LSD 974/~~BOL/LAE(PSI)~~
LAE 45 / BOL / PSI

Published as a separate and in *The Journal of Psychology*, 1961, 52, 445-455.

LYSERGIC ACID DIETHYLAMIDE (LSD-25) XXXIII. EFFECT ON SURFACING BEHAVIOR OF THE CARP AND POSSIBLE APPLICATION TO GAME CONSERVATION AND SURVIVAL KITS* [1]

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Howard A. Loeb (8, 9) has stated that, "None of 1,800 assorted compounds force-fed to carp has produced more than random surfacing or any directed movements of the fish." Any class of compounds which produces surfacing and directed movements of carp, therefore, may be of importance in the control of fish populations, as well as in the study of the physiology of the fish themselves. It is the purpose of this communication to show that a group of compounds related to lysergic acid diethylamide (LSD-25) produces surfacing behavior of carp with the movement, therefore, directed toward the surface, providing the pharmacologic effect that has been sought through forced feeding. Our experiments have not as yet included feeding these drugs to fish, although extensive work on man (2) would indicate that the material is absorbed from the intestinal tract. The drugs are active when given intraperitoneally to the Siamese fighting fish (3).

It has been previously shown in work from this Laboratory that very small quantities of derivatives of d-lysergic acid, like lysergic acid diethylamide (LSD-25) and lysergic acid ethylamide (LAE-32) have an important effect on the Siamese fighting fish (1, 5). Less than 0.5 mcg per ml of LSD-25 in the outside liquid causes most of the fish to go to the surface of the liquid and remain relatively immobile. Figure 1 illustrates, in somewhat less than actual size, three juvenile forms of the Siamese fighting fish at the surface of a small volume of liquid containing 5 mcg of LSD-25 per ml. The nose up-tail down position of the fish is shown. At this concentration the fish may remain stuporous and at the surface for

* Received in the Editorial Office on July 31, 1961, and published immediately at Provincetown, Massachusetts. Copyright by The Journal Press.

[1] This research was supported in part by a grant from Sandoz Pharmaceuticals, Hanover, New Jersey.

several days. All of the fish usually recover from treatment with this type of lysergic acid derivative.

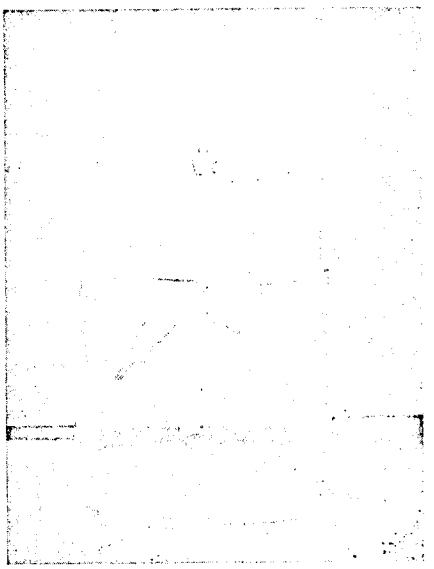

FIGURE 1

Three juvenile forms of the Siamese fighting fish at the surface of a small volume of liquid containing 5 mcg of LSD-25 per ml. The nose up-tail down position of the fish is shown. The fish are less than 2 inches long.

The need for improved sampling methods of fish collection in lakes is well brought out by the recent papers of Loeb (6, 7, 8), who describes both electrical and rotenone methods for capture and recapture of fish in small lakes from 30 to 300 acres in size. It is of importance to investigate the action of compounds like lysergic acid diethylamide on fresh-water fish in larger bodies of water, in connection with game conservation programs and the possibility of employing drugs of this type in survival kits. This paper is a preliminary report on laboratory trials which extend our earlier experiments to the carp. Larger volumes of liquid were employed, and much larger fish than hitherto were investigated.

