better leap year rule for our present Gregorian rule, which is neither simple nor as accurate as it should be. Our present rule makes the average year 365 97/400 days. The actual tropical year is shorter than this, and it is growing steadily shorter by a long-term slow change. The most accurate simple leap year rule just now would be the following: a leap year every 4th year unless the year number is divisible by 128 (this gives an average year that was a perfect fit in 1910). To keep in step for thousands of years ahead, we would prefer a simpler rule giving us a leap year every fourth year unless the year number is divisible by 120. With this rule, there would be no appreciable drift over the next 8000 years. Indeed, the maximum drift up to the year A.D. 10,000 would be scarcely more than the range of drift that is inescapable within any 4-year cycle according to any kind whatever of leap year rule. By comparison, the continued use of our Gregorian leap year rule would shift the calendar more than a week by A.D. 10,000. Besides, the improved rule—every 4th year a leap year unless the year number is divisible by 120—would be easier to remember and easier to apply. Having once gotten our calendar into step with the astronomical tropical year, this rule would keep us in step for a very long time to come.

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7 November 1955

## Effect of Ergot Drugs on Betta splendens

It has been reported in a previous communication (*1*) that the Siamese fighting fish, *Betta splendens,* responds to low concentrations of *d*-lysergic acid diethylamide (LSD-25) with a quiescent state that is typified by at least nine easily observable changes in the vegetative, motor, and behavioral characteristics of the fish. This communication summarizes an attempt to determine which, if any, of these nine changes are, indeed, specific for this drug (*2*).

The method employed consisted of exposing groups of three fish to equimolecular solutions of LSD-25 and of eight other ergot derivatives that included two optical isomers of LSD-25 (*l*-LSD-25 and *d*-isoLSD-25), a monobromo derivative of LSD-25 (BOL-148), *d*-lysergic acid, *d*-lysergic acid ethylamide (LAE-32), ergotamine, dihydroergotamine, and ergonovine. Mescaline and meperidine hydrochloride (Demerol) were also tested. The fish were observed continuously over a period of 4 hours; after this they were washed, transferred to fresh spring water, and observed at longer intervals.

Table 1. Response of *Betta splendens* to ergot drugs, mescaline, and Demerol.

| Response | LSD-25 | *l*-LSD-25 | *d*-Iso-LSD-25 | BOL-148 | LAE-32 | *d*-Lysergic acid | Ergonovine | Ergotamine | Dihydroergotamine | Mescaline | Demerol |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Backward movement with pectoral fins | x | | | x | x | | | | | | |
| Head up at surface | x | | | Atypical | Atypical, usually at bottom | | | | | | x |
| Cartesian diver (vertical) | x | | | Rare | x | | | | | | |
| Barrel-roll (vertical) | x | | | Rare | Rare | | | | | | |
| Body kinking | x | | | Rare | Rare | | | | | | |
| Quiescent state | x | | | x | x | | | | | | |
| Slow deliberate movements | x | | | x | x | x | | x | | | |
| Lateral display | x | x | x | x | x | x | x | x | | x | |
| Darkened pigment | x | | | x | x | | | | x | | |

Experiments were performed at concentrations varying from $5 \times 10^{-7}M$ (approximately 0.2 μg of LSD-25 per milliliter) to $5 \times 10^{-5}M$ for the ergot drugs. LSD-25 was active over the complete range. Mescaline and Demerol were completely inactive at this level and were run at concentrations of 2.5 mg/ml and 0.6 mg/ml, respectively, the highest levels of these drugs that are not rapidly lethal. Table 1 reports the results of an experiment at the $5 \times 10^{-5}M$ level. It can be seen that, even at relatively high concentrations, the first five criteria—which seem to define a syndrome of loss of control of the musculature of the trunk that is possibly accompanied by a derangement of hydrostatic bladder function and the quiescent state—are sufficient to differentiate LSD-25 from the other drugs in the table. Both LAE-32 and BOL-148 resemble LSD-25 relatively closely, but both rarely induce the spastic kinking produced by LSD-25 that causes the fish to look like commas when they are viewed from the side and often like letter *s*'s when they are viewed from above. Neither do LAE-32 and BOL-148 cause the fish to assume an almost vertical position near the surface of the water for long periods of time. The symptoms induced by LAE-32 appear later than those induced by either BOL-148 or LSD-25. Fish exposed to BOL-148 in concentrations above 5 μg/ml often die; concentrations of the order of 0.5 μg/ml show no effect beside an increase in pigmentation and a decrease in activity. Since the induction of the torpor varies inversely with the dosage and may take an hour to develop at dosages of the order of 1 μg/ml, there is a possibility of mistaking the BOL-148 reaction for a response to LSD-25 at this concentration if the fish are not observed long enough.

As previously stated, the fish may become essentially quiescent for days. Arousal occurs at the slightest stimulus but is followed by an immediate return to relative inactivity. During the period of entrance into the quiescent state and during the period of emergence therefrom, the fish have been observed to show their typical rage reaction to other fish. The rage reaction lasts only a few seconds, but the full expansion of dorsal, ventral, and (in the case of LSD-25) pelvic fins frequently occurs even though the fish are otherwise essentially quiescent.

The specific effect on *B. splendens* of the diethyl amide group of LSD-25 is therefore vulnerable to changes in either spatial or chemical variations in the structure of LSD-25. Similarly, in man only LSD-25 shows its special effects (*3*). However, the action on brain metabolism as measured by oxygen consumption does not depend on this spatial specificity but on the chemical structure (*4*).

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### References and Notes

1. H. A. Abramson and L. T. Evans, *Science* 120, 990 (1954).
2. This investigation was supported by grants from the Josiah Macy, Jr., Foundation and the Geschickter Fund for Medical Research, Inc. We are indebted to Sandoz Chemical Works, Inc. for supplies of the lysergic acid diethylamide and its derivatives.
3. M. Jarvik, H. A. Abramson, M. Hirsch, *J. Abnormal Social Psychol.*, in press.
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3 August 1955

## Formation of Radioactive Protein-Bound Monoiodotyrosine by Stored Thyroid Slices

During the course of our investigations of thyroidal iodine metabolism, the observation was made that cattle thyroid slices or lobes that have been stored in the refrigerator (or deep-freeze unit) for 24 hours or more retain much of their ability to form protein-bound $I^{131}$ from iodide-$I^{131}$ present in the Krebs-Ringer bicarbonate buffer incubation medium. We have now investigated the $I^{131}$ metabolism of stored thyroid slices (*1*) in some