PSYCHOPHYSIOLOGICAL INVESTIGATIONS IN EXPERIMENTAL PSYCHOSES: RESULTS OF THE EXHIBITION OF D-LYSERGIC ACID DIETHYLAMIDE TO PSYCHIATRIC PATIENTS.

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[Received 10 June, 1953.]

D-Lysergic acid diethylamide (L.S.D.-25) was first prepared by Stoll and Hoffmann in 1938 (35) as a derivative of rye ergot. Its profound effects in minute doses were discovered accidentally by Hoffmann and reported by Stoll (34) along with additional observations by the latter on 16 healthy controls and six schizophrenic patients. With a dose of 30–130 γ (0·03–0·13 mgm.) Stoll (34) noted motor inco-ordination, disturbances of visual perception with illusions and hallucinations, clouding of consciousness, and affective changes principally in the direction of euphoria and distractibility. Subsequent clinical reports have confirmed these findings (6, 38). Becker (1) using doses of 30–40 γ in healthy controls attempted to predict the quality of the resulting psychosis from the constitutional somatotype of the subject; he contrasted maniacal hyperkinetic states with those showing inhibition and depersonalization and drew attention to the pattern of the visual perceptual disturbances, which were principally those of differences in size, clarity and perspective. Becker's attempts at somatotypological correlation were less successful than those of Condreau (4) who used mentally ill patients as well as healthy subjects and found that L.S.D.-25 did tend to reinforce pre-existing personality characteristics, especially with regard to mood changes. Rinkel and others (30, 7) with doses of 20–90 γ in mixed healthy and psychiatrically disturbed populations stressed the scotopic nature of the hallucinations and the greater frequency of illusions of rippling or wavy lines evolving at times into geometrical designs. Affective blunting with a lack of spontaneity was commoner than the production of major delusions. In epilepsy apparently visual hallucinations are more frequently concomitants of L.S.D.-25 administration than in other mental disorders (31).

Comparison of the effects of d-lysergic acid diethylamide with other agents producing experimental psychoses has been made (9, 39, 13, 38). With doses of 10–120 γ L.S.D.-25 and 0·4–0·6 gm. mescaline in schizophrenics (13), similar qualitative effects were found with both drugs although the changes were considered quantitatively greater with mescaline. Fischer and others (9)

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reported essentially similar findings using doses of 130 γ L.S.D.-25 and 0·5 gm. mescaline, but suggested that the new drug evoked a clinical picture resembling much of the phenomenology of hebephrenia while the mental state in mescaline intoxication was more akin to that of paranoid schizophrenia with catatonia.

Aside from such clinical descriptive studies, some physiological work has been carried out. A pilot study of six schizophrenic patients using ascending doses of 0·5–6·0 γ per kg. body weight (10) showed a leucocytosis but no constant change in the E.E.G., E.K.G., blood N.P.N., liver function tests or urine. Arterial blood pressure and pulse rate tended to be slightly raised and the blood sugar showed a slight elevation of 5–6 mgm. per 100 c.c. Respiration was apparently unaffected but salivation and lacrimation increased and the pupils frequently showed dilatation. A similar lack of response of the blood N.P.N. and the blood sugar, and of the arterial blood pressure and body temperature was noted by Busch and Johnson (2). Rinkel and others (30) observed a tendency towards an increase in the alpha frequency of the E.E.G. by some 1–3 c./sec. Fischer and others (9) found a normal response to the hippuric acid excretion test for L.S.D.-25 as opposed to evidence for impaired liver function after mescaline intoxication using Quick's test. The cinnamic acid test, however, yielded abnormal results for L.S.D.-25 in their hands.

Investigation of the carbohydrate metabolism (25) indicates that L.S.D.-25 administration is followed by an increase in blood glucose and hexosemonophosphate but no change in lactate or pyruvate levels. An increase in glycogen metabolism together with a block in the breakdown of hexosemonophosphate is therefore a possible mechanism of action of L.S.D.-25.

Psychological studies of the lysergic acid psychosis have been made by Stoll (34), de Shon and co-workers (7) and by Matefi (24). Characteristically schizophreniform Rorschach responses were obtained with evidence on other tests of impaired emotional inhibition and tangentiality of thought.

The present psychophysiological investigation was designed in the hope that some of the clinical findings reported in the literature might yield to objective methods of study. In the sense that the deliberate production of an iatrogenic psychosis represents a model experiment, new knowledge of the mechanisms of action of idiopathic psychotic states may follow upon such investigations.

Experimental Procedures.

Clinical Material.

A total of 33 subjects were studied. Of these 14 were healthy controls of a mean age of 28 and an age range of 20–40 years. There was an equal number of males and females. All were volunteers (with the obvious bias of such selection) and all were psychiatrically sophisticated since they represented medical psychiatric colleagues and members of the nursing, occupational therapy and research departments of the Hospital.

