels. LSD produced the usual reactions in our subjects. Most alcoholics responded less and so required larger quantities to induce well-marked reactions.[1, 11] 2-Bromolysergic acid diethylamide (BOL) did not produce any LSD-like experiences (500 μg. in normals) but did produce mild increases in tension. LSM (150 μg.) did not produce any psychological changes resembling those induced by LSD. Mild anxiety similar to what we have obtained with placebo was produced. The effect of LSD upon adrenochrome plasma levels is shown in table II. Neither BOL or LSM increased adrenochrome.

TABLE III

Relationship of Increase in Plasma Adrenochrome to Aspects of the Psychological Experience

Category of change	Number	Adrenochrome levels, μg./liter		
		Initial	Maximum	Increase, %
Perceptual				
No or slight change	7	82	154	88
Moderate change	9	54	125	100
Intense change	2	82	176	114
Anxiety				
None or slight	4	61	211	246
Moderate	9	57	127	123
Intense	5	97	112	15
Paranoid symptoms				
Absent	12	72	152	111
Present	6	60	139	132
Affective change				
Absent	15	69	128	88
Present	3	68	241	254
Withdrawal				
Absent	12	66	161	144
Present	6	74	119	60

The Effect of Ascorbic Acid Given in Large Quantities Before and During LSD. Ascorbic acid decreased the intensity of the experience slightly but altered its quality. Among unsophisticated subjects LSD usually produced moderate or marked perceptual change, disturbance in thought, and marked fluctuation in mood from elation to depression, more frequently depression. With ascorbic acid, perceptual changes were not altered. Disturbances in thought were less marked, and suspicion was less evident. The ability to concentrate and appreciate the perceptual changes was heightened. Mood swings still occurred, but the subjects tended to be cheerful and/or euphoric. Four subjects took the combination and LSD alone, and they have confirmed these conclusions.

In table III subjects are grouped according to the psychological response. Perceptual changes and paranoid symptoms did not depend upon the level of adrenochrome. When the level of adrenochrome was high, much less anxiety was seen. Affective changes were marked and withdrawal less frequent with greater adrenochrome response.

When ascorbic acid was given during the LSD reaction, the level of plasma adrenochrome did not increase except for 1 subject (O.L.) who received ascorbic acid several days before and not during the experience.

Effect of LSD, d-Lysergic Acid Ethylamide, and BOL upon Conversion of Adrenaline to Adrenolutin. Although LSD and *d*-lysergic acid ethylamide (LAE) increased the in vitro conversion of adrenaline to adrenolutin, BOL had no effect. (See table IV.)

Effect of LSD and BOL on Adrenochrome Tolerance Curves. Crystalline adrenochrome dissolved in water or saline solution is quickly destroyed when injected intravenously. The rate of destruction was measured by estimating the plasma adrenochrome values, 15, 30, and 60 minutes after injecting 10 mg. The amount of plasma adrenochrome for different psychiatric conditions and after pretreatment with LSD is shown in table V.

TABLE IV

Effect of LSD, LAE, and BOL upon Conversion of Adrenaline to Adrenolutin in Vitro

	Formation of adrenolutin as measured by increase in optical density at 395 μ			
		d-LSD-25, 50 gamma	LAE, 50 gamma	BOL, 50 gamma
Subject	Control	% change		
1	0.250	+64	+32	—
2	0.210	+37	+62	—
3	0.240	+12	+42	—
4	0.352	+12	+26	—
5	0.256	+10	+22	—
6	0.410	—	—	−11
7	0.332	—	—	0
Mean	0.260	+27	+37	−6

TABLE V

Relationship of Adrenochrome Tolerance to LSD and BOL

Group	Treatment	Number	Initial adrenochrome	% change		
				15 min.	30 min.	60 min.
Not schizophrenic	None	9	51	+170	−45	−22
Schizophrenic	None	6	43	+280	+75	+107
Not schizophrenic	LSD (35 μg.)	6	43	+260	+100	+67
Not schizophrenic	LSD (100 μg.)	2	46	—	—	+170

In nonschizophrenic subjects all the injected adrenochrome was destroyed within 30 minutes. However, in schizophrenics, 60 minutes after injection the plasma levels were twice the base line level.

