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LYSERGIC ACID DIETHYLAMIDE (*LSD*-25): XXIX. THE RESPONSE INDEX AS A MEASURE OF THRESHOLD ACTIVITY OF PSYCHOTROPIC DRUGS IN MAN*

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A. INTRODUCTION

A reliable method of comparing in man the effectiveness of different psychoticomimetic drugs has not as yet been described. In previous studies the effects on man of *d*-lysergic acid diethylamide and certain of its derivatives have been reported (1, 3, 7). Experiments on man become involved, however, because of the recurrence of placebo-positive reactions in subjects thought to be placebo-negative (2). For the past five years part of our program has included the use of a trained group of the same five essentially placebo-negative subjects to whom *LSD*-25 and other psychotropic drugs were administered regularly. It is the purpose of this report to communicate the results of experiments performed under social test conditions with certain derivatives and congeners of *LSD*-25 during the past five years on these five non-psychotic subjects.

It has been found that the questionnaire technique previously employed lends itself to the study of psychotropic drugs. The ratio of the number of responses to the questionnaire to the dose of the drug in micrograms is now presented as a useful index of the relative strengths of this group of compounds. In this way a quantitative measure of the effects of threshold doses is obtained; thus providing a reliable method of comparing the psychoticomimetic activity of various drugs in man.

B. METHOD

A questionnaire was employed to structure the experiments. It was composed originally when the project was started about seven years ago. All of the symptoms and signs reported in the literature for *LSD*-25 were collected at that time and were used as the basis of the questionnaire. As expected, subsequent statistical studies revealed that certain of the questions were not as

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significant for the *LSD* reaction as 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 (orally in this series) or,

$$\text{Response Index} = RI = \frac{\text{n}}{\text{micrograms}}$$

For a given dose, therefore, the higher the value of *RI*, the greater the response to the drug as measured by the questionnaire. The values of *n* are for three and one-half hours.

For the past five years five non-psychotic adults repeatedly used as a group have been the main test subjects of the program. The experiments were under similar social (not laboratory) test conditions at Cold Spring Harbor (3). The drug to be studied was administered in two ounces of distilled water one-half hour before dinner. The remainder of the evening was maintained on a social level with as little intrusion as possible into the group interaction by me or my assistants. This is a very important point, since a single stranger may be threatening to a member of the group; the intruder setting up a psychological chain reaction that could influence the group as a whole.

C. Results

Table 1 illustrates in a condensed form data obtained on the same five test subjects from 1955 to 1958 at threshold levels of *LSD*-25 or slightly above. Note that even though the *RI* for single 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 *RI*, the *Group Average* $RI = .47$. We obtain thus a *number* characterizing the response of this group under the specific non-stressful test conditions. This number (*Group Average RI*), we felt, eliminated many of the variables and gave a representative basic measure of psychotropic activity using the questionnaire technique.

But this question arose: Did this group *RI* fluctuate markedly under different test conditions and with these non-psychotic subjects? Fortunately, other data were available. Table 2 illustrates an experiment where the same subjects took a placebo (blind) for four days, three times daily, prior to taking *LSD*-25. This *Group Average RI* is .51. The average *RI* for each individual in Table 1 checks well with the average *RI* in Table 2.

TABLE 1
d-LYSERGIC ACID DIETHYLAMIDE (LSD-25): THRESHOLD FOR CALCULATION OF GROUP AVERAGE = 25 Mcgm

Subject	Date	Dosage Mcgm	Number responses	*RI*	Subject estimate
C.G.	3/16/56	50	34	.68	50
	2/8/57	35	25	.71	25
	11/15/57	25	34	1.36	> 25
	1/3/58	25	19	.96	25
	5/16/58	35	22	.63	25
				Av. .86 ± .23	
P.B.	11/21/52	50	23	.46	
	1/9/53	75	47	.62	
	3/16/56	50	21	.48	
	3/29/57	50	23	.46*	
	5/16/58	50	17	.34	35
				Av. .47 ± .06	
D.V.G.	3/11/55	25	5	.20	
	3/16/56	50	14	.28	
	11/15/57	35	16	.46	35
				Av. .31 ± .10	
M.Z.	3/16/56	50	12	.26	25
	3/29/57	50	33	.66	25
	11/15/57	35	14	.40	25
	5/16/58	50	11	.22	35-50
				Av. .39 ± .15	
J.G.	3/11/55	50	24	.50	
	4/8/55	25	8	.32	25
	10/2/55	25	6	.24	25
	12/2/55	25	11	.44	25
	3/16/56	50	16	.32	> 25 but < 50
	11/15/57	35	9	.29	35
	5/16/58	50	10	.20	25-35
				Av. .33 ± .08	
				Group Average *RI* = .47	