The remaining 19 subjects were psychiatric in-patients of the Maudsley Hospital. They comprised seven male schizophrenics with a mean age of 28 and a range of 20–32 years. This group included four paranoid schizophrenics, one catatonic, one case of hebephrenia and one of dementia praecox simplex.

The remaining 12 patients suffered from affective disorder—depression. There were nine males and three females and the age range was 23–56, with a mean age of 41 years. The diagnoses in this group ranged from those with comparatively mild reactive depressions through one example of a severe endogenous depression and another complicated by obsessive compulsive complaints up to two patients in whom severe symptoms were linked with delusions and suicidal pre-occupation. Anxiety was not a marked finding in any of the group, all of whose primary symptoms of depression had been sufficiently impelling to demand admission to hospital.

Method.

d-lysergic acid diethylamide was given by mouth to the fasting subject in the form of the freshly prepared tartrate, and in a dose of 40 γ. Additional higher doses up to 120 γ were given to a selected few of the patients, but not to any of the controls. In the case of three of the controls a placebo was administered under identical conditions to those in which the drug was employed.

The subjects were investigated at intervals throughout the period of maximum action of the L.S.D.-25 (i.e., 2–4 hours after its exhibition) and during this time the results of a formal mental-state examination were recorded. A comparable control period of observation was arranged for each subject either one week before or one week after the day on which the drug was given. The subjects were randomized for this purpose and it was hoped that such a procedure might minimize the effect of practice on the scores.

In addition to the mental-state examination, behavioural change was recorded on a modified Maudsley Hospital Behaviour Chart and scored under the headings of speech and thought, motor activity and general behaviour. Mood was rated separately on a five-point scale. Objective and subjective judgments were recorded separately.

A routine neurological examination was made and estimates of the pulse rate, arterial blood pressure and body temperature were made regularly throughout the period of observation.

Psychological Investigations.

Attention and concentration were tested by a battery consisting of the timed "serial sevens," digit retention [from the Wechsler-Bellevue Scale (37)] and a modification of Wittenborn's (40) remembered numbers test. *Memory* was assessed by the Wechsler Memory Scales and by the recall of a name, address and message after a period of five minutes. *Fluency, imagery and emotional lability* were estimated from the responses to cards I, II, IV and X of the Rorschach and Behn-Rorschach series given in two parallel sets, randomization of the subjects being carried out to determine which set should be used first. *Speed of oscillation* (11, 3) was measured in terms of the number of reversals noted passively in a four-inch square Necker cube during a 30-second period of observation. Active and inhibited scores were also determined by instructing the subject to attempt maximally to speed the reversed rate and

then similarly to slow it. *Eidetic imagery* tests (14) were employed to elicit the total duration of the stimulus after-image under controlled conditions, the time during which the after-image has well-defined outlines, the differentiation between the eidetic- and after-image by Emmert's law, the density of the after-image, and "latent" eidetic phenomena. Since perceptual anomalies brook large in the clinical descriptions of the L.S.D.-25 psychosis, all subjects were additionally requested to report their visual sensation both with their eyes closed and later whilst pressure was applied to the globes. A number were taken into a darkened room and a few had music played over to them in an (unsuccessful) attempt to produce synaesthesiae. Assessments of *duration of the passage of time* were made by the subjects following the instruction to estimate four separate periods of 15 seconds; their scores were taken as the mean of these estimates. *Motor efficiency and time duration* were assessed by Kraepelin's test in which the subject is asked to tap with the point of a pencil as quickly as possible on one side of a piece of quarto paper. The test is interrupted at the end of 15 seconds and is then repeated using the other hand on a fresh sheet of paper for a similar period. The score is recorded as the combined total of taps for each hand. At the conclusion of each period of tapping the subject was asked to estimate the length of time he had been tapping the paper.

Physiological Observations.

Spectroscopic oximetry.—The "reduction time" (36, 27) of the arterialized capillary blood in vessels of the skin of the finger nail fold was estimated by a method already described by one of us in detail elsewhere (19). Results are expressed as R.T. secs. and are capable of conversion into equivalent arterial oxygen saturation percentages (18). Combination of the resting levels with the results of such oximetric measurements understand ardized apnoeic stress results in the calculation of an R.T. "efficiency score" (28) and a knowledge of these two dimensions of the oximetric response represents an objective technique for determination of psychiatric diagnosis (19), evaluation of the emotional state (20) and of assessing differential perceptual response patterns (21, 33). Resting levels and efficiency scores were measured in all subjects of the investigation and the results with and without the drug compared. In addition, oximetric determinations were combined with other psychophysiological procedures (*vide inf.*).

