LTH, EDUCATION, AND W FARE
PUBLIC HEALTH SERVICE
Lexington, Kentucky
15 September 1954

IN REPLYING, ADDRESS THE
NIMH Addiction Research Center

(43)

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Since my last letter of 14 July 1954 I have completed a considerable amount more work which is summarized below.

TOLERANCE TO LSD. These experiments, which were described in my letter of 14 July, have been completed and the data have now been analyzed. My conclusions were not altered by the statistical analysis, and are as follows:

1. Once tolerance to LSD has been well developed, it requires four to five times the dose to which the patient is tolerant to restore the LSD-reaction to its original intensity; even then the duration of action is relatively short.

2. Tolerance to LSD is not overcome by administering 200 mg. of the metabolic blocker SKF-525-A.

3. Tolerance to LSD is lost in three days following discontinuation of the drug.

4. No untoward toxic effects were observed, even though the patients consumed as much as 11 mg. of LSD during the course of the experiment.

5. Even though a high grade of tolerence was developed, no abstinence symptoms were observed on withdrawal of the drug.

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ANTIDOTES FOR LSD.

1. Corynanthine. Results with corynanthine have been disappointing. In 10 patients no antidotal results were seen when 15 mg. corynanthine were administered 30 minutes before 40 mcgrm. of LSD. In a second experiment, 15 mg. corynanthine were administered 30 minutes before, 2 hours after, and 4 hours after 40 mcgrm. of LSD, using 9 subjects. Controls included three placebo capsules with 40 mcgrm. LSD, and three placebo capsules with a placebo drink. The timing of the placebo capsule was the same as that used when corynanthine was administered with LSD. Measurements included pupillary size, knee jerks, systolic blood pressure, LSD questionnaire, and estimation of the clinical grade of mental effect. Results are summarized in the table. These results were obtained by plotting the data on pupillary size, knee jerk, and blood pressure, and measuring area under the curve over a 7-hour period. The questionnaire was evaluated by counting the number of positive answers (checks in questions not marked prior to administration of LSD). Clinical grades were assigned as in previous work. Placebo effects were eliminated by subtraction of the proper control. Statistical analysis was done by the "t" test as applied to differences in paired observations. A glance at the table shows there is no significant change in any of the measurements, indicating no significant antidotal effect of corynanthine against LSD.

I should like to learn if you wish me to try larger doses of corynanthine.

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2. Banthine. Banthine alone had no effect on LSD reaction, neither did a combination of banthine plus corynanthine. Experiments, however, are still too few to permit statistical analysis.

3. Chlorpromazine. In contrast, experiments with chlorpromazine are at least promising. Two sets of experiments have been completed. In one set, 50 mg. of chlorpromazine orally was followed in 30 minutes by 40 mcgrm. of LSD orally. In the other set of experiments, 75 mg. chlorpromazine orally was followed by 40 mcgrm. LSD orally. Controls have included (all tests being done in a randomized order) placebo followed by placebo; placebo followed by LSD; chlorpromazine followed by a placebo. The measurements made and method of analysis are the same as those described above. Inspection of the tables shows a significant reduction in the intensity of mental response (number of questions and clinical grade) after 50 mg. chlorpromazine as compared with the response after placebo plus LSD. Diminution in blood pressure and pupillary responses were almost significant, and very likely would be with a larger number of subjects. After 75 mg. chlorpromazine, significant reductions in all responses, except pupillary size, were observed. Failure to obtain a significant reduction in pupillary response was due to an aberrant reaction in one of the 7 patients. The trend, however, is toward reduction of the pupillary response. The antidotal effects of chlorpromazine persist about eight hours; after this time LSD reaction may reappear.

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No significant effects were observed with 50 mg. of chlorpromazine alone. After 75 mg., definite drowsiness ensued which, however, was not accompanied by confusion and ataxia, as is the case with barbiturates.

It seems to me that these observations need extension in the following ways:

1. Confirmation in other laboratories.
2. Extension of my own series to a larger number of subjects.
3. Study of a wider range of doses; first, using more chlorpromazine, and finally more LSD.
4. Administration of chlorpromazine after LSD.
5. Administration of chlorpromazine parenterally rather than orally.