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

TABLE 2
A COMPARISON OF VALUES OF THE AVERAGE RESPONSE INDEX FOR *LSD*-25 ON FIVE SUBJECTS WITH ONE PRETREATMENT (PLACEBO) EXPERIMENT
(The agreement is better than anticipated)

Subject	*RI* (Placebo for four days)	Average *RI* Data from Table 1
P.B.	.56	.47
C.G.	.84	.86
J.G.	.31	.33
D.V.G.	.40	.31
M.Z.	.44	.39
Group *RI*	.51	.47

TABLE 3

LYSERGIC ACID DIETHYLAMIDE: *LSD*-25

(In all cases the values for the number of placebo responses have been subtracted as a corrective factor when available)

Subject	Date	Dosage Mcgm	Number responses	*RI*
A.B.	4/29/53	0	13	—
	5/13/53	50	51	1.0
	5/20/53	100	69	.69
	5/27/53	100	83	.83
			Av.	.84 ± .11
L.B.	4/15/53	0	6	—
	6/3/53	50	49	1.0
	12/3/53	50	9	.11
	12/10/53	100	26	.26
	3/6/54	0	7	—
			Av.	.46
R.C.	2/18/53	0	15	—
	2/28/53	50	39	.78
	3/11/53	100	67	.67
	3/23/53	150	49	.33
	6/10/53	150	94	.62
			Av.	.60 ± .14
C.E.	11/2/53	0	12	—
	11/16/53	50	20	.40
	11/30/53	100	10	.10
			Av.	.25 ± .15
E.E.	3/2/53	0	26	—
	3/23/53	50	33	.66
	3/30/53	100	46	.46
	5/18/53	100	39	.39
			Av.	.50 ± .10
C.G.	6/8/53	50	31	.62
	6/29/53	100	61	.61
	7/21/53	100	60	.60
			Av.	.61 ± .07
L.G.	10/5/53	50	28	.56
	10/19/53	100	53	.53
	12/28/53	100	53	.53
			Av.	.54 ± .01
M.H.	11/17/53	50	18	.36
	11/24/53	100	22	.22
	12/17/53	100	22	.22
	1/18/54	150	28	.18
			Av.	.25 ± .06
M.H.X.	3/30/53	0	23	—
	5/6/53	150	—	—*
A.T.	12/13/52	100	33	.33
	12/16/52	100	52	.52
	1/17/53	125	44	.35
	1/24/53	75	24	.33
			Av.	.38 ± .07
B.S.	11/14/52	200	6	.03
	11/21/52	225	11	.05
	12/5/52	200	12	.06
	1/9/53	200	19	.10
	2/11/53	200	19	.10
	3/11/53	200	43	.21
	4/20/53	150	20	.13
			Av.	.10 ± .04

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

TABLE 4
l-ACETYL *d*-LYSERGIC ACID DIETHYLAMIDE: *ALD-52*

Subject	Date	Dosage Mcgm	Number responses	*RI*
P.B.	1/4/57	25	10	.40
	1/18/57	50	12	.24
				Av. .32 ± .08
C.G.	12/21/56	25	10	.40
	1/4/57	25	19	.76
	1/18/57	50	37	.74
				Av. .63 ± .16
M.Z.	12/21/56	25	19	.76
	1/4/57	25	18	.72
	1/18/57	50	30	.60
				Av. .67 ± .07
J.G.	12/21/56	35	8	.23
	1/4/57	35	8	.23
	1/18/57	70	29	.41
				Av. .29 ± .08
D.V.G.	12/21/56	35	10	.29
	1/4/57	35	7	.20
	1/18/57	70	14	.20
				Av. .23 ± .05