Cardiovascular response to stress.—The Hines-Brown (12) cold pressor test was modified to extend the time of immersion of the hand to three minutes, since pain seems to be the evocative stimulus in this test (42) and it has been shown that pain is maximal within such a three-minute period (41). Arterial blood pressures were estimated sphygmomanometrically as frequently as possible during the time of the test and continued until three consecutive readings at the pre-test level were recorded, or until ten minutes had elapsed after removal of the hand from the ice-water. In several experiments these blood pressure recordings were combined with concurrent spectroscopic oximetric estimations, readings being similarly continued until pre-test conditions had again been attained.

Oxygen consumption and spirometry.—A Benedict-Roth metabolism apparatus was employed to measure the resting metabolic rate and oxygen consumption per minute. Recordings were taken with the subject in a fasting condition and after he had been lying down comfortably for 30 minutes. The tracings were analysed also to determine the respiratory rate and pattern after the method of Finesinger (8) which involves the summation of seven readily determined variables into a numerical score.

The Controlled Stress Test (*C.S.T.*).—This procedure designed (22) from C. G. Jung's (15) discrete word association test and Rapaport's (26) more recent modification of it, consists of the presentation of parallel series of 15 potentially traumatic and neutral words, Rorschach cards and T.A.T. pictures as stimuli to the subject, oximetric determinations being made and reaction times taken at the moment of the subject's response.

Statistical Analysis.

In view of the relatively small number of subjects employed in this investigation, the u test of Lord (16) was computed for purposes of evaluation of the results. This statistical procedure is based on range estimates of standard deviation of the t test.* The use of range estimates sacrifices some of the efficiency of root mean square estimates, but the work of Davies and Pearson (5) suggests that information is not discarded to any serious extent, provided that the number of observations in the sub-samples is not greatly in excess of ten.

RESULTS.

Clinical State.

The findings here are summarized in Table I. They may conveniently be grouped under the following headings :—

Physical signs.—The only frequent physical signs noted were flushing of the face, enlargement of the pupils without impairment of the light or convergence reactions, and unsteadiness of gait and co-ordination which, whilst a frequent subjective complaint, was minimal and never amounted to clinical ataxia. Temperature and blood pressure showed slight and inconstant changes. Complaints of nausea or dry mouth with sensations of chilliness alternating with hot flushing were also common. These physical findings occurred with equal frequency in all groups.

Mental state.—Overt behaviour showed little change in any of the groups, although of the controls four were rated as overactive compared to only one before, and three as underactive. However, many of the subjects, if unstimulated by questions and testing, tended to sit quietly in a soporific manner, but this was never of a sufficient degree to be regarded as withdrawal. Speech was unchanged in both groups of patients and equally increased or decreased in the controls. Mood proved to be a significant variable. The outstanding

* Lord's u is given by $\frac{\Sigma D}{NR}$ where the numerator is the summation of the individual differences and the denominator represents the number of individuals in the group expressed as a multiple of the extent of range deviation summed algebraically.

TABLE I.—*Differential Incidence of Clinical Changes Evoked by L.S.D.-25 Administration in Healthy Controls and Patients with Two Types of Psychiatric Disorder.*

		Healthy controls (10)		Schizophrenics. (6)		Depressives. (12)		Totals. (28)	
		Control period.	L.S.D.-25.	Control period.	L.S.D.-25.	Control period.	L.S.D.-25.	Control period.	L.S.D.-25.
Speech and thought	Deluded	0	0	4	4	2	2	6	6
	Speaks little	1	4	2	2	7	8	10	14
	Speaks much	2	4	1	1	0	0	3	5
	Perplexed	0	0	0	0	0	3	0	3
Activity and behaviour	Foolish giggling	0	5	1	3	0	1	1	9
	Withdrawn and preoccupied	1	3	3	4	6	6	10	13
	Overactive	1	3	1	1	0	0	1	4
	Underactive	1	4	2	3	6	7	9	14
Mood	Suspicious	0	2	0	0	1	1	1	3
	Rapid mood change	1	4	0	0	0	0	1	4
	Depressed	0	2	1	2	12	8	13	12
	Overcheerful	0	6	0	3	0	1	0	10
	Less depressed	0	0	0	0	0	3	0	3
	Anxiety	0	1	1	0	1	3	2	4
Physical	Flushing	0	3	0	3	0	6	0	12
	Enlarged pupils	0	0	0	4	0	9	0	19
	Unsteadiness	0	1	0	0	0	3	0	4
Subjective	Nausea	0	3	0	0	0	1	0	4
	Dry mouth	0	3	0	0	0	4	0	7
	Hot/chilly	0	2	0	1	0	1	0	4
	Unsteadiness	0	6	0	3	0	1	0	12
	Sleepy	0	3	0	3	0	1	0	7
	Forced laughter	0	5	0	2	0	0	0	7
	Time slowed	0	2	0	0	0	1	0	3
	Well being	1	6	0	3	0	1	0	10
	Visual illusion	0	4	0	0	0	0	0	4
	Lack of concentration	0	4	1	2	0	1	1	7
	Apprehension	0	2	0	0	0	5	0	7

