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DISCUSSION SECOND SYMPOSIUM

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---- past seven years my co-workers and I have attempted* to study LSD, LSD derivatives and other types of compounds of *d*-lysergic acid on snails[3], the Siamese fighting fish[2], and man[1,4].**

In this report the quantitative use of a questionnaire employed for six years on man will be reported in connection with the comparison of LSD and related compounds. The questionnaire was composed originally by having my assistant, Mrs. TEIGE, go through the literature on LSD-25. When the project was started about seven years ago, she listed all of the symptoms and signs reported in the literature. As was expected, subsequent statistical studies revealed that certain of the questions are not as significant for the LSD reaction as are others. However, we have continued to use the original form of the questionnaire. Additional justification for this will soon be apparent.

The questions of the questionnaire are constructed so that a positive response, independent of the intensity of the reaction, constitutes one response. By adding the number of responses, a number, n is obtained. The Response Index, a term used in the studies to be reported here, is merely n divided by the dose in micrograms (usually in this series) or,

$$\text{Response Index} = \text{R.I.} = n/\mu g.$$

For a given dose, therefore, the higher the value of R.I., the greater the response to the drug. The values of n are for three and one-half hours.

For the past 4 years 5 non-psychotic adults, repeatedly used as a group, have been the main test subjects of the program. The experiments were under almost exactly similar social (not laboratory) test conditions at Cold Spring Harbor. The drug to be studied was administered one-half hour before dinner. The remainder of the evening was maintained on a social level with as little intrusion as possible by me or my assistants into the group interaction. This is a very important point, since a single stranger may be threatening to a member of the group. This intruder may set up a psychological chain reaction that may influence the group as a whole. Table I illustrates in a condensed form data obtained on the same 5 test subjects from 1955 to 1958 at threshold levels of LSD-25 or slightly above. Note that even though the R.I. for single

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TABLE I

d-LYSERGIC ACID DIETHYLAMIDE LSD-25

Threshold for calculation of group average = 25 μg

Subject	*Date*	*Dosage μg*	*Number responses*	*R.I.*	*Subject estimate*
C.G.	3/16/56	50	34	0.68	50
	2/8/57	35	25	0.71	25
	11/15/57	25	34	1.36	>25
	1/3/58	25	19	0.96	25
	5/16/58	35	22	0.63	25
				Av. 0.86 ± 0.23	
P.B.	11/21/52	50	23	0.46	
	1/9/53	75	47	0.62	
	3/16/56	50	21	0.48	
	3/29/57	50	23	0.46*	
	5/16/58	50	17	0.34	35
				Av. 0.47 ± 0.06	
D.V.G.	3/11/55	25	5	0.20	
	3/16/56	50	14	0.28	
	11/15/57	35	16	0.46	35
				Av. 0.31 ± 0.10	
M.Z.	3/16/56	50	12	0.26	25
	3/29/57	50	33	0.66	25
	11/15/57	35	14	0.40	25
	5/16/58	50	11	0.22	35–50
				Av. 0.39 ± 0.15	
J.G.	3/11/55	50	24	0.50	
	4/8/55	25	8	0.32	25
	10/2/55	25	6	0.24	25
	12/2/55	25	11	0.44	25
	3/16/56	50	16	0.32	>25 but< 50
	11/15/57	35	9	0.29	35
	5/16/58	50	10	0.20	25–35
				Av. 0.33 ± 0.08	

Group average R.I. = 0.47

* At 2 h "I was never so frightened in my life."

TABLE II

PREDNISONE TOLERANCE EXPERIMENT WITH PLACEBO*

Subject	*Date*	*Prep. dose*	*LSD dosage μg*	*Number responses*	*R.I.*	*Subject estimate LSD equivalent*
P.B.	3/9/56	placebo	25	14	0.56	25
C.G.	3/9/56	placebo	25	20	0.84	25
J.G.	3/9/56	placebo	35	11	0.31	25–35
D.V.G.	3/9/56	placebo	35	12	0.40	25
M.Z.	3/9/56	placebo	25	11	0.44	15

Group average R.I. = 0.51

* Three capsules of placebo were administered daily to each subject from 3/6 to 3/9/56.

In all cases the values for the number of placebo responses have been substituted as a corrective factor when available.

Subject	*Date*	*Dosage μg*	*Number responses*	*R.I.*
A.B.	4/29/53	0	13	—
	5/13/53	50	51	1.0
	5/20/53	100	69	0.69
	5/27/53	100	83	0.83
				Av. 0.84 ± 0.11
L.B.	4/15/53	0	6	—
	6/3/53	50	49	1.0
	12/3/53	50	9	0.11
	12/10/53	100	26	0.26
	3/6/54	0	7	—
				Av. 0.46
R.C.	2/18/53	0	15	—
	2/28/53	50	39	0.78
	3/11/53	100	67	0.67
	3/23/53	150	49	0.33
	6/10/53	150	94	0.62
				Av. 0.60 ± 0.14
C.E.	11/2/53	0	12	—
	11/16/53	50	20	0.40
	11/30/53	100	10	0.10
				Av. 0.25 ± 0.15
E.E.	3/2/53	0	26	—
	3/23/53	50	33	0.66
	3/30/53	100	46	0.46
	5/18/53	100	39	0.39
				Av. 0.50 ± 0.10
C.G.	6/8/53	50	31	0.62
	6/29/53	100	61	0.61
	7/21/53	100	60	0.60
				Av. 0.61 ± 0.07
L.G.	10/5/53	50	28	0.56
	10/19/53	100	53	0.53
	12/28/53	100	53	0.53
				Av. 0.54 ± 0.01
M.H.	11/17/53	50	18	0.36
	11/24/53	100	22	0.22
	12/17/53	100	22	0.22
	1/18/54	150	28	0.18
				Av. 0.25 ± 0.06
M.H.	3/30/53	0	23	—
	5/6/53	150	—	—*
A.T.	12/13/52	100	33	0.33
	12/16/52	100	52	0.52
	1/17/53	125	44	0.35
	1/24/53	75	24	0.33
				Av. 0.38 ± 0.07
B.S.	11/14/52	200	6	0.03
	11/21/52	225	11	0.05
	12/5/52	200	12	0.06
	1/9/53	220	19	0.10
	2/11/53	200	19	0.10
	3/11/53	200	43	0.21
	4/20/53	150	20	0.13
				Av. 0.10 ± 0.04