RI group average = .43

TABLE 5
l-OXYMETHYL *d*-LYSERGIC ACID DIETHYLAMIDE: *OML-632*
(Threshold for calculation of group average = 35 Mcgm)

Subject	Date	Dosage Mcgm	Number responses	*RI*	Subject estimate *LSD* equivalent
C.G.	1/10/58	35	16	.46	< 25
				Av. .46	
P.B.	1/3/58	35	12	.37	25
	1/10/58	50	18	.36	35
				Av. .37 ± .005	
D.V.G.	1/3/58	35	11	.31	< 25
	1/10/58	50	18	.36	> 35
				Av. .34 ± .03	
M.Z.	1/10/58	50	16	.32	35
				Av. .32	
J.G.	1/3/58	35	2	.07	< 25
	1/10/58	50	3	.06	35
				Av. .07 ± .005	

Group average *RI* = .31

Another test of the employment of the *RI* 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 3 illustrates calculations for these data. Omitted from our calculations are data obtained

TABLE 6
l-METHYL *d*-LYSERGIC ACID DIETHYLAMIDE: *MLD*-41
(Threshold for calculation of group average = 50 Mcgm)

Subject	Date	Dosage Mcgm	Number responses	*RI*	Subject estimate
C.G.	10/26/56	25	0	0	< 15
	11/9/56	50	23	.46	25
	11/16/56	25	0	0	0
				Av. .46	
P.B.	10/12/56	10	0	0	0
	10/26/56	25	0	0	0
	11/9/56	50	0	0	0
	11/16/56	75	15	.20	15
	11/30/56	115	22	.19	35
				Av. .13 ± .086	
D.V.G.	10/12/56	10	1	.10	0
	10/26/56	25	0	0	0
	11/9/56	70	0	0	0
	11/16/56	100	3	.03	0
	11/30/56	140	20	.14	35 ?
				Av. .056 ± .055	
M.Z.	10/12/56	10	0	0	0
	10/26/56	25	0	0	0
	11/9/56	50	0	0	0
	11/16/56	75	2	.027	0
	11/30/56	115	33	.29	35
				Av. .11 ± .16	
J.G.	10/12/56	10	2	.20	
	10/26/56	25	0	0	
	11/9/56	70	5	.071	
	11/16/56	100	7	.07	
	11/30/56	140	21	.15	
				Av. .097 ± .035	

Group average *RI* = .17

on subjects *B.S.* and *M.H.X.* Consider the other nine subjects listed in Table 3 all of whom are different from our five subjects of the last five years. The *RI* for each subject was corrected for placebo response when available by subtracting the value of *n* for the placebo. Note also that these subjects were not carefully screened to be placebo negative and have an inherent error

due to their response to a water control. The *Group RI* for the first five subjects with corrected placebo data is .53 and for all nine subjects .49 compared with .47 on the group studied from 1955-1958. These calculations, I believe, strikingly confirm the general validity of the method of using our questionnaire as a measure of psychopharmacologic activity.