effect in both controls and schizophrenics was a euphoriant one, combined with a subjective feeling of well being and episodic foolish and rather forced laughter. However, in the group of depressives this reaction was only shown in one patient, although three others showed some slight lightening of mood. Contrasting with these, two of the controls showed slight depression. Where anxiety and tension were originally present they were heightened and in no case diminished. Where delusions were present they remained unchanged but no fresh ones were produced. Increased suspiciousness was shown by a few subjects both amongst patients and controls, but this never extended to persecutory ideas. Where aural hallucinations were present these were also unchanged, but neither fresh aural nor visual ones were produced. Four of the controls complained of unformed visual illusions usually consisting of flickering lights with an heightened perception both for intensity of illumination and colour. In no case were such visual changes impressive. In all cases there was complete retention of insight, any effects produced being attributed to the drug by both patients and controls.

The Effect of a Placebo.

The changes manifested by the three members of the control group to whom this was given appeared to be directly related to their degree of "clinical sophistication." Thus the first produced complaints of depression, lability, which he likened to alcoholic intoxication, restriction of the lateral fields of vision, slight deafness, dulling of smell, feelings of pressure and fever, loss of libido and of

sense of time combined with difficulty in thinking and of finding correct words. The second, with less knowledge, merely complained of a sense of intoxication with difficulty in concentration and the finding of words, whereas the third, with little knowledge of the expected reaction, noticed no untoward changes. The test scores of these three, however, were not significantly altered in any measures.

Psychological State.

Attention and concentration.—The mean time for performing the serial sevens test was increased in all groups without however appreciable impairment of accuracy. Statistical analysis showed these increases to be significant at the 5 per cent. level of confidence for both the normals and the schizophrenics. In the concentration test there was a slight increase of score in the normals with a decrease in the schizophrenics and depressives, but these changes were not significant. Table II gives the data on these two tests.

TABLE II.—*Effect of L.S.D.-25 on Attention and Concentration.*

Test.	Group.	N.	Mean scores. Control period.	L.S.D.-25.	Difference.	"t"	P.
Serial sevens (time in seconds)	Controls	10	29·9	34·7	+4·8	0·23	5%
	Schizophrenics	5	47	57	+10	0·68	2%
	Depressives	8	60	65	+5	0·11	N.S.
Serial sevens (errors)	Controls	10	0·2	0·2	0	—	—
	Schizophrenics	5	1	1·6	+0·6	0·6	2%
	Depressives	8	1	−0·36	−0·36	0·04	N.S.
Concentration	Controls	10	54·2	58·7	+4·5	0·08	N.S.
	Schizophrenics	5	50·6	43·8	−6·8	0·42	N.S.
	Depressives	10	43·6	38·3	+5·3	0·12	N.S.

Memory.—The effect of the drug on visual memory scores was to show a slight and insignificant decrease in all groups which was maximal in that of the depressives. There was no significant decrease in the accuracy of recall of a message, although such a response tends to be global and unsuited for the detection of small changes of memory. Digit retention showed no significant change in any group. Table III lists the data on these tests.

TABLE III.—*Effect of L.S.D.-25 on Memory.*

Test.	Group.	N.	Mean scores. Control period.	L.S.D.-25.	Difference.
Visual memory	Controls	10	13·8	13	−0·8
	Schizophrenics	5	12·6	11·2	−1·4
	Depressives	10	9	5·8	−3·2
Digit retention	Controls	10	14·4	14·1	−0·3
	Schizophrenics	5	11·2	11	−0·2
	Depressives	10	10·7	10	−0·7
Errors of recall	Controls	10	0·3	0·3	0
	Schizophrenics	5	0·2	0·2	+0·2
	Depressives	10	0·25	0·6	+0·37

Time.—Estimation of duration showed a slight but insignificant mean reduction in normals and in depressives, i.e., time appeared to pass more quickly (Table IV).

TABLE IV.—*Effect of L.S.D.-25 on Apparent Duration.*

Group.	N.	Mean scores (seconds). Control period.	L.S.D.-25.	Difference.
Controls	5	13·4	11·2	−2·2
Depressives	8	8·4	7·7	−0·7

Oscillation.—There was no significant difference in rate or in ability to change the frequency of reversal in either the controls or depressives on whom the test was performed. The subjects used were too few to make any valid correlations with mood change (Table V).