It should be emphasized that chlorpromazine is not a perfect antidote for LSD, at least in the dose combinations studied. It does not completely obliterate the response in all subjects. The effect is antidotal rather than competitive. With the larger doses of chlorpromazine, drowsiness becomes a definite drawback, even though patients have received LSD. There is, however, no confusion or motor incoordination as is the case with doses of barbiturates sufficiently large to alleviate anxiety caused by LSD.

CA-101. Results with this interesting compound was partly summarized in my letter of 14 July 1954, and since that time it has been discussed with [redacted] We have also now made measurements of the blood pressure response on standing, before

and after administration of CA-101. Results show that this compound induces profound postural hypotension in doses of only 2 mg. Further work with CA-101 has been deferred in order to concentrate on bufotenine. However, CA-101 appears worthy of further study. Closer evaluation of mental effects utilizing a variety of definite psychological tests in a larger number of individuals might be illuminating. A more detailed study of the cardiovascular response is also indicated in the hope of elucidating the mechanism. An antidote for drugs of this sort may also be needed.

BUFOTENINE: We now have carried out over one-hundred preliminary trials with this substance. This was done in an effort to locate a dose-range and to obtain some idea of the effects induced. The dose has been gradually elevated from 5 mcgrm. total dose to 500 mcgrm. total dose. With doses of less than 250 mcgrm. neither subjective nor objective effects were observed. Between 250 to 500 mcgrm., we have had scattered reports of dizziness, confusion and slight nervousness lasting for only an hour or two. As yet no consistent effects on the blood pressure, knee jerk, pupillary size, pulse rate, etc., have been observed. I intend to keep elevating the dose, following my return from Europe. As far as the work has gone, however, results with this compound are not promising.

Harris Isbell, M.D.

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EFFECTS OF 15 MGM. CORYNANTHINE (CC-I)

GIVEN BEFORE AND 2 HOURS AND 4 HOURS AFTER LSD-25

	Placeco* + LSD	CC-I* + LSD	Diff.	"t" of Diff.	Significance of Diff.
Knee Jerk	1.78	1.51	0.27	0.3	> 0.5
Pupils	3.08	2.84	0.24	0.57	> 0.5
Blood Pressure	1.94	2.38	-0.44	0.94	> 0.5
Questions	62.5	66.1	3.6	0.49	> 0.5
Grade	1.11	1.11	0	0	1.0

* Values are means of 9 subjects and are corrected for placebo responses.

EFFECTS OF 50 MGM. CHLORPROMAZINE

GIVEN 30 MINUTES BEFORE 40 MCGRM. LSD

	Placebo + LSD *	CPM + LSD *	Diff.	"t" of Diff.	Significance of Diff.
Knee Jerks	1.33	1.31	0.02	0.209	> 0.5
Pupillary Size	4.00	2.93	1.07	1.71	> 0.1
Blood Pressure	2.09	0.77	1.32	1.41	> 0.1
Questions	77	44	33	3.72	< 0.05 *
Grade	1.33	0.66	0.67	2.68	< 0.05 *

* Means per cent on 6 patients. Values corrected for placebo effect.

Under knee jerk, pupils and blood pressure, figures represent square inches under curve.

Questions - Number of positive answers on questionnaire.

Grade - Clinical grade.

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EFFECT OF 75 MGM. OF CHLORPROMAZINE
GIVEN 30 MIN. BEFORE 40 MCGRM. LSD

	Placebo* ± LSD	CPM * ± LSD	Diff.	"t" of Diff.	Significance of Difference
Knee Jerk	± 0.64	- 0.83	1.47	2.98	< 0.05 *
Pupillary Size	± 3.50	± 2.14	1.36	1.52	> 0.1
Blood Pressure	± 2.31	± 1.06	1.25	2.14	> 0.05 *
Questions	91	35	56	2.35	< 0.05 *
Grade	±.71	0.86	0.85	3.00	< 0.05 *

* Values are means on 7 patients and are corrected for placebo effect.

Under knee jerk, pupils and blood pressure, figures represent square inches under curve.

Questions - Number of positive answers on questionnaire.

Grade - Clinical grade.