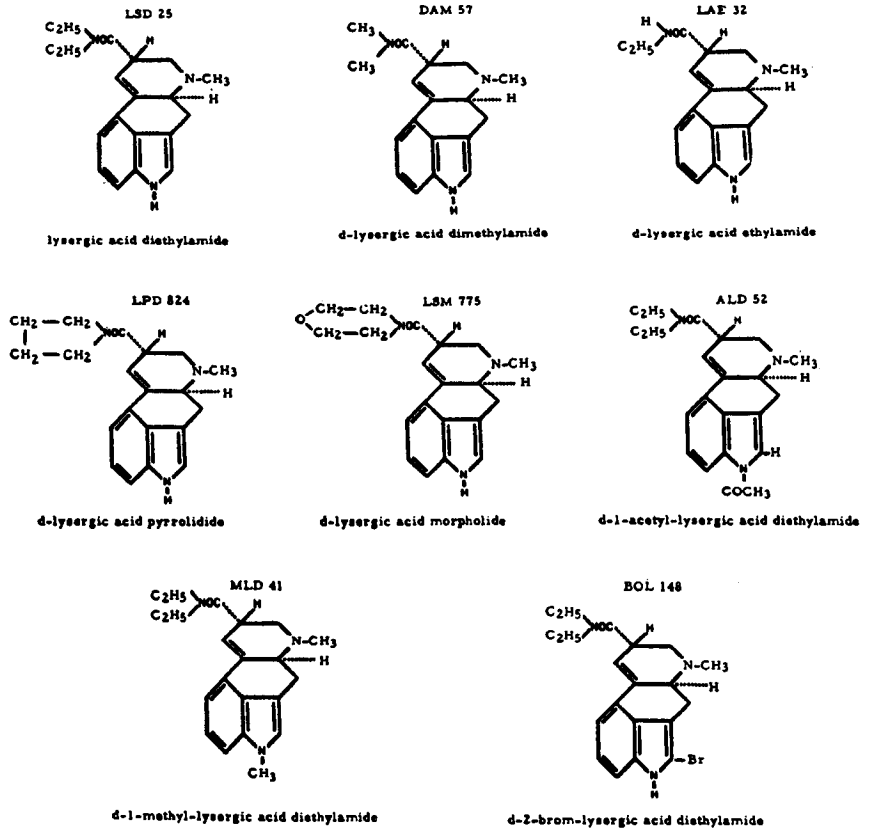

FIGURE 1
LSD AND RELATED COMPOUNDS

Experiments on test subjects used for the past five years included *LSD* derivatives. Some of these derivatives are illustrated in Figure 1.

The experiments dealing with these derivatives are to be found in Tables 1-13 listed with their Group Response Indices in Tables *A* and *B*. All of these are modified in the 1-position. *ALD*-52, the 1-acetyl derivative of *LSD*,

TABLE 7
d-LYSERGIC ACID MORPHOLIDE: *LSM*-775
(Threshold for calculation of group average = 100 Mcgm)

Subject	Date	Dosage Mcgm	Number responses	*RI*	Subject estimate *LSD* equivalent
C.G.	3/14/58	35	9	.26*	< 15
	4/4/58	50	0	0	
				Av. 0	
P.B.	3/14/58	50	0	0	0
	4/4/58	100	3	.03	15
	4/18/58	150	15	.1	35
				Av. .06 ± .04	
D.V.G.	4/4/58	100	0	0	0
	4/18/58	150	11	.07	25
				Av. .035	
M.Z.	3/14/58	50	0	0	0
	4/4/58	100	0	0	0
	4/18/58	150	15	.1	0
				Av. .05	
J.G.	3/14/58	50	0	0	0
	4/4/58	100	7	.07	< 15
				Av. .07	

Group average *RI* = .054

* This is believed to be a "placebo positive" equivalent in view of the other data.

is for practical purposes as strong as *LSD* itself. However, the other two compounds, *OML* and *MLD*, diminish in effectiveness.

TABLE *A*

	Group *RI*
Table 4, 1-Acetyl d-Lysergic Acid Diethylamide (*ALD*-52)	.43
Table 5, 1-Oxymethyl d-Lysergic Acid Diethylamide (*OML*-632)	.31
Table 6, 1-Methyl d-Lysergic Acid Diethylamide (*MLD*-41)	.17

Changing the group on the amide linkage reduces the activity even further. Thus, the values found in Table *B* show a more marked diminution in activity as the amide structure is varied.

TABLE *B*

	Group *RI*
Table 7, d-Lysergic Acid Morpholide (*LSM*-775)	.054
Table 8, d-Lysergic Acid Diethylamide (*DAM*-57)	.052
Table 9, 2-Brom-d-Lysergic Acid Diethylamide (*BOL*-148)	.034
Table 10, d-Lysergic Acid Pyrrolidide (*LPD*-824)	.025
Table 11, d-Lysergic Acid Ethylamide (*LAE*-32)	.016
Table 12, l-Methyl d-Lysergic Acid Butanolamide (Tartrate) (*UML*-491)	.005

Finally, Table 13 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 psychopharmacologic experiments dealing with effectiveness of psychoticomimetic drug effects, tolerance, cross-tolerance, antagonism, synergism, and therapy.