TABLE V.—*Effect of L.S.D.-25 on Rate of Reversal of Necker's Cube.*

Test.	Group.	N.	Mean scores—Reversals/min. Control period.	L.S.D.-25.	Difference.
Passive	Controls	3	11	9·4	−1·6
	Depressives	7	9	8·2	−0·8
Active	Controls	3	22	18·6	−3·4
	Depressives	7	11·4	11·4	0
Inhibited	Controls	3	8	5·4	−2·6
	Depressives	7	6·4	6·4	0

Rorschach.—Measurements of the total number of responses, the number of human responses and the sum of the weighted colour responses were undertaken.

In the control group, five subjects showed an increase in their number of responses under lysergic acid and five a decrease. This change did not appear dependent on whether the control record followed or preceded the one under the drug. It should be noted that, in all cases except one, the subjects showed fewer responses on the Behn cards than on the Rorschach ones. The number of human responses decreased in three cases, remained the same in five and increased in two. The sum of weighted colour decreased in three cases, remained the same in two and increased in five. Four of the six subjects who were clinically rated as overcheerful gave this increased response. A qualitative comparison of the records again showed no marked trends of change: two of the subjects gave much poorer records in terms of fantasy and two brought up many more sex responses.

Of the eight members of the depressive group who completed the test, only one showed an increase of the total number of responses, whereas four showed a decrease. None increased in the number of movement responses, whereas three decreased. The sum of the weighted colour increased in three cases, decreased in one and was the same in the other four. These three who increased included the patient who was clinically rated as overcheerful and one of the two who were considered to be less depressed under the drug. However, of

the four patients who refused one or more cards on the control day, only one refused a card when under the drug and even she one card only, whereas before she had refused two. This might indicate some greater degree of participation or interest in the task.

In the six schizophrenics the changes were random and inconsistent and there was no relationship between weighted colour responses and mood.

Controlled Stress Test: Reaction times.—In the normals the mean speed of response to stimuli which were considered non-traumatic showed no consistent trend, and this was also the case in the depressive and schizophrenic group. The difference between the speed of response to traumatic and to non-traumatic stimuli was also insignificantly and inconsistently changed. Oximetric results will be considered below.

Eidetic imagery.—No subject showed eidetic imagery as judged by Jaensch's (14) criteria. The mean time of duration of the after-image showed a trend towards an increase in all groups, but this was not statistically significant. The size of the after-image conformed closely to Emmert's law both under control conditions and under the drug and again there was no significant change in the measurement (Table VI).

TABLE VI.—*Influence of L.S.D.-25 on Eidetic Variables.*

	Group.	N.	Mean scores. Control period.	L.S.D.-25.	Difference.
Duration of A.I. in seconds	Control	6	34·4	43·5	+9·1
	Schizophrenics	3	35·2	38·2	+3·0
	Depressives	9	29·0	29·9	+0·9
Mean size of A.I. at 25 cm. in cm.	Controls	6	6·6	6·9	+0·3
	Schizophrenics	3	6·5	6·5	0
	Depressives	8	6·2	6·2	0

Physiological State.

Arterial blood pressure: (a) *Systolic.*—The mean resting levels of both the depressives and schizophrenics were significantly higher than the healthy normals and there was a correspondingly greater maximal and mean rise following the pain stimulus, although this was in fact relatively smaller than in the controls. However these measures, with in addition, the mean level of fall (from five minutes to the cessation of recording), the time to return to resting levels and pulse pressure, all showed no significant variation under the drug.

(b) *Diastolic.*—The resting diastolic levels were again higher in the depressives and schizophrenics with corresponding higher mean and maximal rises after stimulation than in the controls. The relative rise (between resting level and the maximal and mean heights) was greatest, however, in the schizophrenics and least in the depressives. Again all these means with, in addition, the mean of the level of fall and the time required to return to resting level showed no significant difference under the drug.

It was interesting to note, in confirmation of the work of Malmo and Shagass (23), that the schizophrenic patients showed a normal reactivity to stress although, of course, none of these subjects was deteriorated. The detailed results are given in Table VII.

TABLE VII.—*Effects of L.S.D.-25 on the Arterial Blood Pressure in the Modified (Three Minute) Cold Pressor Test.*

