no previous descriptions of the testicular tumor in teleost have been noted. Since the tumors were not found in normal untreated fish in our laboratory the question of hereditary predisposition of the neoplasm cannot be answered at the present.

The tumor-producing action of corn oil on tissue has been investigated by Burrows and Johnston.[20] Literature reveals that sesame oil may act as a stimulator or inhibitor to certain physiologic activities of tissues or organs. Caspari and Ottensooser[21] claimed that peroral administration of this oil may even impede the growth of transplanted tumors. The chemical nature of sesame oil has been discussed by Bruce and Tobin.[5] It seems that the actions of this oil might be due to some inclusions in the oil. Further studies now in progress using extracted fractions of this oil should help to settle the problem.

Summary. Interstitial cell tumors of the testicle occurred in 3 of 40 adult male teleost (*Xiphophorus helleri*) that had received retroperitoneal injections of sesame oil. Two of the tumors were malignant and the other was local nodular hyperplasia. Damage to other organs and some other effects of the oil treatment were observed. No neoplastic changes were found in the untreated adult male fishes.

[20] Burrows, M. T., and Johnston, C. G., *Arch. Int. Med.*, 1925, **36**, 293.

[21] Caspari, W., and Ottensooser, F., *Z. f. Krebsforsch.*, 1930, **32**, 74; 1932, **38**, 351 (Stern, K., and Willheim, R., *The Biochemistry of Malignant Tumors*, p. 406, p. 450, Reference Press, N.Y., 1943.)

14741

A Difference in Cardiodecelerator Action Between Digitoxin and Digitoxigenin.*

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The cardiodecelerator action of the cardiac glycosides is not due to a single mechanism. A direct effect upon the mammalian heart, demonstrable in the isolated denervated organ, as well as effects mediated by the nervous system, play a role. One of the established sites of action involving the vagal mechanism is the carotid sinus, as was shown by Heymans and Heymans.[1] A central vagal stimulation was assumed by Cushny.[2] However, direct experimental evidence for it rests only on experiments by Greene and Peeler[3] on the innervated turtle heart in which the head was included in a perfusion system separate from that of the heart; while in dogs Heymans and Heymans were unable to observe a central vagus stimulating action of strophanthin when this was applied to the central nervous system in cross-circulation experiments.

Recently Walther[4] has drawn attention to a pharmacological difference between digitoxin and its aglucone, digitoxigenin. In electrocardiographic studies in intact cats, he noticed an immediate decrease in heart rate after the intravenous administration of digitoxigenin. No such change occurred after digitoxin.

Employing the innervated isolated heart of the dog in a cross-circulation method in

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[1] Heymans, J. F., and Heymans, C., *J. Pharm. and Exp. Therap.*, 1926, **29**, 203; *Arch. internat. de Pharmacodyn. et de Thérap.*, 1926, **32**, 9.

[2] Cushny, A. R., *J. Exp. Med.*, 1897, **2**, 233. For complete literature, see Lendle, L., in Heffter's *Handbuch der Pharmakologie. Erganzungswerk*, 1935, **1**, 161.

[3] Greene, C. W., and Peeler, J. O., *J. Pharm. and Exp. Therap.*, 1915, **7**, 591.

[4] Walther, R., *Arch. f. exp. Path. u. Pharmakol.*, 1940, **195**, 709; 1943, **201**, 611.

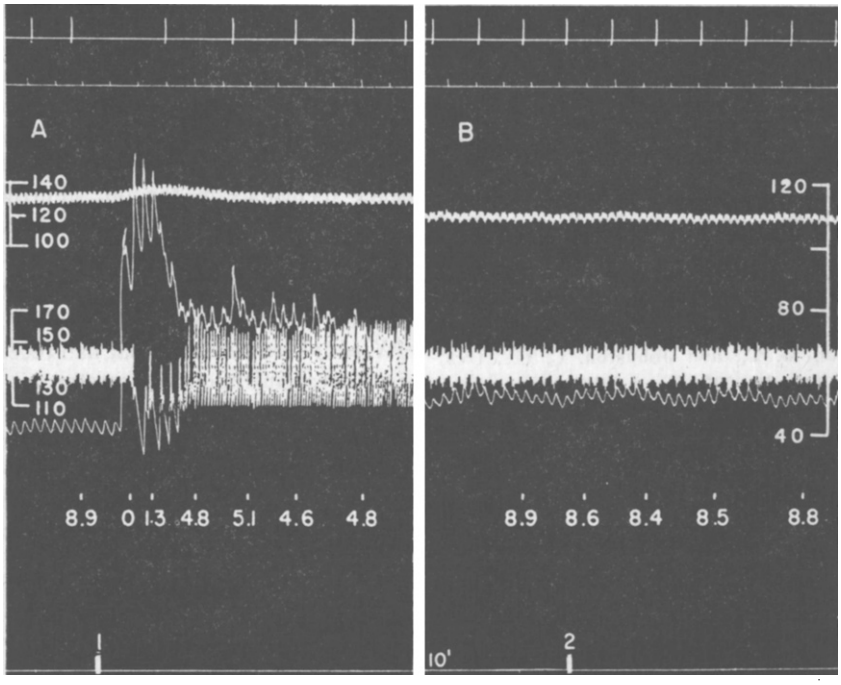

FIG. 1.

