

NEUROPHARMACOLOGY

TRANSACTIONS OF THE FOURTH CONFERENCE

SEPTEMBER 25, 26 and 27, 1957

CONTENTS

**The Effect of Respiratory Poisons and Anoxia on
Siamese Fighting Fish in Relation to LSD-25 Reaction**

Clinical Studies With Taraxein

"Stop" and "Start" Systems

**Some Relations Between Chemical Structure and
Physiologic Action of Mescaline and Related Compounds**

Editor

HAROLD A. ABRAMSON, M.D.

Biological Laboratory, Cold Spring Harbor and
State Hospital, Central Islip, New York

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September 25, 26, and 27, 1957, Princeton, N. J.

Edited by

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STATE HOSPITAL, CENTRAL ISLIP, NEW YORK

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TABLE OF CONTENTS

Fourth Conference on Neuropharmacology

The Josiah Macy, Jr. Foundation Conference Program:

<i>Frank Fremont-Smith</i>	9
----------------------------------	---

The Effect of Respiratory Poisons and Anoxia on Siamese Fighting Fish in Relation to LSD-25 Reaction:

<i>Harold A. Abramson</i>	11
---------------------------------	----

Group Interchange

References	35
------------------	----

Clinical Studies with Taraxein:

<i>Robert G. Heath</i>	37
------------------------------	----

Group Interchange

References	148
------------------	-----

"Stop" and "Start" Systems:

<i>John C. Lilly</i>	153
----------------------------	-----

Group Interchange

References	178
------------------	-----

Some Relations between Chemical Structure and Physiological Action of Mescaline and Related Compounds:

<i>Gordon A. Alles</i>	181
------------------------------	-----

Group Interchange

References	266
------------------	-----

Index	269
-------------	-----

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TABLE OF CONTENTS

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The Josiah Macy, Jr. Foundation Conference Program:

<i>Frank Fremont-Smith</i>	9
----------------------------------	---

The Effect of Respiratory Poisons and Anoxia on Siamese Fighting Fish in Relation to LSD-25 Reaction:

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---------------------------------	----

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References	35
------------------	----

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------------------------------	----

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References	148
------------------	-----

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References	178
------------------	-----

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Group Interchange

References	266
------------------	-----

Index	269
-------------	-----

THE JOSIAH MACY, JR. FOUNDATION CONFERENCE PROGRAM

DURING THE PAST fifteen years the Josiah Macy, Jr. Foundation has organized more than twenty conference groups, each group meeting for at least two days annually over a period of five or more years. Each meeting is limited to twenty-five participants (members and guests), selected to represent a multidiscipline approach to some urgent problem in the field of medicine and health. The goal of this conference program is the promotion of communication, the exchange of ideas, and the stimulation of creativity among the participants. The purpose of the publication of the Transactions of the meetings is to share, as far as possible, the conference process with a larger audience than could participate personally in the discussions.

These conferences provide an opportunity for informal give and take among the participants. To further this purpose, the number of presentations planned for each day is generally restricted to one or two. The member, or guest, selected to give such a presentation is requested not to "read a paper," but rather to highlight, in an informal manner, some of the more interesting aspects of his or her research, with the expectation that there will be frequent interruptions by participants in the form of questions, criticism, or comment. Such interruptions during the course of a presentation are encouraged and form an essential part of the "group interchange."

The conference program has always been viewed by the Foundation as an experiment in communication in which there is room for improvement and need for frequent reappraisal. Sufficient experience has already been gained to justify the conclusion that this type of conference is an effective way of improving understanding among scientists in medicine and allied disciplines, of broadening perspectives, of changing attitudes, and of overcoming prejudices. The further conclusion has been reached, as the result of this experiment, that a major obstruction to understanding among scientists lies in the resistance of human attitudes to change, rather than in difficulties of technical comprehension. Less extensive experience with non-scientists has indicated that the effectiveness of this type of conference is not limited to groups of scientists, but will function in any group meeting where more effective

communication is the primary goal. It is also clear that the same conference technique, with minor changes, is readily adapted to small international conferences.

The style of publication of the Transactions has aroused considerable interest and some criticism. The criticism has been directed primarily to editorial permissiveness which has allowed in the final text, in some instances, too many questions, remarks, or comments which, although perhaps useful during a heated discussion, seem out of context and interrupt the sequence of thought. A few have objected to the principle of publishing in this style and would prefer a depersonalized summary without interruptions.