			Systolic.			Diastolic.		
			Mean scores (mm. Hg.).			Mean scores (mm. Hg.).		
Measure.	Group.	N.	Control period.	L.S.D.-25.	Difference.	Control period.	L.S.D.-25.	Difference.
Resting level	Controls	10	117	116	−1	72	74	+2
	Schizophrenics	5	134	127	−7	77	76	−1
	Depressives	8	128	134	+6	81	82	+1
Maximal rise	Controls	10	148·2	143·1	−5·1	101	101·4	+0·4
	Schizophrenics	5	160·8	159·6	−1	112	116·4	+4·4
	Depressives	8	153·7	160	+6·3	100·2	102·7	+2·5
Mean rise	Controls	10	136	133	−3	91	94	+3
	Schizophrenics	5	149	147	−2	100	105	+5
	Depressives	8	141	133	−8	92	92	0
Difference—Resting level and mean rise	Controls	10	18·1	15·8	−2·3	18·8	19·7	+0·8
	Schizophrenics	5	12·4	18	+5·6	23·4	26·8	+3·4
	Depressives	8	13·8	12·9	−0·9	12·7	11	−1·7
Difference—Resting level and maximal rise	Controls	10	31·2	27·1	−4·1	29	27·4	−1·6
	Schizophrenics	5	26·8	32·6	−5·8	35	40·4	+5·4
	Depressives	8	25·7	26	−0·3	19·2	20·7	+1·5
Level of fall 5 minutes	Controls	10	117	120	+3	77	79	+2
	Schizophrenics	5	126	128	+2	76	81	+5
	Depressives	8	130	139	+9	81	84	+3
Time to fall (minutes)	Controls	10	7	7	0	7	7	0
	Schizophrenics	5	5	6	+1	6	6	0
	Depressives	8	5·7	5·7	0	5·7	5·5	−0·2
Pulse pressure	Controls	10	44·3	41·9	−2·4	—	—	—
	Schizophrenics	5	56·4	51·2	+5·2	—	—	—
	Depressives	8	45·1	50·7	+5·6	—	—	—

Spectroscopic Oximetry : (a) *Resting oximetric status.*—The effect of L.S.D.-25 on this variable was to raise the reduction time values in the healthy and depressed groups of subjects and to leave the schizophrenic patients unchanged. Lord's test showed these results to possess statistical significance ($u = \cdot 25$; $p < \cdot 05$ for healthy normals. $u = \cdot 23$; $p < \cdot 05$ for the depressed patients. $u = \cdot 08$; p is N.S. for the schizophrenics). A similar pattern of change was also observed after computation of the "efficiency score," marked rises occurring in the patients with affective disorders, lesser rises in the healthy group and no change in the schizophrenics. Table VIII gives the actual figures obtained.

TABLE VIII.—*Effect of L.S.D.-25 on Oximetric Status. The Efficiency Score is Given by* $\frac{\text{(R.T.)} - \text{(R.T. } \textit{with Apnoea)}}{\text{(R.T.)}} \times 100$ *and may therefore Result in Negative as well as Positive Quantities.*

		Mean resting oximetric status.					Mean efficiency scores.				
Group.	N.	Control period. R.T. (secs.).	L.S.D.-25. (R.T. (secs.)	Difference. (secs.).	u.	P.	Control period.	L.S.D.-25	Difference.	u.	P.
Controls	11	45·54	59·92	+14·38	0·25	0·05	+26·7	+32·4	+5·7	0·14	N.S.
Schizophrenia	7	35·00	35·60	+0·60	0·08	N.S.	+26·0	+25·0	−1·0	0·13	N.S.
Depressives	12	36·57	50·92	+14·35	0·23	0·05	+6·6	+31·6	+25·0	0·43	0·001

https://doi.org/10.1192/bjp.100.418.129 Published online by Cambridge University Press

(b) *Oximetric monitoring of the Cold Pressor Test.*—Oximetric estimations were made simultaneously with the recordings of the blood pressure. As may be seen from Table IX, the usual result of the application of cold water stress

TABLE IX. *Effect of L.S.D.-25 on the Oximetric Response to the Standardized Pain Stress Provided by a 3-minute Modification of the Hines-Brown Cold Pressor Test.*

		Oximetry before lysergic acid.		Oximetry 4 hours after 40 gamma lysergic acid.	
Group.	N.	R.T. secs.	"Efficiency score."	R.T. secs.	"Efficiency score."
Controls	11	45·538	+26·69	59·923	+32·38
Schizophrenics	7	35·000	+26·00	35·600	+25·00
Depressives	12	36·570	+ 6·64	50·923	+31·62
Totals and Means	30	39·969	+17·81	50·625	+31·156

is to produce a marked fall in the R.T. (sec.) values. Under the influence of L.S.D.-25 the extent of this fall was increased ($u = \cdot 56$; $p = \cdot 01$ for depressed patients), and similarly the duration of the fall is prolonged before pre-stress levels are again attained ($u = \cdot 37$; $p = \cdot 02$ for depressed patients).