A. Experimental

1. *Effect of LSD-25 on Goldfish*

The first experiments were performed on small goldfish commonly available in pet shops. In our earlier experiments it was found that goldfish

respond to LSD-25 in somewhat the same way that Siamese fighting fish do. The reaction of goldfish was not so readily observed in small volumes of liquid (100 ml for 10 fish). For this reason a small aquarium was used to study goldfish. A 6-liter tank was found suitable for studies of this type. Note in Figure 2 the effect of 2 mcg per ml of LSD-25 on goldfish observed in two 6-liter tanks. Tank 1 is the control tank to which no LSD-25 or other chemical was added. The darkish forms at the bottom of Tank 1 are clusters of 10 goldfish. In the absence of disturbing influences the fish rarely rise to the surface during the course of the experiment. Tank 2, also containing 10 goldfish of the same size, strikingly illustrates the effect of 2 mcg per ml of LSD-25 on their surfacing behavior. After 5 minutes movement of the fish is readily observed with surfacing behavior almost complete after 10 minutes. This effect is very similar to the phenomena observed on the Siamese fighting fish. The surfacing behavior also occurs when a slow stream of air is bubbled through the tank. It should be noted that streaming air bubbles stimulate the fish. That is, the bubbles of air do not destroy the compound very rapidly. For this reason 2 minutes should elapse after turning off the air stream before a count is made of the fish at the surface. The size of the small goldfish may be readily estimated from the tank height which is 8 inches.

2. *Effect of LSD-25 on Large Carp*

Through the kindness of Dr. Howard A. Loeb of the New York State Conservation Department, carp at least 2 pounds in weight were sent to this Laboratory for study. The fish were kept in a running spring close to the Laboratory. Compare Figure 3, an experiment on these large carp in cold winter tap water, with an experiment on the much smaller species of carp, the goldfish (Figure 2). Each cylindrical glass tank in Figure 3 contains 44 liters of solution. The size of the fish may be estimated from the tank diameter which is 15.5 inches. Note in Figure 3 that Tank 2 rather than Tank 1 is the control tank. During the course of an hour, throughout which air was bubbled through both tanks, the control fish in Tank 2 remained at the bottom of the tank. However, the fish in Tank 1, to which 2 mcg per ml of LSD-25 were added, had reached the surface of the liquid in the tank within 45 minutes. They remained there in very much the same way as the Siamese fighting fish and goldfish (see Figures 1 and 2).

