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NATIONAL INSTITUTES OF HEALTH

28 January 1955

IN REPLYING, ADDRESS THE
ADDICTION RESEARCH CENTER
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Since writing to you last December 6th we have completed a number of experiments which are described below.

Bufotenine. No further work has been carried out with this substance due to the ~~length~~^{length} of effects of doses ranging up to 2 mg. orally. Letter received from Dr. Everts of the National Institute of Mental Health indicates that no significant effects other than a transient drop in blood pressure occurred after as much as 1 mg. intravenously to normal volunteers. The Institute appears to be turning its attention to other substances found in the cohoba beans and I will await with interest any information from this source. The Institutes have kindly agreed to supply me with cohoba snuff so that we can ascertain whether there is anything in this bean that induces sufficient mental change to be of interest.

Chlorpromazine as an Antidote to LSD-25. We have now completed seven experiments. The first two of these were reported on September 15, 1954. The remaining experiments are described in order and are numbered 3 to 7. In general the effects of chlorpromazine have not been as good as would have been anticipated from the two original experiments. Although, in general, there is a trend indicating reduction of the LSD-effects the only consistently significant change has been in pupillary size.

Experiment 3. In this experiment the antidotal effects of 100 mg. chlorpromazine given 30 minutes before 60 mcg. of LSD were studied in 7 patients, including 6 whites and 1 negro. The purpose of the experiment was to study the dose range over which antidotal effects could be expected. The dose of chlorpromazine was elevated 25 mg. above that given in Experiment 2, and the dose of LSD was elevated 20 mcg. Observations included knee jerks pupillary size, systolic blood pressure, and questionnaire. All these measures were obtained hourly for two hours prior to administration and for eight hours after administration of LSD.



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Chlorpromazine was given orally 30 minutes before the LSD. Controls included administration of a double placebo; placebo plus LSD; and chlorpromazine plus a placebo. Measurements of knee jerks, pupillary size, and blood pressure were plotted in the usual way and the area under the curves determined with a planimeter. The number of positive answers on the questionnaire was counted over the observation period and the clinical grade assigned on the basis of the questionnaire plus the attendant's notes. The results for the placebo and LSD, and for chlorpromazine plus LSD were corrected for placebo effects and the difference between the conditions analyzed by the "t" test. The results are shown in the table. Although all the results are in the direction of chlorpromazine reducing the LSD-effects, the only significant changes were seen in pupillary size and in the grade of the reaction.

Experiment 4. This experiment was carried out in the same way, using 6 white and 1 negro patient (a different group from that used in Experiment 3). Results are shown in the table. It is noted that this was the most successful experiment, significant antidotal effects being observed on knee jerks, pupillary size, number of questions, and nearly significant results being obtained on blood pressure and clinical grade of response.

Experiment 5. This was essentially a repetition of Experiment 4, using an entirely new group of 12 negro patients. The only significant effect was on pupillary size. Nearly significant effects on clinical grade were observed.

Experiment 6. This experiment was designed to test the effects of chlorpromazine in reversing the effects of LSD. The 12 negro patients received LSD one and one-half hours prior to receiving chlorpromazine. The results are shown in the table. The only significant effect was on pupillary size.

Experiment 7. This experiment was carried out exactly as was Experiment 6, except that 25 mg. chlorpromazine was given intramuscularly one and one-half hours after a large individualized dose of LSD (designed to obtain a grade 2 response in all patients). There was a significant decrease in pupillary dilatation and in the clinical grade of the reaction.

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Discussion. As stated above, the original promising experiments on the effects of chlorpromazine in blocking the effects of LSD have not been borne out too well by additional experiments. Although the experiments show an overall trend to reduction in the LSD-reaction, it is doubtful that further work with chlorpromazine is indicated. Part of the difficulty is probably due to the fact that the response to both LSD and chlorpromazine is highly individual. The best experiment would be one in which the dose of both drugs was individualized.

CA-101. Another lot of this material was obtained and the effects compared with those of the original lot. The second lot proved to be just as potent as the first in inducing typical marijuana-like subjective effects, plus a marked degree of postural hypotension in doses of 1 to 2 mg. orally.

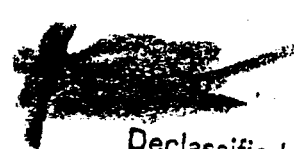
In experiments using 6 subjects, the effects of smoking tobacco on which the drug had been dried were studied and compared with those seen in the same subjects after oral administration of the compound. In general it is certain that the drug is effective when smoked in this way. Larger amounts are required and the results are more erratic. For example, in 2 patients, definite subjective and cardiovascular effects were seen after smoking only 1 mg. of the drug. In some of the other patients, only mild effects were observed after smoking as much as 4 mg. of the drug. Attempts to improve consistence of the effects by more careful distribution in drying of the drug on the tobacco are underway.