(c) *Oximetric monitoring of the Controlled Stress Test.*—The spectroscopic oximetric responses to the potentially non-traumatic (N.T.) and to the potentially stressful (T.) stimuli were pooled for each diagnostic group both for the untreated and drug-influenced conditions. Lord's test showed that, for the healthy controls, a significant rise occurred in the (N.T.) responses ($u = \cdot 26$; $p = \cdot 05$) and in the (T.) responses ($u = \cdot 27$; $p = \cdot 02$). The rise was not however significant for either (N.T.) or (T.) in the depressive or schizophrenic patients.

An estimate of total reactivity in terms of the emotionally conditioned psychological stimuli in the C.S.T. is given by the individual differences. [(N.T.) — (T.)] between the two types of stimuli. These estimates were computed for each diagnostic group and evaluated statistically. Increased reactivity resulting from the exhibition of the drug was found in the controls ($u = \cdot 21$; $p = \cdot 05$) but no such increase occurred in the case of the psychiatric patients.

Comment.—It is of interest that the results of determining the resting oximetric status of the present healthy control group are in accordance with those obtained in a previous investigation (19) in which an entirely different, military control population was sampled. In that latter research it was shown that such a healthy group was capable of differentiation from a variety of mentally-ill groups on the basis of a combination of the resting oximetric status and the efficiency score. Apposite to our present purpose is the distinction found for the "organic neurological" group of patients for these showed abnormally high resting R.T. values, their range corresponding almost exactly to the raised values found in subjects intoxicated by L.S.D.-25. This is presumptive evidence of the organic nature of the psychosis provoked by this drug.

Of equal relevance is the behaviour of the efficiency score which has been found to provide a delicate means of differentiating as well between healthy groups with regard to their physical status (29) as between health and organic disease (28) and as between health and mental disturbance (17, 19). In the latter connection, it was found that efficiency scores below + 5 were associated with psychoneurotic reaction patterns (19). The effect of L.S.D.-25 on the depressed patients in the present investigation was to cause a marked and highly significant ($p = \cdot001$) increase from a mean of + 6·7 to a mean of + 33·4. By contrast, the healthy control subjects, who could be regarded by the criterion as physiologically efficient, showed merely an insignificant trend from a mean of + 26·63 to one of + 31·54.

The interpretation of these findings is complicated by the heterogeneity of the depressive group, including as it did patients of differing categories, who have been found in the past to yield quite distinct oximetric readings. However, as a group, they may be said to have reacted homogeneously in this respect, although the lowest rises of R.T. score were found in the endogenously depressed patients, and conversely the highest in those whose illness was predominantly reactive. These highest rises did in fact occur in those whose very low resting scores (all zero or below), in addition to the clinical evidence, placed them in the neurotic group. In four of the six these increases could be correlated with both subjective and objective lightening of mood.

Thus, if the R.T. score be regarded as a valid measure of improved physiological efficiency, this change could be equated with an improved affective state. However, it must be added that the smallness of both the numbers of the subjects and the clinical changes manifested prohibited more than inference being drawn.

In the schizophrenics, however, there was merely a non-significant trend toward a reduction of R.T., both resting and under the stress of breath holding. The R.T. scores showed a mean increase of 9·5 which was not significant.

Thus the schizophrenics could be regarded as showing a diminished or unchanged autonomic reactivity under the drug, although it should be kept in mind that their levels, although lower than those of the present group of controls, lay within previous control limits (19).

The influence of the vasodilatation, showed by the majority of the subjects on this test, remains undetermined, and it is hoped to investigate this point further. However, for the purposes of this study, namely objective differentiating measures, the findings would appear to remain valid.

Kraepelin's Tapping Test.—Only random changes were noted in all groups when the results under the drug were compared with those of the control period.

Pulmonary function and oxygen consumption.—Spirograms could only be run in eight of the controls and three of the schizophrenics, and the smallness of the latter group hampered comparison.

However, the schizophrenics, although showing a mean resting oxygen consumption of 18·5 c.c. per minute more than the controls, increased this by a further mean of 18·3 c.c., which was just below the 5 per cent. confidence level. This was associated with a mean increase of respiratory rate of 3·3 respirations

per minute and of total score of 1·3, neither of which were significant. By contrast, the controls showed random changes only in oxygen consumption, but a raised respiratory rate of 2 per minute, which was significant at the ·001 level of confidence.

In addition the total score showed a tendency towards an increase (mean = 3·4), which was not significant. Of the subscores, that recording "major fluctuations" showed the greatest mean increase of 2·1, but this was also not significant.

Thus in both groups there was an increased irregularity of respiratory pattern, and quickening of respiratory rate, with, in the schizophrenics, an increased oxygen consumption.

Discussion.

The clinical changes resulting from a dosage of 40 γ of d-lysergic acid diethylamide were not gross, although euphoria, when present, was unmistakable.