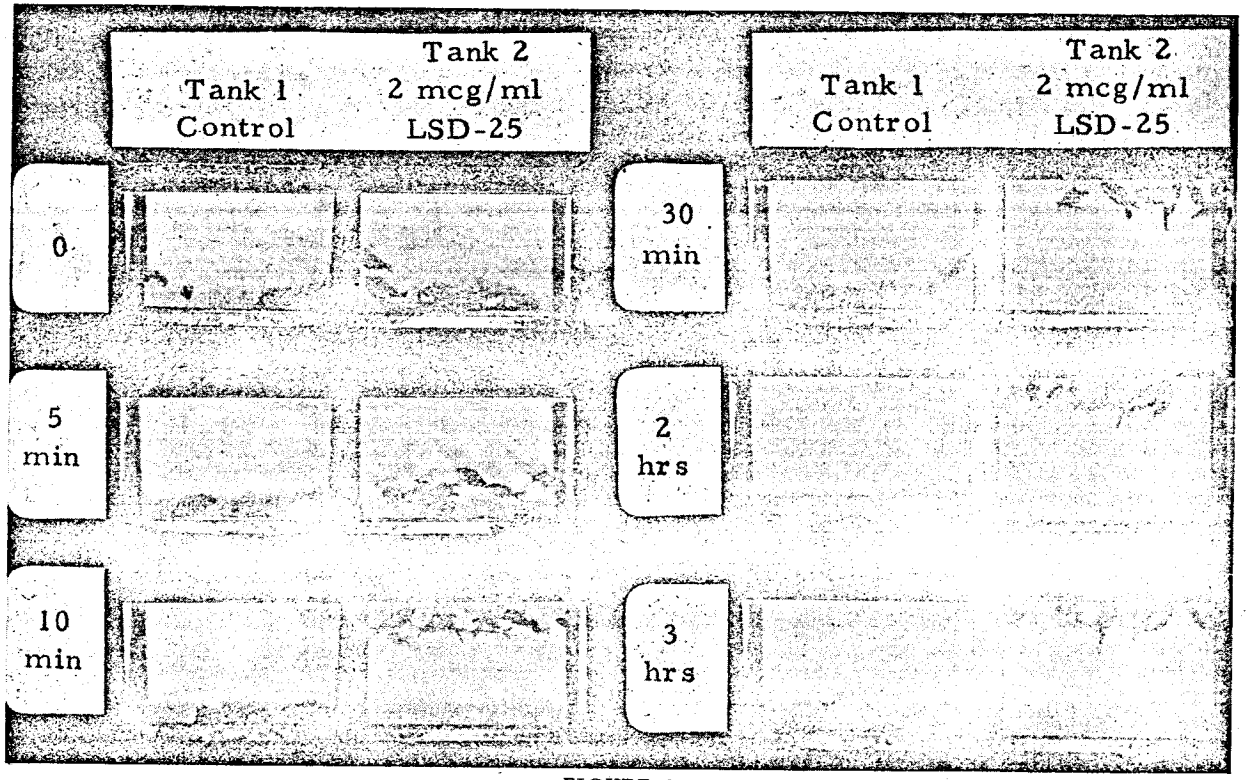

FIGURE 2

The effect of 2 mcg per ml of LSD-25 on goldfish observed in two 6-liter tanks. Tank 1 is the control tank to which no LSD-25 or other chemical was added. The darkish forms at the bottom of Tank 1 are clusters of 10 goldfish. Tank 2 also containing 10 goldfish of the same size, strikingly illustrates the effect of 2 mcg per ml of LSD-25 on their surfacing behavior. Note that the effect of LSD-25 is visible within 5 minutes and complete within 10 minutes under experimental conditions.

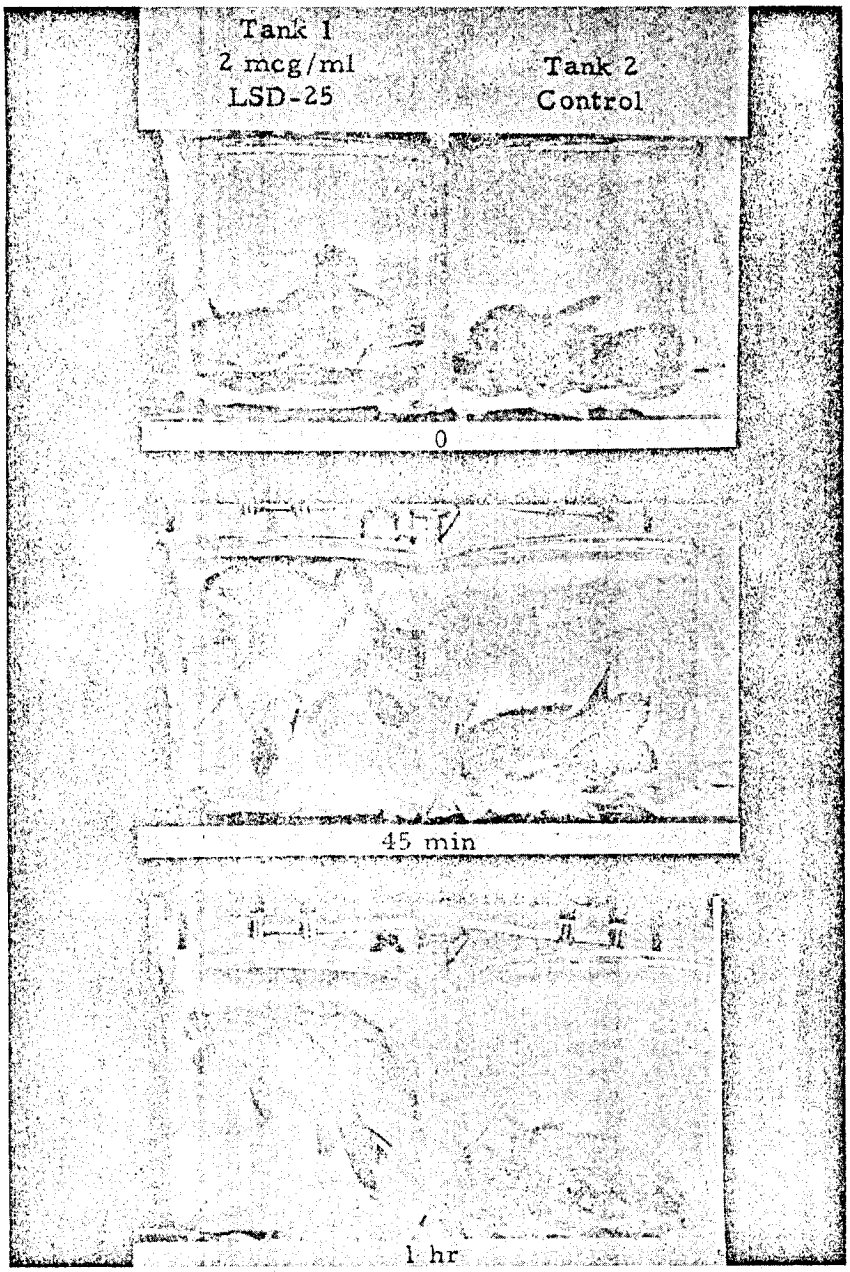

FIGURE 3

The effect of LSD-25 on large carp. Tank 2 is the control tank. Typical surfacing behavior due to LSD-25 is shown by the fish in Tank 1.