Group average R.I. (for first 5 subjects) = 0.53

Group average R.I. (for 9 subjects) = 0.49

* Completely withdrawn; required hospitalization. Became communicative at 10:00 p.m. (13 h later).

experiments varies somewhat, the subjects' estimate of the dose of LSD is fairly accurate. If the averages obtained for each subject are used to calculate a *Group R.I.*, the Group Average R.I. = 0.47. We obtained thus a *number* characterizing the response of this group under the specific non-stressful test conditions. This number (Group Average R.I.), we felt, eliminated many of the variables and gave a representative basic measure using the questionnaire technique.

But this question arose: Did this Group R.I. fluctuate markedly under different test conditions and with these non-psychotic subjects? Fortunately other data were available. Table II illustrates an experiment where the same subjects took a placebo (blind) for 4 days, 3 times daily, prior to taking LSD-25. The Group Average R.I. is 0.51. The R.I. for each individual checks well with the average R.I. in Table I, as follows:

Subject	*Placebo for 4 days*	*Average R.I.*
P.B.	0.56	0.47
C.G.	0.84	0.86
J.G.	0.31	0.33
D.V.G.	0.40	0.31
M.Z.	0.44	0.39

Another test of the employment of the R.I. as a basis of study was to look over older data obtained under hospital, not social, test conditions on a completely different group of non-psychotic paid volunteers. Table III illustrates calculations for these data. Omitted from our calculations are data obtained on subjects B.S. and M.H. Consider the other 9 subjects, all of whom are different from our 5 subjects of the last 4 years. The R.I. for each subject was corrected for placebo response when available by subtracting the value of *n* for the placebo. The Group R.I. for the first 5 subjects with corrected placebo data is 0.53 and 0.49 for all 9 subjects compared with 0.47 on the group studied from 1955–1958. These calculations, I believe, strikingly confirm the validity of the method of using our questionnaire as a measure of psychopharmacology activity.

Experiments on test subjects used for the past 4 years included LSD derivatives:

	Group R.I.
1-Acetyl *d*-Lysergic Acid Diethylamide (ALD-52)	0.43
1-Oxymethyl *d*-Lysergic Acid Diethylamide (OML-632)	0.31
1-Methyl *d*-Lysergic Acid Diethylamide (MLD-41)	0.17

all of which are modified in the 1-position. ALD-52, the 2-acetyl derivative of LSD is for practical purposes as strong as LSD itself. However, the other compounds diminish in effectiveness.

Changing the group on the amide linkage reduces the activity even further. Thus, the values:

	Group R.I.
d-Lysergic Acid Morpholide (LSD-775) (LSM 775)	0.054
d-Lysergic Acid Dimethylamide (DAM-57)	0.052
d-Lysergic Acid Pyrrolidide (LPD-824)	0.025
d-Lysergic Acid Ethylamide (LAE-32) LAE	0.016
1-Methyl *d*-Lysergic Acid Butanolamide (Tartrate) (UML-491) DES	0.005

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Finally, Table IV gives the relative strengths, LSD = 100, of the compounds thus far studied with our method. Using this method we hope to obtain on man more quantitative measures in psychopharmacological experiments dealing with the effectiveness of psychotomimetic effects, tolerance, cross tolerance, antagonism, synergism and therapy.

TABLE IV

THE RELATIVE ORDER OF ACTIVITY OF CERTAIN COMPOUNDS OF *d*-LYSERGIC ACID AND OF LSD

Drug	*R.I.*	*R.I. Recalculated LSD = 100*
LSD	0.47	100
ALD	0.43	91
OML	0.31	66
MLD	0.17	36
LSM	0.054	11
DAM	0.052	10
LPD	0.025	5.3
LAE	0.016	3.4
(BOL)	(0.010)	(2.1)*
~~UML-(?)~~ DES	0.005	1.1

* Interpolated from data on another group of non-psychotic subjects in 1954.

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Alle precise osservazioni dei precedenti Relatori sarà opportuno, ritengo, fare qualche aggiunta, dato, anche, che su questi argomenti chi ha l'onore di parlarvi ora ha un'esperienza personale, dix 37 anni ormai, basata su ricerche, condotte anche con i propri collaboratori[1b–24, 26–35], nelle direttive più varie, secondo i dettami della medicina scientifica, noti da tempo. Qualsiasi evento, infatti, più o meno patologico è il risultato dell'azione di un *quid*. Ma risulta anche dall'azione del *terreno* su cui il "*quid*" agisce (con tutti i problemi etiologici, patogenetici, fenomenologici, anatomo-patologici ed eventualmente terapeutici del caso).

Un esempio dimostrativo[25]: 9 mg di bulbocapnina in un cane di taglia normale non producono nulla. Ne occorrono ben 400 mg per provocare catalessia. In un cane, però, della stessa taglia, in cui le interferenze epatiche siano state eliminate previa fistola di Eck, i 9 mg suddetti provocano una catalessia tipica. E'opportuno, perciò,

Bibliografia p. 78/79.