TABLE 8

d-LYSERGIC ACID DIMETHYLAMIDE: *DAM*-57
(Threshold for calculation of group average = 35 Mcgm)

Subject	Date	Dosage Mcgm	Number responses	*RI*	Subject estimate *LSD* equivalent
C.G.	11/22/57	35	1	.03	0
	12/6/57	70	12	.17	15
	12/13/57	115	14	.15	35
	12/20/57	115	7	.06	20
	2/7/58	150	26	.17	25
				Av. .12 ± .06	
P.B.	11/22/57	35	0	0	0
	12/6/57	70	0	0	0
	12/13/57	115	7	.06	0
	12/20/57	115	4	.03	0
	2/7/58	180	15	.08	25
				Av. .03 ± .03	
D.V.G.	11/22/57	35	0	0	0
	12/6/57	70	0	0	< 15 if anything
	12/20/57	140	0	0	< 15 (4 oz. Scotch 2 hrs. previously)
M.Z.	11/22/57	35	0	0	0
	12/6/57	70	2	.03	15
	12/13/57	140	2	.01	Atypical, not LSD
	12/20/57	140	8	.06	20
	2/7/58	180	9	.05	35
				Av. .03 ± .02	
J.G.	11/22/57	35	4	.11	15
	12/6/57	70	1	.03	0
	12/13/57	140	17	.12	50
	12/20/57	140	2	.03	20
				Av. .07 ± .04	

Group average *RI* = .052

D. Discussion

Heath (6) has maintained that during his studies on the psychosis producing compound, taraxein, he has never observed placebo positive responses in his subjects. That is, control injection never produced a psychotic response. My coworkers and I have repeatedly observed all types of positive responses

TABLE 9
2-Brom-*d*-Lysergic Acid Diethylamide: *BOL*-148
(Threshold for calculation of group average = 100 Mcgm)

Subject	Date	Dosage Mcgm	Number responses	*RI*
R.B.	12/12/58	200	3	.06
	12/19/58	300	5	.017
				Av. .039 ± .027
P.B.	12/5/58	100	0	0
	12/12/58	200	3	.06
	12/19/58	300	17	.053
				Av. .038 ± .025
C.G.	12/12/58	200	0	0
	12/19/58	300	19	.063
				Av. .032 ± .031
J.G.	12/5/58	100	0	0
	12/12/58	200	3	.06
	12/19/58	300	1	.003
				Av. .021 ± .026
D.V.G.	12/5/58	100	0	0
	12/12/58	200	0	0
	12/19/58	300	0	0
				Av. 0 ± 0
M.Z.	12/5/58	100	11	.11
	12/12/58	200	11	.055
	12/19/58	300	18	.06
				Av. .075 ± .023
			Group average = .034	

to water placebos. Indeed, these ranged from paralyses to hallucinations. These data have been published in extenso. Even the essentially placebo-negative group used for five years in this series occasionally reported *LSD* reactions when only water was administered. Either Heath was especially fortunate in accidentally choosing placebo-negative subjects or his controls are unsuitable. It is difficult to understand, also, how Heath can vary his questioning technique and thus use an unstructured observation procedure

without seeding the situation toward positive results. This point of view is confirmed by the data of Robins (8) who after injecting taraxein could not distinguish between experiments with taraxein and controls. Using the technique employed here, the controversy regarding the psychoticomimetic properties of taraxein could be readily resolved.

