

Toxicity of Thiouracil in Normal and Thyroidectomized Rats.

A. E. MEYER, M. B. COLLINS, AND D. MARINE.

From the Research Laboratories, The Maltine Company, and the Laboratory Division, Montefiore Hospital, New York City.

The mode of action of the group of anti-thyroid substances investigated by Mackenzie¹ and Astwood and his collaborators² consists, according to these authors, in an inhibition of formation of the metabolic hormone of the thyroid. It seems, however, that one possible explanation was not completely excluded, namely, that the thyroid hormone was consumed in the process of detoxifying, metabolizing the sulfur compounds, and thus was no longer available for maintenance of the metabolic rate of the animal. This theory was supported by Astwood's³ observation that the most active antithyroid compounds were of the lowest toxicity, which admits of the interpretation that the toxicity of some substances was due to the resistance to destruction by the effect of thyroid hormone. If the mechanism of action were according to this hypothesis, the toxicity of a compound should be higher in the thyroidectomized rat, where no thyroid hormone is available, than in the normal rat. Since our laboratory has always a large number of thyroidectomized rats on hand, we decided to determine the 50% lethal dose of thiouracil on both types of animals.

Method. The intake of a definite quantity of the toxic substance is essential for comparative tests, and, therefore, accurately measured amounts were administered by stomach tube. To dissolve the thiouracil in the drinking water or mix it with the food is less suitable for toxicity experiments. Even if the drinking fountain does not drip when touched by the rat's mouth and thus spill part of the water, and if spillage of food can be avoided absolutely, there is still the diffi-

culty that the quantity of ingestion varies with the rat's desire for food and drink.

A difficulty was encountered in the low solubility of thiouracil in water as compared with the dose necessary to cause toxic symptoms. The substance had to be given in the form of an aqueous suspension, in order to administer sufficient quantities in a volume of liquid not damaging to the animal's stomach. Astwood (*l.c.*) reported that one gram per kilo body weight daily had to be exceeded to cause toxic symptoms. Although in our experience the innocuousness of the substance was not quite that high, it was soon evident that the drug had to be given in amounts so large as to preclude the possibility of complete absorption and so as to appear in the stool, before any signs of poisoning were noted. In view of the uncertain ratio between the dose administered and portion absorbed, the 50% MLD became quite meaningless.

There was no difference between the normal and thyroidectomized animals in their reaction to the treatment. The results are condensed in Table I without keeping the two groups separated. The first symptoms of beginning intoxication were a reduction in food intake and roughness of the fur. Subsequently, most

TABLE I.

No. of rats	Daily dosage, mg/kg wt	Length of treatment in days	Pathological changes
1	0.25	10 K	None
3	0.25	10-15 K	Mild
3	0.50	15-22 K	None
2	0.50	6; 7 D	Severe
3	0.50	9-16 K	Moderate
4	1.00	3-5 D	Severe
4	2.00	3 D	"
2	2.00	2 K	"
4	3.00	2-5 D	"
4	4.00	1-4 D	"

All animals were males varying in weight from 150-231 g with an average of 200. In column "Length of treatment" D means died, K means killed.

¹ Mackenzie, C. G., and Mackenzie, J. B., *Endocrinology*, 1943, **32**, 185.

² Astwood, E. B., Sullivan, J., Bissell, A., and Tyslowitz, R., *Ibid.*, 1943, **32**, 210.

³ Astwood, E. B., *J. Pharm. and Exp. Therap.*, 1943, **78**, 88.

animals developed bloody urine, some also bled from the nose and had diarrhea, and a large number showed tremor. At autopsy the first impression was always the more or less generalized congestion of all internal organs and the whiteness of the intestines caused by the diffuse filling with the thiouracil. This latter was occasionally obliterated in part by intestinal hemorrhage. Lung edema, as observed by Mackenzie and Mackenzie⁴ after thiourea treatment occurred occasionally but

⁴ Mackenzie, J. B., and Mackenzie, C. G., *Proc. Soc. Exp. Biol. and Med.*, 1943, **54**, 34.

was not always the first pathological change. When the lungs were congested, hemorrhage was usually absent. The most damaged organs were, first, the kidneys and, secondly, the liver; occasionally the spleen showed signs of damage, also.

Conclusion. Thiouracil is relatively non-toxic. Continued large doses cause cachexia, tremor, convulsions, bloody urine and feces. Most internal organs show hemorrhagic congestion; kidneys and liver seem to be damaged invariably; edema of the lungs is often, but not always, present.

14529

Increased Growth Produced by Gelatin in Trout Fed Meatless Diets.*

JOHN B. FIELD, ELMER F. HERMAN,[†] AND C. A. ELVEHJEM.

From the Department of Biochemistry, College of Agriculture, University of Wisconsin, Madison.

For many years research on the nutrition of fish has indicated that trout require fresh meat in their diet for normal growth and maintenance.^{1,2,3} The more recent work of McCay and his collaborators points to the existence of an indispensable labile factor present in fresh meat which has been termed "Factor H."⁴ It has been demonstrated that the latter is required for growth and normal erythrocyte production in trout.

Restrictions in the use of meat as an animal feed during the present war food emergency threaten to restrict seriously the culture of trout in hatcheries throughout this country.

* Published with the approval of the Director of the Wisconsin Agricultural Experiment Station and supported through special grants from the Graduate School of the University.

[†] Biologist, Wisconsin Conservation Department.

¹ Davis, H. S., and Lord, R. F., *U. S. Dept. Comm., Bur. of Fish, Doc. No. 1079*, 1930, 130.

² McCay, C. H., *Ann. Rev. Biochem.*, 1937, **6**, 453.

³ Tunison, A. V., Brockway, D. R., Maxwell, J. M., Dorr, A. L., and McCay, C. M., *Cortland Hatchery Report*, No. 11, N. Y. State Conserv. Dept., Albany, New York.

⁴ McCay, C. M., *Science*, 1928, **67**, 249.

This situation prompted a search for satisfactory substitutes for meat in fish diets.

Methods. All experiments were carried out in the Biological Laboratories of the James Nevin State Hatchery,[†] Madison. Healthy rainbow trout, *Salmo gairdnerii irideus*, were obtained directly from the stock raceways of the hatchery. The hatchery stock diet, consisting of ground fresh liver 47.5, ground carp 47.5, and dried brewer's yeast 5, was fed prior to the beginning of the experiment.

The procedure consisted of feeding the same experimental diet to 2 tanks of fish once daily, 6 days a week. An equal number of fish, from the same lot and chosen for their uniformity, were placed into one tank; 300 or more fish per tank were always used. Average weights were obtained once a week by transferring all the fish in a tank to a weighed quantity of water, and dividing the resultant fish weight by the total number of surviving fish.

Of an extensive series of diets which have

[†] This project was made possible by the cooperation of the Biology Division of the Wisconsin Conservation Department and its Chief, Dr. Edward Schneberger.