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Anterior Lobe Substance, the Thyroid Stimulator. I. Induces Precocious Metamorphosis.

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In previous work[1] we found that Armour's commercial anterior lobe powder contains a specific substance which, when injected intraperitoneally, not only induces precocious metamorphosis of the injected salamander larvae *(Ambystoma tigrinum)*, but alone among other substances tested (inorganic iodine, thyroid substance, adrenalin, pilocarpin) causes a typical display of the complete functional phase of the thyroid gland of the injected larvae, such as takes place normally during metamorphosis. We concluded that anterior lobe is the extrinsic thyroid stimulator for which one of us has been searching since 1919, and that it causes metamorphosis of the amphibian larvae only indirectly, by forcing the thyroid to excrete. The existence and action of an extrinsic thyroid stimulator (excretor substance) has been shown in a long series of experiments,[2] but the stimulator itself could not be found until 1926.[1] Hogben[3] and later Spaul[4] had found that intraperitoneal injection of an extract made from Armour's anterior lobe powder and other commercial anterior lobe products induces precocious metamorphosis of the Mexican axolotl. But Smith claimed[5, 6] that the metamorphosis-accelerating action of Armour's commercial anterior lobe product is the effect, not of anterior lobe substance, but of a very high iodine content of the commercial product and probably of an admixture of thyroid substance. Spaul[7] demonstrated that an extract prepared from fresh anterior lobe had the same effect as Armour's anterior lobe powder, provided that the anterior lobe is separated from the posterior lobe immediately after the death of the bovine donator. Contamination of the anterior lobe by the posterior lobe takes place otherwise and

* This work was made possible by the "Julius Friedenwald Fund for Research" of the University of Maryland Medical School.

1 Uhlenhuth, E., and Schwartzbach, S., *Anat. Rec.*, 1926, xxxiv, 119. *Brit. J. Exp. Biol.*, 1927, v, 1.

2 Uhlenhuth, E., *J. Gen. Physiol.*, 1919, i, 473.

3 Hogben, L. T., *Proc. Roy. Soc.*, B., 1923, xciv, 204.

4 Spaul, E. A., *Brit. J. Exp. Biol.*, 1924, ii, 33.

5 Smith, P. E., and Smith, I. P., PROC. SOC. EXP. BIOL. AND MED., 1922, xx, 51.

6 Smith, P. E., *Brit. J. Exp. Biol.*, 1926, iii, 239.

7 Spaul, E. A., *Brit. J. Exp. Biol.*, 1925, ii, 427.

such extracts are not only ineffective, but may inhibit metamorphosis. Smith,[6] however, insists that the only active extract to be obtained from anterior lobe must be prepared from the fresh gland according to the method described by Evans and Long.[8] Intraperitoneal injection of such extract *retards* metamorphosis.

In this article will be described the effects upon metamorphosis of extracts prepared in our own laboratory. Aided by 3 assistants, Messrs. M. Dawson, P. C. Jett and H. S. Shelley, we collected the bovine glands in one of the Baltimore abattoirs.† Separation of the 2 lobes was effected one hour after death (by bleeding) of the donators (cows and oxen), the glands cut into small pieces, dried, at room temperature, on glass plates and put away into bottles. Before use the glands were subjected to thorough grinding and desiccation; the fat was not extracted. Extracts were prepared by the method of Spaul, neutralized and injected intraperitoneally 3 times a week.

Larvae of the Utah axolotl (raised from eggs in the laboratory and kept under identical conditions) were injected beginning at an age of 91 days. The average body length was 33.7 mm. (controls) and 35.1 mm. (experimentals). The body length of the metamorphosing control larvae exceeded that of the metamorphosing experimentals by 20 mm.; the experimentals metamorphosed 36 days before the controls. In another experiment, with the larvae of the Long Island *Ambystoma tigrinum*,‡ raised from the eggs in the laboratory and kept under identical conditions, the body length of the metamorphosing experimentals was 10 mm. less than that of the metamorphosing controls. In a third experiment, with Long Island larvae of *A. tigrinum*, the body length of the metamorphosing controls exceeded that of the metamorphosing experimentals by 9 mm. In a fourth experiment with the larvae of the Utah axolotl, in which only one control and 2 experimentals were used the body length of the experimentals was 10.6 mm. less than that of the controls, when metamorphosis took place.

Intraperitoneal injections of Ringer solution and muscle extract had no effect on metamorphosis.

These experiments prove conclusively that anterior lobe substance, even when dried anterior lobe powder is used, enforces promptly the metamorphosis of Urodelan larvae. Evidently Smith,

[8] Evans, H. M., and Long, J. A., *Anat. Rec.*, 1921, xxi, 62.

† We wish to express our gratitude to the Kaufman Packing Co. of Baltimore, for the most generous assistance which they have given us throughout our work.

‡ The spawn of the Long Island larvae was secured through the kindness of Dr. S. C. Bishop, Department of Biology, University of Rochester, N. Y., who collected it for us.

who in his earliest experiments on the larvae of tailless amphibians, obtained results comparable to those reported here, is working now, in his experiments on mammals and urodelan amphibians, with anterior lobe products which are polluted by posterior lobe substance. The latter circumstance seems to be of considerable importance as some of the effects in mammals, claimed by Smith to be caused by anterior lobe substance, may be really caused by admixture of posterior lobe.

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Anterior Lobe Substance, the Thyroid Stimulator. II. Effect of Feeding Anterior Lobe Upon Amphibian Metamorphosis.

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In 1921 one of us showed that feeding fresh anterior lobe of the hypophysis of cattle has no effect on the metamorphosis of *Urodelan* amphibian larvae.[1] As Smith[2] obtained precocious metamorphosis by feeding Armour's anterior lobe powder, he felt certain that this preparation is not pure anterior lobe powder, but owes its action to the presence of iodine or thyroid substance in it.

We fed anterior lobe powder to larvae of the Utah axolotl, raised from eggs in the laboratory and kept under identical conditions. A 1928 sample of Armour's commercial anterior lobe powder and anterior lobe powder prepared in our own laboratory by the method described in Article I of this series were used.

In one experiment 2 controls metamorphosed at an average body length of 58.2 mm., average age 141 days; 3 experimentals fed on our own anterior lobe preparation metamorphosed at an average body length of 63.7 mm., average age 140 days; and 2 experimentals fed on Armour's anterior lobe powder metamorphosed at an average age body length of 65 mm., average age 135 days; one of the latter 2 animals attained the largest size before metamorphosis (68.1 mm.) among the entire 1928 material. The feeding lasted for a period of approximately 102 days. Feeding of a 1928 sample of Armour's

* These experiments were carried out with the aid of the "Julius Friedenwald Research Fund" of the University of Maryland Medical School.

[1] Uhlenhuth, PROC. SOC. EXP. BIOL. AND MED., 1921, xviii, 11.

[2] Smith, P. E., *Brit. J. Exp. Biol.*, 1926, iii, 239.