Experiment June 8, 1944. The effect of digitoxigenin and digitoxin upon heart rate. Innervated heart-lung preparation; cross-circulation. Head perfused from donor dog. Donor dog, male, 21.2 kg. Heart-lung dog, male, 12.0 kg. Chloralose anesthesia, 0.09 g per kilo. The blood of both animals was heparinized with 3 mg heparin per kilo. The donor received in addition a continuous infusion of heparin into the right femoral vein at a rate of 1 mg per minute. The rectal temperature of the donor dog was 37.3°C. The temperature of the blood in the heart-lung preparation was 38.2°C. The tracings from top to bottom indicate: output of heart-lung preparation in 100 cc; time in 10-second intervals; blood pressure of head region, scale at left in mm Hg; arterial pressure of heart-lung preparation, scale at left in mm Hg; right auricular pressure of heart-lung preparation, scale at right in mm water; signal line. The horizontal row of figures indicates heart rate in 5-second intervals taken from ECG. The zero means that the heart was arrested for 4.5 seconds. Between A and B there was an interval of 10 minutes.

At 1, injection of 0.2 mg of digitoxigenin in 0.1 cc. Blood flow to head 430 cc per minute. Drug concentration approximately 1:75,000. At 2, injection of 0.3 mg of digitoxin in 0.15 cc. Blood flow to head 430 cc per minute. Drug concentration in blood approximately 1:50,000. The injections were made into the arterial supply of the recipient head.

which the circulation of the head was kept separate from the heart-lung circuit, we made observations similar to those of Walther and were able to investigate the site of the cardiodecelerator action of digitoxigenin. Five experiments were performed which uniformly revealed the effect illustrated in Fig. 1.

The details of the type of method used were described by Krayer and Verney.[5] In two of the present experiments the perfusion of the head of the recipient dog was made from one carotid artery of the intact donor dog. The blood returned to the donor dog through one external jugular vein. The cardiac glycosides and genins were dissolved in a mixture of equal volumes of absolute ethyl alcohol and 0.9% sodium chloride solution. The injections were made into the arterial supply of

[5] Krayer, O., and Verney, E. B., *Arch. f. exp. Path. u. Pharmakol.*, 1935, **180**, 75. See also Krayer, O., Wood, E. H., and Montes, G., *J. Pharm. and Exp. Therap.*, 1943, **79**, 215.

the recipient head. The total amount of the solution injected was between 0.05 and 0.2 cc. The temperature of the solution was approximately 38°C at the time of injection, and the pH of the solution was approximately 7.0.

Results. Digitoxigenin injected into the head circulation of the recipient dog in doses of 0.05 to 0.2 mg exerted an influence upon the heart which was transmitted by way of the vagus nerves and resulted in a transient slowing of the heart rate. This effect was not dependent upon a blood pressure increase in the head, as could be shown by including in the head circulation a compensating device which prevented pressure changes. Furthermore, if in an uncompensated system a blood pressure increase of about 10 mm Hg did occur (as in the experiment of Fig. 1) the accompanying heart rate decrease was much more pronounced than that caused by a mechanical increase of the blood pressure in the head of 20 to 40 mm Hg. The type of anesthetic agent used proved to be of importance for an investigation of the quantitative relation between dose and effect. When pentobarbital sodium was employed, the action was much less pronounced than with the animals kept under chloralose.

This effect of digitoxigenin cannot be explained by a sensitization of muscular elements of the heart to vagal impulses in the sense of Straub,[6] as the method used separates the head circulation from the heart-lung circuit. Denervation of the carotid sinus areas, which were included in the head circuit, did not abolish the effect. Therefore the action cannot be identical with that of the cardiac glycosides upon the carotid sinus reported by Heymans and Heymans[1] and by Hering.[7]

The site of this action must be in the central nervous system, and it is well to remember in this connection that digitoxigenin is a convulsant agent.[8] It is possible that this central vagal action is a property of the aglucones of the cardiac glycosides. In a single experiment with gitoxigenin, equimolar amounts showed an effect similar to that of digitoxigenin, but less in intensity.

The central stimulating effect upon the vagus of the mammal caused by digitoxigenin and gitoxigenin is not a property of the corresponding cardiac glycosides. Digitoxin, even in larger than equimolar doses, did not cause any significant change in heart rate, irrespective of whether the injection of the glycoside preceded or followed the injection of the aglucone. Gitoxin, which was compared with gitoxigenin, also was without effect in equimolar doses. That strophanthin had no central stimulating effect upon the vagus was already shown in earlier experiments.[1,9]

In interpreting the results of experiments reported in the older literature one has to take cognizance of the fact that impure preparations were often used—as, for instance, in the experiments of Greene and Peeler with soluble digitalis Mallinckrodt—and it is not improbable that such impure preparations were mixtures of glycosides and genins.

Summary. There is a qualitative difference between the circulatory action of digitoxin and that of its aglucone, digitoxigenin. Digitoxigenin causes an immediate and transient cardiodeceleration due to a central stimulation of the vagus. Digitoxin is without effect if administered in equimolar doses under the same experimental conditions. This pharmacological difference between digitoxin and its genin was demonstrated and analyzed with the use of the innervated heart-lung preparation of the dog in which the drugs could be administered into the blood supply to the central nervous system without reaching the heart-lung circuit.

The digitoxigenin and gitoxigenin used in our experiments were prepared by R. P. Linstead and D. Todd, from the Department of Chemistry, Harvard University. The digitoxin and gitoxin were generously supplied by Burroughs Wellcome, Ltd., London. The pharmacological experiments were carried out with the help of Dr. Rafael Mendez and Dr. Gordon K. Moe.

[6] Straub, W., Heffter's *Handbuch der Pharmakologie,* 1924, **2**, part 2, 1419.

[7] Hering, H. E., *Arch. f. d. ges. Physiol.,* 1924, **206**, 721; *Z. Kreislaufforschung,* 1930, **22**, 287.

[8] Trendelenburg, P., Heffter's *Handbuch der Pharmakologie,* 1920, **2**, part **1**, 427.

[9] Heymans, C., Bouckaert, I. I., and Regniers, P., *Arch. internat. de Pharmacodyn. et de Thérap.,* 1932, **44**, 31.