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Comparative Effects of Dinitrophenol and Thyroxin on Tadpole Metamorphosis.*

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Since a fundamental action of thyroid is an increase in the metabolic rate, it might be supposed that such metabolic stimulation might be responsible for the well known acceleration of metamorphosis in tadpoles.[1] If this were true, the rate of metamorphosis might be increased by dinitrophenol (1-2-4), which has been shown to increase mammalian metabolism to a remarkable degree.[2] However, the results of this study indicate that, in this respect, these 2 metabolic stimulants differ, as indeed they do also clinically.[3]

Tadpoles of *Bufo halophilus* from the same and neighboring egg strings and in the same stage of development were selected at random from a swarm of about 1,000 and divided into 13 groups of 10 each. Two groups were used as untreated controls, 3 for various concentrations of thyroxin, and 8 for various concentrations of alpha-dinitrophenol (1-2-4). Each group of 10 was kept in 200 cc. of tap water which contained a clump of green algae and about 5 cc. of pond water. The solutions and algae were changed every second day. Later in the experiment, 1 cc. of raw minced liver was fed each group every second day, about an hour before changing the solutions. Solutions of crystalline thyroxin (E. R. Squibb and Sons) were added to the baths to give final concentrations ranging between 1:150,000 and 1:2,000,000, and of dinitrophenol to give final concentrations ranging from 1:5,000 to 1:4,000,000. The pH of all the final solutions, including the controls, was between 7.21 and 7.47.

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[1] Gudernatsch, J. F., *Arch. f. Entwich. Mech. d. Organ.*, 1912, **35**, 475.

[2] Cutting, W. C., and Tainter, M. L., PROC. SOC. EXP. BIOL. AND MED., 1932, **29**, 1268. Tainter, M. L., Boyes, J. H., and DeEds, F., *Arch. Int. de Pharm. et de Therap.*, 1933, **45**, 235. Cutting, W. C., Mehrtens, H. G., and Tainter, M. L., *J. Am. Med. Assn.*, 1933, **101**, 193. Tainter, M. L., and Cutting, W. C., *J. Pharm. Exp. Therap.*, 1933, **48**, 410. Tainter, M. L., and Cutting, W. C., *J. Pharm. Exp. Therap.*, 1933, **49**, 187. Hall, V. E., Field, J., Sahyun, M., Cutting, W. C., and Tainter, M. L., *Am. J. Physiol.*, in press. Cutting, W. C., and Tainter, M. L., *J. Am. Med. Assn.*, in press. Tainter, M. L., Stockton, A. B., and Cutting, W. C., *J. Am. Med. Assn.*, in press.

[3] Cutting, W. C., Rytand, D., and Tainter, M. L., in press.

This close similarity in the pH values is important, since Zondek and Ucko[4] have shown that the increase in rate of metamorphosis in tadpoles by thyroid extract is modified by the H-ion concentration of the medium. The experiments were made at a fairly constant room temperature of about 22°C. and in dull sunlight. Records of the growth and development were made at frequent intervals and accurate measurements of length were made by photographing the tadpoles against a millimeter scale.

Results. The average initial length of the tadpoles was 9.5 mm., the external gills were still present and the heads were slender and oval. In the stronger concentrations of dinitrophenol the tadpoles swam excitedly and incessantly until death, often colliding with each other. All the members of these groups died at about the same time; those in 1:5,000 dinitrophenol within 30 minutes, in 1:10,000 within 1½ hours, and in 1:50,000 within 12 hours. In the weaker concentrations of dinitrophenol, the external gills, which were present on the first day, entirely disappeared on the second day and the slender oval heads gradually became more rhomboid and blunt, the eyes more prominent and the stomach pouchy.

In 5 days, the tadpoles in 1:150,000 thyroxin were definitely smaller than those in any of the control or dinitrophenol groups, and 3 of the 10 tadpoles in this thyroxin-group showed hind limb buds. In 7 days, the hind limb buds were well developed on all tadpoles in 1:150,000 thyroxin and also on 3 tadpoles in 1:500,000 thyroxin. The tails showed evidences of deformity and the mouths were wider and strikingly more jaw-like than the sucking mouths still present in the tadpoles of the other groups. In the latter, the eyes were less prominent and heads less rhomboid than in the tadpoles on thyroxin. On the 10th day, there were evident the first fore limb buds, these in one tadpole on thyroxin 1:150,000. By this time, the hind limbs were beginning to differentiate into upper and lower legs, and toes appeared. Deaths at this stage were frequent in the 1:150,000 thyroxin, but none occurred in the other groups. Although no hind limb buds had appeared in either the control or the dinitrophenol groups, these tadpoles were definitely larger and stronger than their metamorphosing neighbors on thyroxin. On the 20th day, the first limb buds appeared in the control and dinitrophenol groups, one being present in the controls and one in 1:4,000,000 dinitrophenol. On the following day, one such bud appeared in 1:500,000 dinitrophenol. At this time, all tadpoles on thyroxin had well developed hind limbs which were one-fourth to one-half the tail length.