B. Protocol of Typical Experiments

Date: February 23, 1961

Control Tank: (Capacity 20 liters) Contained 3 carp approximately 2 pounds each.

Experimental Tank: (Capacity 20 liters) Contained 4 carp approximately 2 pounds each.

Air was bubbled through each tank. In the control tank, observed for 1 hour and 40 minutes, the fish stayed very quietly at the bottom. In the experimental tank, to which 40 mg of LSD-25 were added, the fish showed some signs of reacting within 10 minutes. Within 30 minutes they started to show typical surfacing behavior. At 30 minutes an additional 20 mg of LSD-25 were added. At 50 minutes all the carp in the experimental tank were at the surface and stayed there until removed from the tank at 3½ hours.

In order to test the reactivity of the control fish 40 mg of LSD-25 were added to the control tank at 1 hour and 40 minutes. Ten minutes later they began to show a typical LSD-25 reaction which was completed within 20 minutes probably because of the higher temperature of the water.

Date: March 2, 1961

Control Tank: (Capacity 44 liters) Contained 3 carp approximately 2 pounds each.

Experimental Tank: (Capacity 44 liters) Contained 3 carp approximately 2 pounds each.

At 12:30 p.m. 88 mg of LSD-25 were dissolved in the water of the experimental tank. After the fish had been exposed to LSD-25 for 10 minutes they showed signs of LSD-25 activity. Respiration was apparently increased and the mouth movements of the drugged fish were different from those of the control fish. At 30 minutes all 3 fish in the tank containing LSD-25 were at the surface of the liquid in a nose up-tail down position, with the control fish showing some restlessness but remaining at the bottom of their tank. For the subsequent hour the fish in the tank containing LSD-25 remained at the surface, from time to time moving and even swimming backwards. Of course, they were somewhat cramped in the round tanks and their movements were governed, perhaps in part, by their difficulty

in maneuvering for space. It was extremely difficult for all three fish to be completely at the surface at one time.

The fish were returned to our outside running water pool after 1½ hours in the tank containing LSD-25. In the pool they continued to stay at the surface, moving around but not going to the bottom at all. Two hours after these 3 fish were placed in the pool they were still at the surface. Normal carp cluster at the bottom even when food is introduced. The fish under LSD-25 ignored food scattered in the pool.

Through the kindness of Mr. Edward White of the New York State Fish Hatchery at Cold Spring Harbor an experiment was done to estimate if eastern brook trout reacted similarly as carp to LSD-25. This single experiment is reported because of the possible importance of LSD-25 on brook trout in conservation programs.

1. *Effect of LSD-25 on Brook Trout*

Eight Salvelinus fontinalis (eastern brook trout) were placed in a large vessel (30 liters) of artesian well water at 11:55 a.m. Shortly before this the fish had been fed. At 12 noon, 40 mg of LSD-25 were added. The fish varied in size from 5 to 10 inches and were approximately 1 year old. At 12:15 p.m. the fish vomited. Most of the water was drawn off. New water was added and the 40 mg of LSD-25 were replaced. The fish vomited again at 12:20 p.m. At 12:25 an additional 20 mg of LSD-25 were added. The swimming function seemed to be impaired in some of the fish, and they remained on the bottom of the vessel until the effect of the LSD-25 apparently decreased. A few fish went to the surface of the water but did not remain there. Their reaction was not similar to the carp.

At 1:10 p.m. when the experiment was discontinued all fish were swimming slowly around in the vessel. They appeared to be somewhat drugged, but not enough to interfere with essentially normal behavior. Mr. White thought their behavior might represent oxygen deprivation.

All of the trout survived treatment with this dosage of LSD-25.