Normal volunteers in whom all the adrenochrome was destroyed in 30 minutes in a previous experiment were given 35 μg. of LSD by mouth and the adrenochrome injected two hours later. One hour after the injection some of the adrenochrome was still circulating. It would appear that the reduced ability of schizophrenics to destroy adrenochrome is equal to the effect of 35 μg. of LSD. Perhaps we can use this adrenochrome tolerance test to develop a titer for schizophrenia. After 100 μg. of LSD, the ability to destroy adrenochrome was markedly reduced. BOL did not alter the adrenochrome tolerance.

DISCUSSION

We define a good LSD experience as one in which insight is maintained and during which the subject feels he has been drawn closer to humanity and away from autism. This may be associated with vivid perceptual changes, especially during the first or second experience, but may occur in the absence of visual changes.

We have found that "good" experiences seem to be associated with substantial increases in plasma adrenochrome levels. The subjects were less anxious and were aware of fluctuations of mood from depression to euphoria with little tendency to withdraw from other people in the experimental setting. When plasma adrenochrome levels did not increase, the subjects remained very anxious and tense. In some instances the tension was of psychotic proportions. They complained primarily of depression and found it difficult to participate with other subjects. Paranoid thinking and visual changes occurred independently of adrenochrome levels.

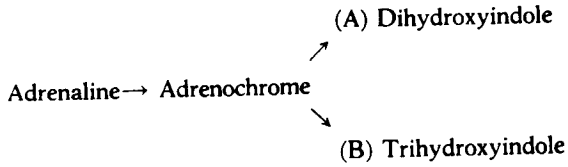
Alcoholics treated with LSD do better clinically after an intense experience (little anxiety).[6, 11] Alcoholics and other subjects subject to great tension or subjects especially tense before receiving LSD tend to become more tense or depressed and usually do not benefit from the experience. Giving them more LSD does not necessarily produce a better reaction but may increase the tension. Much of the tension may be removed by the intravenous injection of adrenochrome or adrenolutin. This allows the more desirable aspects of the reaction to appear. Subject Y.A. was very anxious the first time she received LSD.

Two hours after getting LSD the second time, she was given 10 mg. of adrenochrome. The third time she received LSD, several weeks later, she was relatively free of anxiety. Subjects D.O. and N.O. also received 10 mg. of adrenochrome two hours after LSD. In each case intense anxiety with slight perceptual change was replaced by slight or moderate anxiety and an increase in perceptual change.

Since the plasma adrenochrome value is clearly related to the psychological experience after LSD, it seems likely that it is the intermediate by which LSD acts. BOL, which like LSD antagonizes serotonin and poisons choline esterase, has no effect on adrenochrome levels.

Adrenochrome is converted in vitro by many reducing substances into at least two classes of compounds: (1) dihydroxyindoles and (2) trihydroxyindoles.[2] The major dihydroxyindole is 5,6-dihydroxy-N-methylindole. Melander[7] found that adrenochrome reduced by ascorbic acid is not psychotomimetic for animals. We have found in a large series of tests with volunteers that this pure indole is not psychotomimetic. Adrenolutin is the best-known example of the trihydroxyindoles. It is a pale yellow highly fluorescent psychotomimetic substance. In vivo, adrenochrome may thus be converted into either the dihydroxy or trihydroxy series depending upon the biochemical conditions.

These changes can be shown diagrammatically thus:



We suggest that reaction A is the preferred pathway, and that LSD poisons the enzyme that catalyzes this reaction. As a result there is: (1) An increase in adrenochrome since it is not destroyed so quickly and the excess appears in blood and urine, (2) some diversion of the adrenochrome into adrenolutin, and (3) consequently a decrease in the rate of destruction of injected adrenochrome. This inhibition probably occurs in the brain as well as peripherally.

The psychological experience produced by LSD continues long after practically all the compound has been either destroyed or excreted. If the suggestion that the enzyme necessary to reaction A is poisoned is correct, then it would account for the prolonged psychological reaction. Many natural enzymes are regenerated rather slowly.