Only incidental observations were made of the effect of larger amounts of the drug, which were not given to the controls. Doubling or trebling the dose to 80 γ and 120 γ did not produce significantly different results in the few subjects in whom it was tried, but these were mostly the schizophrenic patients who had been noted to be resistant to its effects. In one member of the depressive group, however, a mood slightly lightened by 40 γ became despondent and suicidal on 80 γ.

In general, mood changes seemed dependent upon the original affective state of the subject, equanimity and cheerfulness tending toward euphoria, whereas anxiety and depression were usually heightened. There was some suggestion, however, of a possible differential response between those patients with endogenous and those with reactive depression in that there was a higher proportion of the latter who showed some improvement of mood, but this may merely have been a product of the differing severity of the two groups of illness. Certainly in the present state of knowledge, the drug would seem of little therapeutic value in depressive states.

The absence of significant changes in concentration and memory contrasted with the subjective impressions of distractibility and intoxication, although the influence of what we have termed "clinical sophistication" in the controls, and suggestion in the other groups on subjective estimates, remains a variable factor in such investigations.

The Rorschach test would seem unsuitable in the assessment of minor changes of mood and outlook where the "historical perspective" of the individual is basically unchanged.

Perceptual changes were certainly not notable and the illusions manifested were minimal in degree. Thus paucity of clinical change was merely confirmed by the test of eidetic imagery, but it would be instructive to repeat this with larger, hallucinatory doses. It should, however, be noted that a recent study by Saltzman and Machover (32) failed to show eidetic imagery by a similar experimental procedure in hallucinating alcoholics.

In general, it appeared that slight, although clinically apparent, changes produced by the drug were difficult to verify objectively. At present many of

our distinguishing tests, both physical and mental, are too crude and new measures are required. Illustrative of this was the apparent increased discriminatory power of oximetry, an estimate of capillary change, when compared to oscillomentry, dependent upon arterial change.

Similarly a study of respiratory function, closely linked as it is as well with speech as with bodily homeostasis, would appear profitable and, although for the present comparative purposes the Benedict Roth machine proved adequate, a more sensitive and less restrictive apparatus might prove more rewarding. It seems important, however, to measure oxygen consumption in addition to respiratory excursions.

Thus future investigation, in producing further refinements of such functional tests, may not only yield profiles of psychophysiological pattern serving to amplify and extend clinical description, but also lead to an increased understanding of bodily mechanisms in mental disease.

Summary.

(1) d-lysergic acid diethylamide (L.S.D.-25) was given to 11 healthy controls, 12 patients with predominant depression and 7 patients with schizophrenia, in an attempt to obtain comparative objective estimates of some of the psychological and physiological changes produced. 40 γ of the tartrate was given orally and a few incidental observations made of the effects of larger doses up to 120 γ.

(2) Clinically the changes resembled those previously described and were not gross. Accentuation of pre-existing affect was commonest, with associated lability of mood, and retention of insight.

(3) There was no measurable impairment of memory and concentration.

(4) Perceptual changes were uncommon and confined to unformed visual illusions in four of the controls. Tests of eidetic imagery showed no eidetic tendency under the drug.

(5) Reversal of perspective in an ambiguous figure was unchanged in the depressives.

(6) Qualitative and quantitative estimations of the Rorschach showed no significant change.

(7) An increased uptake of oxygen in the three schizophrenics who had spirograms taken while under the drug contrasted with only random changes in the controls. Both groups showed an increased respiratory rate.

(8) The response of the blood pressure to a pain stress showed no significant variation or differential response between the groups.

(9) Spectroscopic oximetry carried out during this pain test and in the "controlled stress" of a word association test showed significant changes however, which were interpreted as indicative of increased autonomic lability in the controls and depressives as contrasted with unmodified functioning in the schizophrenics. It seemed that oximetry had detected a change not apparent in the grosser measures of oscillometry.

(10) Similarly resting oximetric readings showed a differential response pattern between the schizophrenics, the controls and the depressives.

The efficiency score was very significantly raised in the depressive group, the greatest change being manifested in those whose illness was predominantly reactive. If this finding be regarded as indicative of improved physiological functioning, it could be correlated in four of the six patients with some alleviation of their depression.

(11) In conclusion, it proved difficult to obtain valid differentiating measures of clinically apparent changes.

The difficulty was felt to lie in the paucity of tests which were sufficiently discriminative, and it was considered that an elaboration of sensitive physiological recordings would facilitate the study of experimental intoxications in particular and of mental disease in general.

Acknowledgments.

Our grateful thanks are due to Dr. D. L. Davies for suggesting the present investigation; to Professor Aubrey Lewis for providing facilities enabling it to be carried out; to Miss M. Israel for administering the Rorschach tests and interpreting the findings; and to Mr. P. Chappell who gave help with the oxygen consumption procedures. We are indebted to Messrs. Sandoz Products (London), Ltd., for a generous supply of the drug.

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