2. *Effect of LAE-32 on the Carp*

Figure 4 illustrates the effect of LAE-32 on small goldfish ½ hour after 2 mcg per ml of LAE-32 were added to their 6-liter tank. Air was bubbled through both tanks. The goldfish, stimulated by the air bubbling, show more activity in the control tank on the left than in the absence of bubbling.

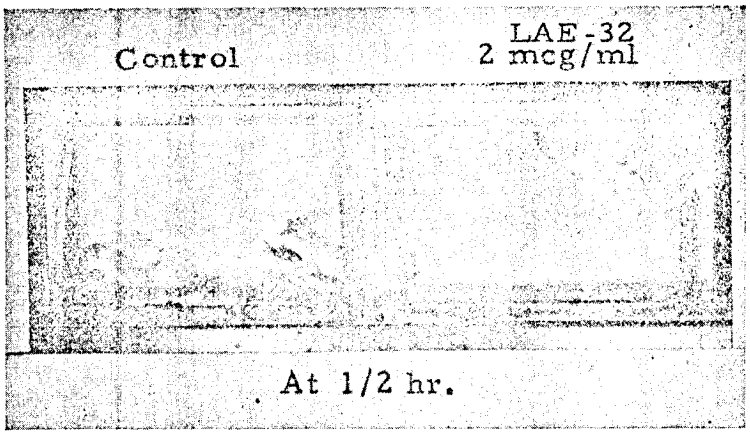

FIGURE 4

The effect of LAE-32 on small goldfish ½ hour after 2 mcg per ml of LAE-32 were added to their 6-liter tank. Note the surfacing behavior.

However, the fish in the right tank treated with LAE-32 show an effect identical with LSD-25. The similarity of the effect of LAE to LSD, however, was pointed out in one of our earlier papers on the Siamese fighting fish (5). The larger carp were next tested with LAE-32. Figure 5 shows that 2 mcg per ml of LAE-32 also affect the larger fish, qualitatively speaking, in the same way as LSD-25. There is a difference, however, in the rate at which LAE-32 reacts. LAE-32 takes longer to act and the larger carp do not remain as consistently at the surface as they do with a similar concentration of LSD-25.

Experiments with LAE-32 are significant for the following reasons. If drugs of this type are to be used to produce surfacing behavior of carp and possibly other fish, the less toxic the drug to man, the simpler would be the application of the method to field studies and to survival kits. Table 1 illustrates the order of activity of certain LSD-25 derivatives and congeners obtained on the nonpsychotic test group used for the past 5 years at this Laboratory. Note in Table 1 that LAE-32 is 1/30 as active in man as LSD-25. Other things being equal, it would appear that LAE-32 might well take the place of LSD-25 in experiments and field trials proposed.

C. Discussion

The mechanism of action of LSD-25 on the fish is unknown. As we have reported previously (4), certain oxidase poisons like sodium azide act

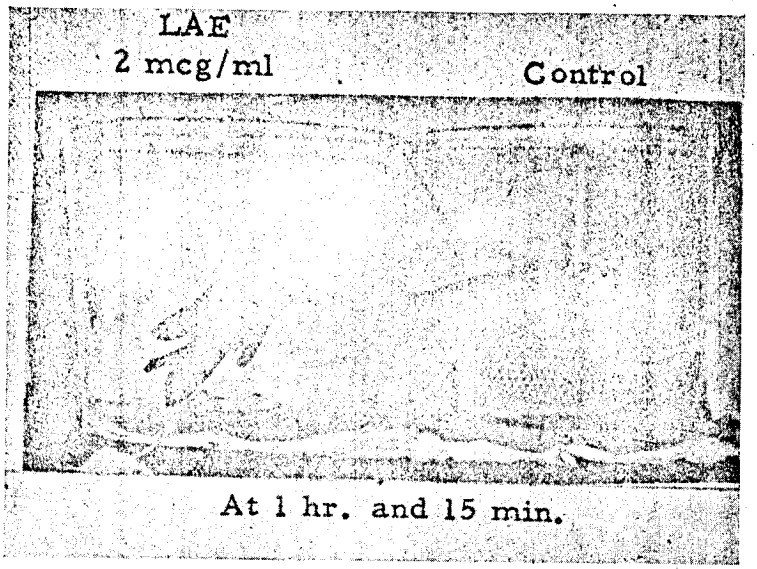

FIGURE 5

Illustrates that 2 mcg per ml of LAE-32 also affect the large fish, quantitatively speaking, the same way as LSD-25. There is a difference, however, in the rate at which LAE-32 reacts. LAE-32 takes longer to act and the larger carp do not remain as consistently at the surface as they do with a smaller concentration of LSD-25.