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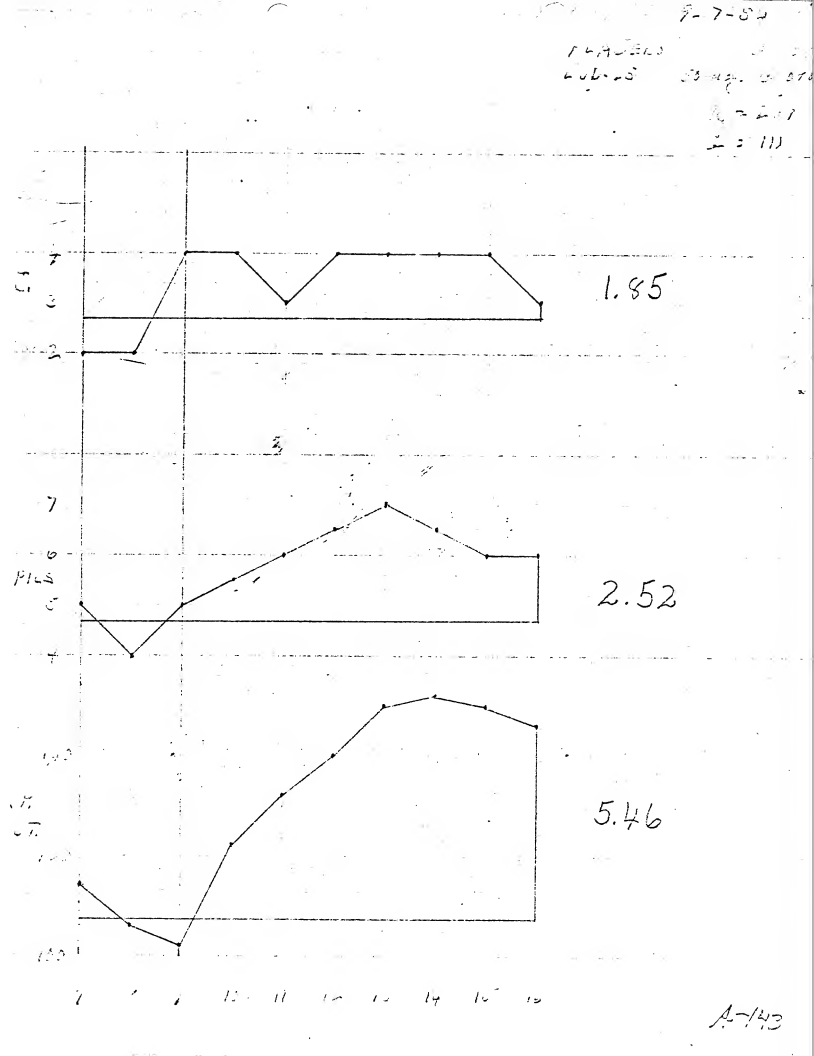
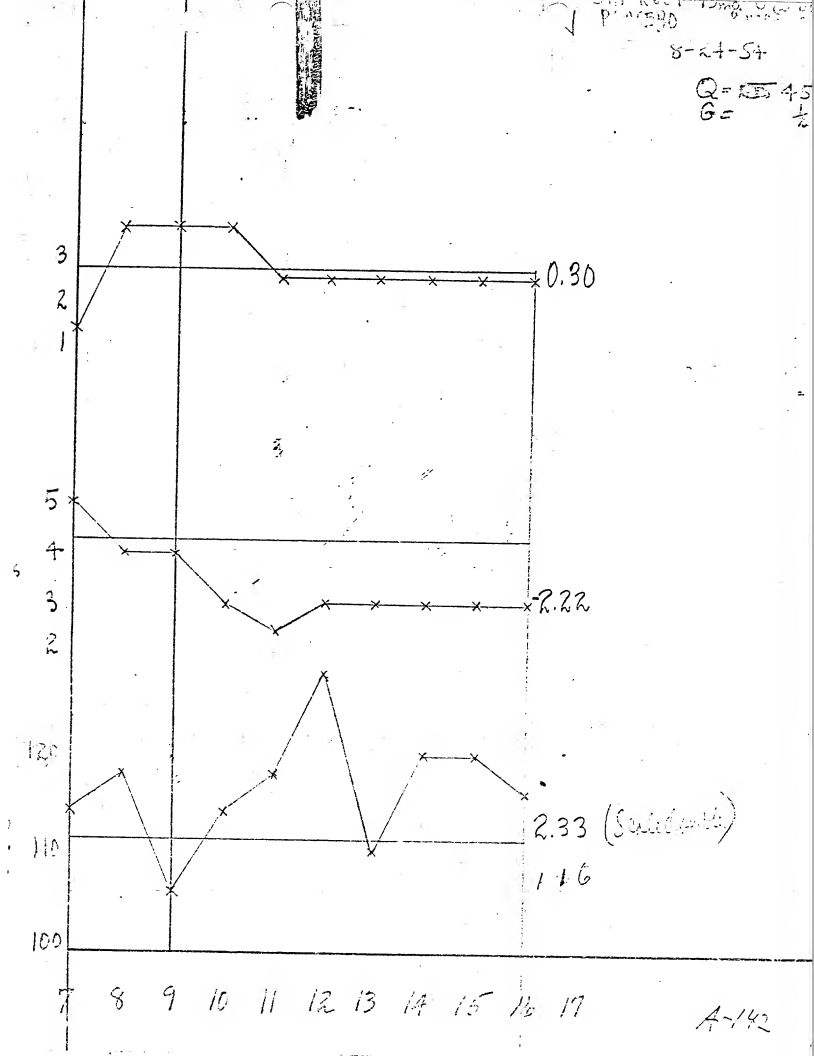