Ascorbic acid converts adrenochrome into both types of compounds. It therefore prevents any increase in concentration of adrenochrome without interfering with the production of adrenolutin and the other indoles. This may be why large quantities of ascorbic acid do not inhibit but merely alter the nature of the LSD experience. It is also possible that ascorbic acid has less effect upon intracellular adrenochrome in the brain and elsewhere than upon extracellular adrenochrome.

Ascorbic acid altered the experience by decreasing depression, withdrawal, and paranoid

thinking. Perhaps these psychological reactions are a function of adrenochrome concentration rather than of adrenolutin.

SUMMARY AND CONCLUSIONS

d-Lysergic acid diethylamide-25 elevates plasma adrenochrome, reduces the ability of the blood to destroy adrenochrome, and increases the conversion in vitro of adrenaline into adrenochrome and adrenolutin by plasma. 2-Bromolysergic acid diethylamide has no effect on adrenochrome. We therefore suggest that *d*-lysergic acid diethylamide-25 inhibits an enzyme responsible for the conversion of adrenochrome into dihydroxyindoles.

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RESUMEN

El compuesto ácido *d*-lisérgico-diatilamida-25 eleva el adenocromo del plasma, reduce la capacidad de la sangre para desintegrar el adrenocromo y aumenta la proporción de conversión del plasma, *in vitro*, de la adrenalina en adrenocromo y adrenolutina. El ácido 2-bromo-lisérgico-dietilamida no ejerce acción alguna sobre el adrenocromo. Por esto, sugerimos que el ácido *d*-lisérgico-dietilamida-25 inhibe una enzima responsable de la conversión del adrenocromo en dihidroxiindoles.

RESUME

L'acide *d*-lysergique-diéthylamide-25 élève l'adrénochrome du plasma, réduit la capacité du sang à détruire l'adrénochrome et à augmenter *in vitro* la conversion de l'adrénaline en adrénochrome et en adrénolutine par le plasma. Le diéthylamide de l'acide 2-bromolysergique est dépourvu d'action sur l'adrénochrome. En conséquence, nous présumons que l'acide *d*-lysergique diéthylamide-25 inhibe un enzyme responsable de la conversion de l'adrénochrome en dihydroxyindoles.

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Annual Workshop in Projective Drawings

The 1959 Annual Workshop in Projective Drawings, to include the House-Tree-Person, Draw-A-Person, Draw-A-Family, Unpleasant Concept, Draw-An-Animal, and Eight Card Re-Drawing tests, and doodles, will be conducted at the New York State Psychiatric Institute, New York City, by Emanuel F. Hammer, Ph.D., and Selma Landisberg, M.A., July 27 through July 30, 1959, from 9:30 a.m. to 12 noon and from 1:30 p.m. to 3 p.m. daily. The workshop will provide a grounding in fundamentals, advanced considerations of differential diagnosis, psychodynamic appraisal, psychological resources as treatment potentials, and the application of drawings in therapy. Requests for information on admission or requirements should be addressed to Miss Selma Landisberg, 116 East 35th Street, New York 16, N. Y.

Karen Horney Award

The Association for the Advancement of Psychoanalysis announces the establishment of the Karen Horney Award. The purposes of the award are twofold: The first is to commemorate Karen Horney, who, pioneering in the integration of various scientific disciplines, deepened our understanding of human motivation, and who was a founder of the American Institute for Psychoanalysis and of the Association for the Advancement of Psychoanalysis. The second is to stimulate research in the theory and practice of psychoanalysis and to underline the new developments in psychoanalysis and related sciences. The award will be in the amount of $150 and will be made to the author whose paper makes such a contribution to the advancement of psychoanalysis. The paper will be published in the *American Journal of Psychoanalysis*, the journal of the association, and should be submitted by October 31, 1959. The award will be presented at the time of the Karen Horney Memorial Lecture, which usually is given in March. Entries should be forwarded to Louis E. Rosis, M.D., Chairman, Award Committee, 815 Park Avenue, New York 21, N. Y.