The Foundation Staff and the Scientific Editors of these volumes welcome criticism and hope to profit thereby in increasing the usefulness of the Transactions to scientists in this country and abroad.

FRANK FREMONT-SMITH, M.D.

Medical Director

THE EFFECT OF RESPIRATORY POISONS AND ANOXIA ON SIAMESE FIGHTING FISH IN RELATION TO LSD-25 REACTION

HAROLD A. ABRAMSON

*The Biological Laboratory
Cold Spring Harbor, N. Y.*

I ASSUME THAT THE ACTION OF LSD-25 (or lysergic acid diethylamide) on man is well known by now, and I need not dwell on it. Whether or not it produces a psychosis that resembles schizophrenia is not a suitable topic for us at this time. However, I assume that it is rather important that we know, if possible, how LSD-25 and similar drugs work on man, even if we must work on lower animals to do so.

The work I shall discuss is still in progress at Cold Spring Harbor, and it is being done in collaboration with Mr. B. Weiss, who is a medical student in the College of Physicians and Surgeons at Columbia, and Mrs. M. O. Baron, who has been working with me for some years on the Siamese fighting fish (1,2,3,4).

Figure 1 illustrates the technique of studying Siamese fighting fish,

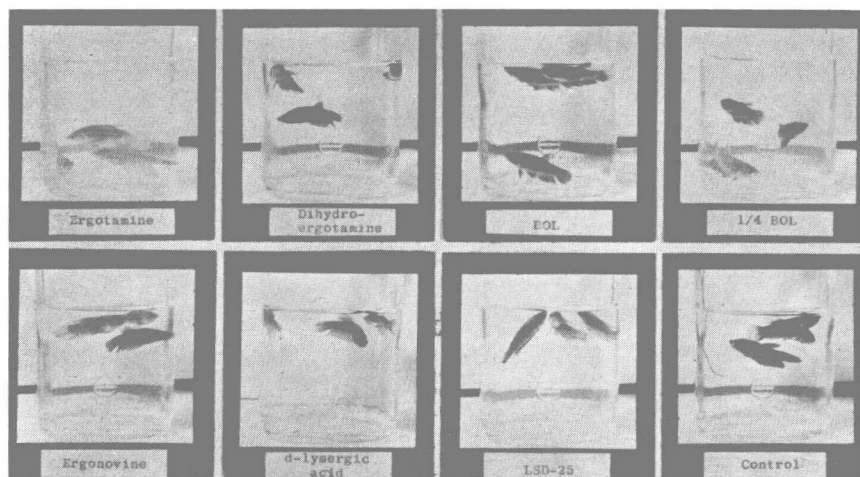


FIGURE 1. Characteristic position of Siamese fighting fish in LSD-25 compared with some other ergot compounds, $5\mu\text{g./ml.}$ of each compound in the outside liquid.