TABLE 1

ORDER OF ACTION OF LYSERGIC ACID DIETHYLAMIDE (LSD-25) DERIVATIVES IN MAN

		Data From Cold Spring Harbor
LSD-25	(d-lysergic acid diethylamide)	100
ALD-52	(1-acetyl d-lysergic acid diethylamide)	91
MLD-41	(1-methyl d-lysergic acid diethylamide)	36
LSM-775	(d-lysergic acid morpholide)	11
DAM-57	(d-lysergic acid dimethylamide)	11
BOL-148	(2-brom-d-lysergic acid diethylamide)	7
LPD-824	(d-lysergic acid pyrrolidide)	5
LAE-32	(d-lysergic acid ethylamide)	3

similarly to LSD-25 on the Siamese fighting fish. The surfacing behavior of the Siamese fighting fish may also be readily brought about by simple anoxia. It would appear that LSD-25 probably acts by poisoning one of the many oxidase systems which are found in living tissue, because the action of LSD-25 occurs whether the LSD-25 is injected intraperitoneally or placed in the outside liquid. As a matter of fact, the regression lines for the reaction-dose curves of LSD-25, whether in the outside liquid or injected, and Psilocybin when injected, are parallel.

Psilocybin has a much simpler chemical formula. The fact that injected Psilocybin acts like LSD-25 on the Siamese fighting fish (3) brings up the possibility that other compounds simpler than LSD-25 may be effective in inducing surfacing behavior. At present, the cost of LSD-25 prevents its use in large scale experiments. However, it is understood that a fermentation process used in Italy for producing d-lysergic acid might lead to a considerable reduction in the cost of the diethylamide derivative.

This question arises: Can fish, surfacing after exposure to minimal surfacing doses of LSD-25, be safely eaten by man? The question can be solved only by experimentation. However, the half-life of LSD-25 in warm-blooded animals is very short. Probably keeping the fish alive an hour or so after surfacing might lead to an almost complete disappearance of LSD-25 in the tissues. In this connection, experiments in this Laboratory concerned with boiling LSD-25 show that it is not rapidly destroyed by the heat of boiling water. However, we have no data on the effect of boiling LSD-25 in the presence of fish tissue. There is no doubt that LSD-25 does become inactive in the presence of light and of chlorine. The chlorine usually found in drinking water did not appreciably destroy LSD-25 in our earlier experiments (2).

In the preliminary experiments reported here, emphasis must be placed on the use of lysergic acid ethylamide (LAE-32) which is only 1/30th as active in man as LSD-25 (2). Rather large quantities of LAE-32 can be ingested by man without a psychosis developing. It would be of considerable importance to study the effects of LSD-25, LAE-32, and similar compounds in small ponds to determine if these materials or similar materials can be used as fish bait or pellets in survival kits. For example, a suitable pellet of LAE-32 dropped to the bottom of a lake inlet might provide sufficient edible fish, which might otherwise be unobtainable, by the surfacing phenomena.

Of importance to the problem of conservation is the feeding to fish of

substances which would induce surfacing behavior. Experiments are planned in which LSD-25 and LAE-32 will be fed to carp to determine if absorption of these compounds takes place through the intestinal tract. Methods of forced feeding in carp have been worked out by Loeb and his co-workers (8).

D. Summary

Although 1,800 assorted compounds force-fed to carp have not produced directed movements of the fish, the psychotomimetic compound d-lysergic acid diethylamide (LSD-25) as well as other derivatives and congeners do produce surfacing behavior. Preliminary data were obtained by exposing the fish to these compounds in the outside liquid. Carp, as much as 2 pounds in weight, responded, in general, to the same concentration of LSD-25 as did Siamese fighting fish weighing only one gram. Laboratory data are presented on goldfish, carp, and trout. It is proposed that extension of the present experiments to the field might lead to new methods of game conservation and the development of new formulations for survival kits.

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Addendum: Since this paper was submitted for publication, the effect of feeding Psilocybin and Psilocin to goldfish has been observed. Both of these compounds are apparently absorbed through the intestinal tract of the fish when the drugs were incorporated in their food. Rather typical LSD effects are observed.