1.85
2.52
5.46


8-24-54
Q= 4.5
3
2
1
0.30
5
4
3
2
2.22
120
110
100
2.33 (Sediment)
1.16
7
8
9
10
11
12
13
14
15
16
17

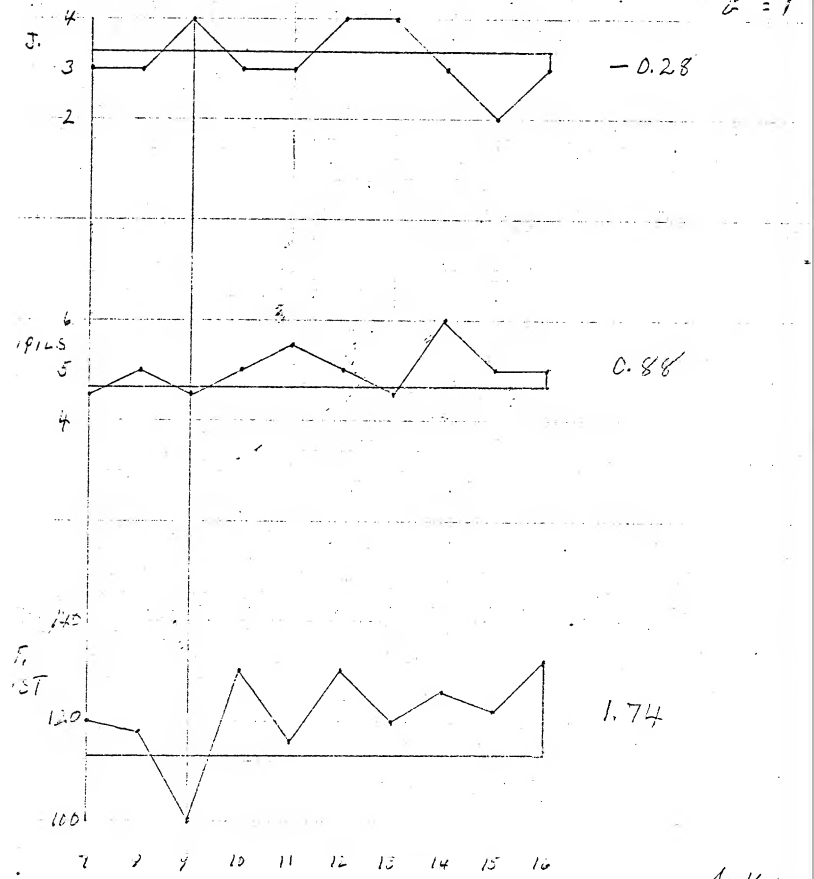
6-31-54

CR-2601 [illegible]

LSD-25 48 mg. [illegible]

$\bar{x}$ = 1.16

σ = 1



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