TABLE 10
d-LYSERGIC ACID PYRROLIDIDE: *LPD*-824
(Threshold for calculation of group average = 75 Mcgm)

Subject	Date	Dosage Mcgm	Number responses	*RI*	Subject estimate *LSD* equivalent
C.G.	2/14/58	50	0	0	0
	3/7/58	75	5	.06	< 15
	3/28/58	125	9	.07	15-20
	5/2/58	150	7	.046	Similar to Serpasil
				Av. .058 ± .08	
P.B.	3/7/58	100	6	.06	< 15
	3/28/58	150	0	0	0
	5/2/58	200	5	.025	< 25
				Av. .03 ± .11	
D.V.G.	2/14/58	50	0	0	0
	3/7/58	100	0	0	0
	3/28/58	150	0	0	0
	5/2/58	200	0	0	0
				Av. 0	
M.Z.	2/14/58	50	0	0	0
	3/7/58	100	0	0	0
	3/28/58	150	0	0	0
	5/2/58	200	10	.05	25
				Av. .016 ± .012	

Group average *RI* = .025

Our experiments on the Siamese fighting fish have indicated that *LSD*-25 is the most active of the compounds studied here (4, 5). However, because our bioassay method depended upon diffusion of the drugs from the outside liquid, variability apparently dependent upon this factor has prevented us from presenting comparable data on fish at this time.

In the data reported there is a difference in effect when the amide group or the indole group is modified. Adding a methyl or acetyl group in the 1-position on the indole ring produced a reduction in pharmacologic activity, but not as great a change as had been anticipated. Modifying the diethyl

TABLE 11

d-LYSERGIC ACID ETHYLAMIDE: *LAE*-32
(Threshold for calculation of group average = 100 Mcgm)

Subject	Date	Dosage Mcgm	Number responses	*RI*	Subject estimate *LSD* equivalent
C.G.	1/17/58	100	3	.03	15
P.B.	1/17/58	100	0	0	0
	1/24/58	150	0	0	0
				Av. 0	
D.V.G.	1/17/58	100	0	0	0
	1/24/58	150	4	.03	0
				Av. .02 ± .005	
M.Z.	1/24/58	150	0	0	0
J.G.	1/24/58	150	3	.02	0
			Group average *RI* = .016		

TABLE 12

l-METHYL-*d*-LYSERGIC ACID BUTANOLAMIDE (TARTRATE): *UML*-491
(Threshold for calculation of group average = 1000 Mcgm)

Subject	Date	Dosage Mcgm	Number responses	*RI*	Subject estimate *LSD* equivalent
C.G.	5/30/58	1000	10	.01	15
P.B.	5/30/58	1000	3	.003	10-15
D.V.G.	5/30/58	1000	6	.006	< 25
M.Z.	5/30/58	1000	4	.004	15
			Group average *RI* = .005		

TABLE 13

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

Drug	*RI*	*RI* recalculated *LSD* = 100
LSD	.47	100
ALD	.43	91
OML	.31	66
MLD	.17	36
LSM	.054	11
DAM	.052	11
BOL	.034	7.2
LPD	.025	5.3
LAE	.016	3.4
UML	.005	1.1

structure, however, markedly reduced the activity. Further studies are planned as compounds are made available by Sandoz Pharmaceuticals. The data are also incomplete because higher dosages have not been studied. Cross-tolerance has been studied but not synergism (3).

Another question not solved by these data is the relative values of compounds of this series in psychotherapy. Would, for example, a compound like *OML* be more useful than *LSD* as an adjuvant to psychotherapy?

E. Summary

1. Data were obtained on the same group of five non-psychotic subjects over a period of several years for the threshold doses of *LSD*-25 and related psychotropic compounds.

2. In order to compare the data a structured questionnaire was employed. The number of responses to the questionnaire divided by the dose in micrograms of the drug is designated as the Response Index. The method is designed to compare the relative effectiveness of certain psychotropic drugs.

3. The Response Index for a series of psychotropic compounds related to *LSD*-25 on the basis of *LSD*-25 = 100 indicates the following order of activity:

LSD-25	100
ALD-52	91
OML-632	66
MLD-41	36
LSM-775	11
DAM-57	11
BOL-148	7
LPD-824	5
LAE-32	3
UML-491	1

4. In view of the frequency of false (placebo-positive) reactions either suitable corrections or a screened test group of placebo-negative trained observers must be employed in testing psychoticomimetic compounds. If placebo-positive reactions are not encountered in a large series of such tests on man, the method is probably erroneous.

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