Combined administration of LSD and CA-101. These experiments are currently in progress. Patients are receiving orally 60 mcg. of LSD plus 1/2 mg. of CA-101. Controls include a placebo; LSD alone; and CA-101 alone. Results so far indicate (1) Even 0.5 mg. CA-101 will induce definite mild subjective effects in the majority of subjects; (2) One-half mg. of CA-101 induces definite cardiovascular effects (but not great weakness or fainting) in all the subjects; (3) LSD does not block the cardiovascular effects of CA-101; (4) CA-101 does not block the subjective effects of LSD; (5) The subjective effects of 1/2 mg. CA-101 are so mild that no accentuation of the effects of the LSD are observed when the mixture is given. These experiments will eventually be extended to include combinations of a larger dose of CA-101 with LSD.

Sincerely yours,


Harris Isbell, M.D.
Director of Research

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EXPERIMENT 3

EFFECTS OF 100 MG. CHLORPROMAZINE
GIVEN 30 MINUTES BEFORE 60 MCG. LSD-25

MEASURE	PLACEBO + LSD	CPM + LSD	DIFFERENCE	SIGNIFICANCE OF DIFFERENCE
Knee Jerk	1.47	1.44	+ 0.03	N.S.
Pupillary Size	2.72	0.22	+ 2.50	< 0.01
Blood Pressure	1.10	0.75	+ 0.35	N.S.
Questions	32	20	12	N.S.
Grade	1.1	0.5	0.6	< 0.05

Figures are means on 7 patients, 6 white and 1 negro.

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EXPERIMENT 4

75 MG. OF CHLORPROMAZINE

GIVEN 30 MINUTES BEFORE 60 MCG OF LSD-25

MEASURE	PLACEBO + LSD	CPM + LSD	DIFFERENCE	"t"	SIGNIFICANCE OF DIFFERENCE
Knee Jerk	0.95	-0.08	1.03	4.68	< 0.01
Pupillary size	4.78	2.80	1.98	3.91	< 0.01
Blood Pressure	3.07 $\frac{1}{2}$	1.88	1.29	2.3	< .10 > 0.05
Question	135	40	95	5.25	< 0.01
Grade	2.2	1.0	1.2	2.36	< .10 > 0.05

Figures are means of 7 patients, 6 white and 1 negro.
 Figures for knee jerks, pupillary size, and blood pressure
 represent area under time-action curves (8 hours).
 Questions show number of positive answers in 8 hours.
 Clinical grades on 1-4 basis.

EXPERIMENT 5

75 MG. OF CHLORPROMAZINE

GIVEN 30 MINUTES BEFORE 60 MCG. OF LSD

MEASURE	PLACEBO + LSD	CPM + LSD	DIFFERENCE		SIGNIFICANCE OF DIFFERENCE
Knee Jerk	200	2.02	-.02		N.S.
Pupillary Size	2.95	0.90	2.06	4.3	<0.01
Blood Pressure	1.35	1.12	0.23		N.S.
Questions	76	56	20		N.S.
Clinical Grade	1.3	0.8	0.5	2	<.10>5

Figures are means of observations on 12 negro patients.
 Figures in knee jerk, pupillary size and blood pressure represent
 areas under curve.
 Questions, number of positive answers in 8-hour period after drug.
 Clinical Grades on 1-4 basis.

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EXPERIMENT 6

EFFECTS OF 75 MG. CHLORPRIMAZINE ORALLY
GIVEN 1-1/2 HOURS AFTER 60 MCG. LSD-25.

MEASURE	PLACEBO + LSD	CPM + LSD	DIFFERENCE	"t"	SIGNIFICANCE OF DIFFERENCE
Knee Jerk	3.28	2.55	0.73	1.49	N.S.
Pupillary Size	3.59	2.07	1.42	4.38	< 0.01
Blood Pressure	1.81 $\frac{1}{2}$	1.32	0.49	1.57	N.S.
Questions	67	70	3	-	N.S.
Grade	1.1	1.0	0.1	-	N.S.

Figures are means of observations on 12 negro patients over 6-1/2 hour period after CPM given.
Figures represent area under time-action curve (knee jerk, blood pressure, pupillary size).
Questions show number of positive answers during 6 hours.
Clinical grade on basis of 1-4.

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EXPERIMENT 7

EFFECTS OF 25 MG. OF CHLORPROMAZINE I.M.
GIVEN 1-1/2 HRS. AFTER VARIABLE DOSE OF LSD-25.

MEASURE	PLACEBO + LSD	CPM + LSD	DIFFERENCE	"t" OF DIFFERENCE	SIGNIFICA OF DIFF.
Knee Jerk	1.66	1.90	-0.24	-	N.S.
Pupillary Size	2.57	1.35	1.22	2.62	< 0.05
Blood Pressure	1.23	0.90	0.33	-	N.S.
Questions	74	63	11	-	N.S.
Clinical Grade	1.9	1.4	0.5	3.1	< 0.05

Figures are averages of observations on 12 negro patients over 6-1/2 hour period after administration of CPM.
Dose of LSD varied between 60 and 150 mcg.