[4] Zondek and Ucko, *Klin. Wochschr.*, 1924, **3**, 1752.

One early fore limb bud was present in thyroxin 1:500,000. On the 24th day, all the tadpoles in 1:2,000,000 thyroxin had well developed hind limbs and 2 had early fore limb buds. One control and one tadpole in each of 1:500,000 and 1:4,000,000 dinitrophenol had early hind limb buds.

Tadpoles in thyroxin 1:500,000 were completely metamorphosed by the 30th day, and those in thyroxin 1:2,000,000 were metamorphosed by the 50th day, while only 30% of those on dinitrophenol and 20% of the controls had even limb buds as yet. By the 70th day, only 60% of both control and dinitrophenol groups showed hind limb buds, but no fore limbs at all. The characteristic curve of metamorphosis shown by the tadpoles on thyroxin and the striking similarity between the unmedicated and dinitrophenol groups are illustrated in Fig. 1.

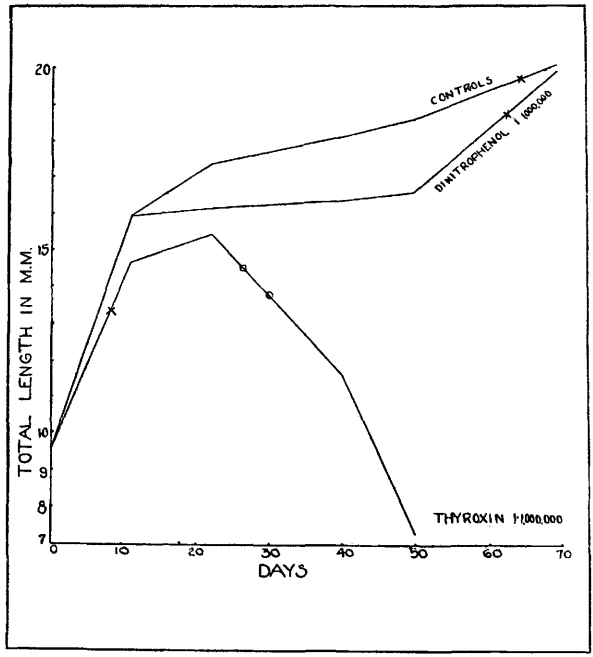

FIG. 1.

Effects of thyroxin and dinitrophenol on growth and metamorphosis of tadpoles. Each curve shows the average changes in length of 10 tadpoles in a given solution. The times at which 50% of the tadpoles developed hind limb buds are indicated by crosses, fore limb buds by a square, and complete atrophy of the tail by a circle.

Another experiment was made on the same species of tadpoles, about one week after leaving their jelly strings. The procedure was the same as in the previous experiment, except that dried grated liver was used for feed throughout. The thyroxin used was a solution

containing 1 mg. per cc. in ampules (Roche; N. N. R.) diluted freshly to a 1:1,000,000 solution with tap water. It seemed to be more toxic to the tadpoles, so that weaker concentrations were necessary. Otherwise, the results agreed entirely with those described above and hence need not be repeated.

Conclusions. 1. Toad tadpoles were found to metamorphose no more rapidly in up to lethal concentrations of dinitrophenol than in the absence of medication, whereas the usual acceleration of metamorphosis was demonstrated in tadpoles on thyroxin. This difference in action agrees with clinical differences in human subjects. 2. Although dinitrophenol can cause increases in metabolism comparable to those of thyroxin, it appears to lack the power of thyroxin to accelerate developmental processes. Apparently, the effect of thyroxin on metamorphosis is not the direct result of increased metabolism, but presumably an independent action. 3. Accordingly, dinitrophenol lacks the hormonal actions of thyroid, and should probably not be used therapeutically to replace the gland in true thyroid deficiencies.

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Effect of Arm Compression on Local Venous Pressure in Patients with Normal and Abnormal Hearts.*

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It is well known that interference with the flow in a vein will cause a rise in venous pressure within that vessel. Villaret, Saint-Girons and Justin-Besançon,[1] and others, have observed that mediastinal tumor or aortic aneurysm may lead to an elevation in venous pressure in one arm if its veins are obstructed. Runge[2] found a higher pressure in the saphenous vein than in the arm veins during pregnancy; a difference which disappeared after delivery. A similar difference was found by Villaret, Saint-Girons and Justin-Besançon[1] in cases of ascites or abdominal tumor. Brams, Katz and Kohn[3] noted a marked rise in pressure in the iliac veins with little or no change in the superior vena cava in experimentally induced abdominal disten-

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