of $MgCl_2$ to water from Olalla Pond, by a high concentration of Mg. The reduction, as in Hot Lake, of the second zone or sodium "salt" in the presence of a very high concentration of magnesium is possibly due to competition for attachment sites by the ions.

Lakes, then, have a reasonably uniform complement of organic "salts" or perhaps "complexes," the uniformity resting largely on the inorganic ions common to all. High *p*H values or a very high concentration of a single ion may modify the pattern. That the yellow acids are intimately associated with the ionic metabolism of lakes is clear. In addition to the connection of these acids with the major ions, preliminary studies have shown possible involvement with such less abundant, but biologically important, ions as cobalt, iron, manganese, copper, and zinc.

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Reference

1. J. Shapiro, *Limnol. & Oceanog.* 2, 161 (1957).

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Effect of Iproniazid on Brain Levels of Norepinephrine and Serotonin

Iproniazid (1-isonicotinyl-2-isopropylhydrazine; Marsilid) was originally introduced as a drug for the treatment of tuberculosis, but was soon found to induce signs of central stimulation. Recent observations (*1*) indicate that the action on the central nervous system may be of value in treatment of depressed mental conditions.

Zeller *et al.* (*2*) were the first to observe that iproniazid inhibits monoamine oxidase, an enzyme which can inactivate norepinephrine and serotonin, substances which may be involved in central regulatory mechanisms (*3*). In a recent paper (*4*) we have presented evidence that monoamine oxidase has a major role in the physiologic inactivation of both monoamines in the brain. The data presented in this report show that repeated doses of iproniazid induce a marked rise in the brain levels of both norepinephrine and serotonin, together with signs of central stimulation.

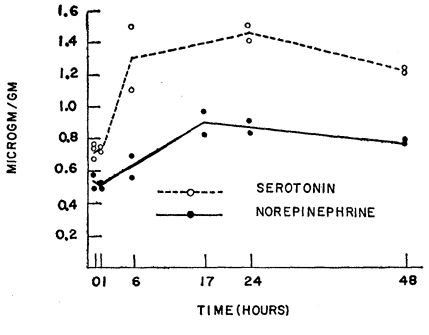

Fig. 1. Effect of a single large dose of iproniazid on serotonin and norepinephrine concentration in rabbit brain stem. Iproniazid (100 mg/kg) was injected subcutaneously. At various times thereafter animals were killed by intravenous injection of air, and the brain stems were analyzed. Each point represents the value from a single animal.

Iproniazid (100 mg/kg) was administered subcutaneously to rabbits, and the concentrations of norepinephrine and serotonin in the brain stem were measured at various times by previously described methods (*5, 6*). As is also reported by other workers (*7, 8*), the serotonin level increased markedly within a few hours after the administration of iproniazid. Norepinephrine levels also increased, but not as rapidly as those of serotonin (Fig. 1). No obvious pharmacological signs were evident.

Iproniazid was given daily in doses of 25 mg/kg subcutaneously to another group of rabbits. Serotonin and norepinephrine levels in the brain stem rose slowly, reaching about twice the normal value in 2 or 3 days (Fig. 2). By the third or fourth day a variable degree of central excitation was evident. Experiments in which the daily dose of iproniazid was 50 mg/kg elicited marked excitement in the animals on about the third day, when serotonin and norepinephrine levels had again risen about twofold. With a smaller daily dose of iproniazid (10 mg/kg), excitation was observed after 4 or 5 days, at which time the brain levels of both amines were again about twice the normal values.

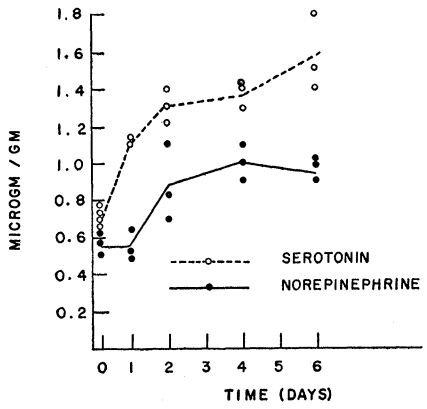

Fig. 2. Effect of daily doses of iproniazid on serotonin and norepinephrine concentration in rabbit brain stem. Iproniazid (25 mg/kg) was injected daily, subcutaneously. Animals were killed at various times by an intravenous injection of air, and the brain stems were analyzed. Each point represents the value from a single animal.

Isoniazid (isonicotinylhydrazine), a congener of iproniazid, is a poor inhibitor of amine oxidase. In daily doses of 50 mg/kg it caused neither a rise in the brain concentration of the amines nor any obvious pharmacologic effect. On the other hand, α-methyl, β-phenylethylhydrazine (JB 516, Lakeside Laboratories) a potent monoamine oxidase inhibitor of a different chemical series, when given daily in doses of 1 mg/kg, induced in 3 to 5 days pharmacologic effects similar to those seen after administration of iproniazid and raised the brain level of the amines about twofold.

It is not possible to conclude from the data given in this report that the central stimulatory effects of iproniazid are causally related to the increase in brain amines. It is noteworthy, however, that the administration of large doses of 3,4-dihydroxyphenylalanine (*9*), a norepinephrine precursor, or of 5-hydroxytryptophan (*7*), a serotonin precursor, causes central excitation which is enhanced by pretreatment with iproniazid.

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References and Notes

1. H. P. Loomer, J. C. Saunders, N. S. Kline, *Psychiat. Research Repts.*, in press.
2. E. A. Zeller *et al.*, *Experientia* 8, 349 (1952).
3. B. B. Brodie and P. A. Shore, *Ann. N.Y. Acad. Sci.* 66, 631 (1957).
4. P. A. Shore *et al.*, *Science* 126, 1063 (1957).
5. D. F. Bogdanski *et al.*, *J. Pharmacol, Exptl. Therap.* 117, 82 (1956).
6. P. A. Shore and J. S. Olin, *J. Pharmacol. Exptl. Therap.*, in press.
7. S. Undenfriend, H. Weissbach, D. Bogdanski, *Ann. N.Y. Acad. Sci.* 66, 602 (1957).
8. A. Pletscher, *Helv. Physiol. et Pharmacol. Acta* 14, C76 (1956).
9. A. Carlsson, M. Lindqvist, T. Magnusson, *Nature* 180, 1200 (1957).

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Inhibition of Adrenocortical Steroid Secretion by Δ^4-Cholestenone

In the course of studies on Δ^4-cholestenone as an inhibitor of cholesterol biosynthesis it was noted that rats fed high doses of the compound developed striking (six- to eight-fold) hypertrophy of the adrenal glands (*1*). The effectiveness of Δ^4-cholestenone in depressing cholesterol synthesis (*1, 2*) and the demonstrated role of cholesterol as an intermediate in adrenal steroid synthesis (*3*) suggested that the latter might also be depressed. By direct measurement of cor-