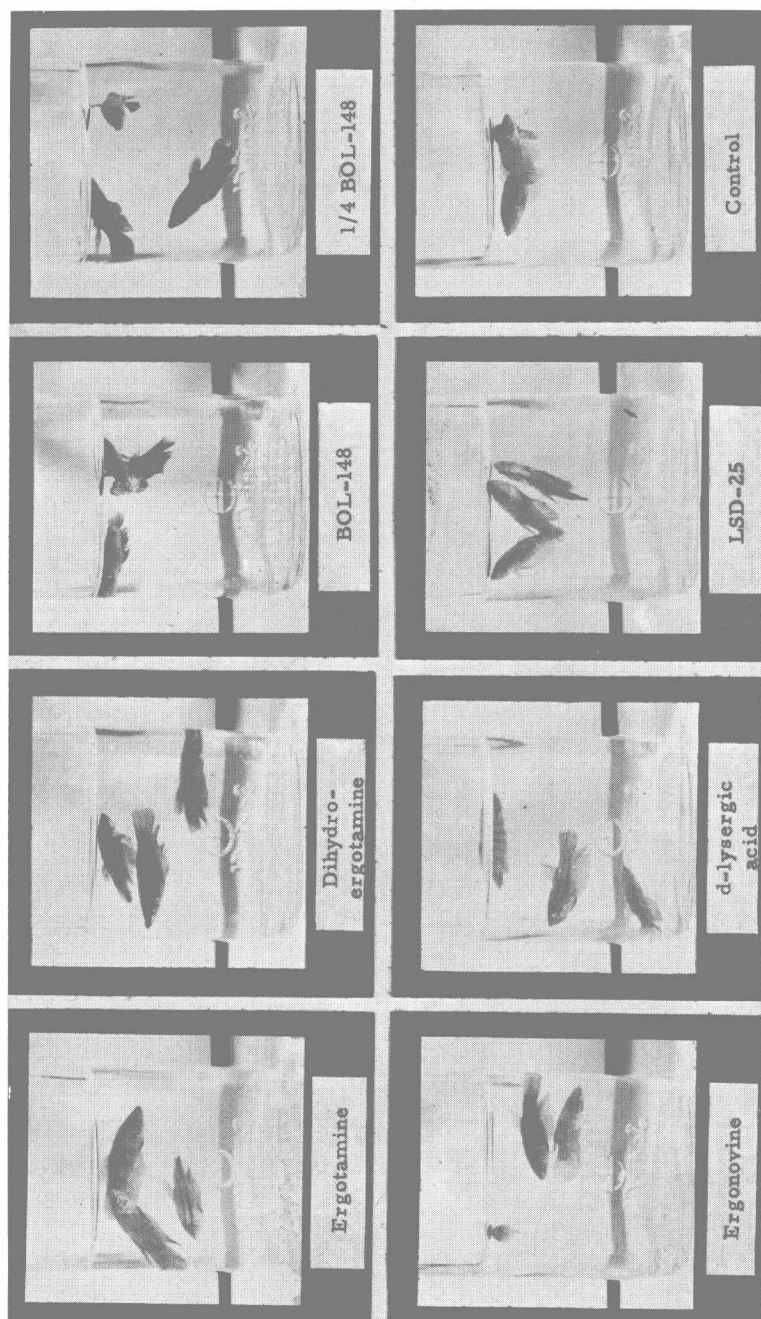


FIGURE 2. Characteristic positions of Siamese fighting fish from the same experiment illustrated in Figure 1.

using drugs of this type, and it also shows the characteristic reaction. The ergot drugs, such as ergotamine, dihydroergotamine, 2-brom-lysergic acid diethylamide, and ergonovine, do not alter the position of the fish in the way in which LSD-25 does. If you were watching the fish, you would see that these were swimming around fairly normally, but the fish under the influence of LSD-25 go into a quiescent state or stupor and show many other characteristics, such as kink in the tail, a change in pigmentation, barrel roll, and the Cartesian diver effect. They go up and down in an almost vertical position. This is very easily observed in 1 $\mu\text{g./ml.}$ of LSD in the outside liquid. It is possible to detect about 0.1 $\mu\text{g.}$ of LSD-25 in this way.

Figure 2 illustrates the same experiment at a different time. Again, the nose-up, tail-down position is seen, with the angle of the fish at the surface at about 45 degrees or more.

Figure 3 illustrates per cent response-time curves that are used as the basis of the bio-assay. These are data from about 240 fish. At about 15 minutes, 70 to 100 per cent of the fish are in the nose-up, tail-down position, with 1 $\mu\text{g./ml.}$ in the outside liquid. Since quite a number of fish died in these experiments, we never reach 100 per cent reaction. This family of curves represents the bio-assay technique which we use routinely in all our experiments.

Hoagland: How do the points fit on those curves, Dr. Abramson? How are the curves drawn?

Abramson: The curves were freely drawn through the points illustrated in Figure 4, showing the raw data.

Figure 5 is a typical experiment which shows the way the assays are conducted. The smooth curves are the LSD curves and serve to compare LSD-25 with 1-methyl-LSD-25 (MLD-41). Ten $\mu\text{g./ml.}$ of MLD-41 in the outside liquid acts roughly like 1 $\mu\text{g./ml.}$ of LSD-25.

Figure 6 also illustrates the way we make comparative studies of LSD-25 and its derivatives, in this case, 1-acetyl-LSD-25 (ALD-52). Figure 6 shows an anomalous reaction, but one which reaches 100 per cent, and it shows that ALD is also, roughly speaking, about one-tenth as strong as LSD-25. I might add here that we have data on what the 1-methyl and what the 1-acetyl derivatives of LSD-25 do to man.

Marrazzi: You must have had a reason for not using the standard presentation of the log of the dose, which would straighten out the curve.

Abramson: I prefer to deal with the actual data rather than a log.

Hoagland: Are they log relationships or semilog plots?

Abramson: Semilog plots will straighten some of them out.

Marrazzi: That system weights the curve according to probability, at both ends, so you have a truer representation of the data, actually.