esterol in one experiment are shown in Fig. 1. The effects produced on cholesterol esters are especially striking. As shown in the chart, this lipid constituent rose from 5 to 81 mg %. Experiments to determine the nature of the substance that produces these lipid changes are in progress.

Summary. The external secretion of the pancreas contains a substance that causes a marked rise above the normal in the blood lipid levels of the depancreatized dog maintained with insulin.

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Influence of K-Strophanthosid on Elasticity of the Tortoise Ventricle.

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There has been uncertainty as to whether digitalis glucosides act to decrease the diastolic ventricular volume mainly by virtue of an increase in the efficiency of doing work[1] or by an increase in elasticity, frequently referred to as an increased tonus.[2] This problem has been attacked by several investigators. Cushny[3] misinterpreted his own data in stating that no change in elasticity occurred with large doses of glucoside. Other observers[4, 5] found either little or no change in elasticity with small doses of digitalis which were adequate to increase the force of contraction, and very large increases in elasticity with doses causing contracture. Working with strips of frog ventricle[6] and cat's papillary muscle,[7] other workers have found that great increases in work capacity occur with doses of drug which are without influence on resting elasticity.

We have performed experiments in which the diastolic and systolic elasticity and work of the tortoise ventricle were measured, and the influence of the cardiac glucoside K-Strophanthosid* upon

1 Peters, H. C., and Visscher, M. B., *Am. Heart J.*, 1936, **11**, 273.

2 Cohn, E. J., and Steele, M., *J. Clin. Invest.*, 1932, **11**, 871.

3 Cushny, A. R., *The Action and Uses in Medicine of Digitalis and Its Allies*, Longmans Green & Co., London, 1925, fig. 15.

4 Eismayer, *Ergeb. d. Physiol.*, 1930, **30**, 126.

5 Sulzer, R., *Z. f. Biol.*, 1932, **74**, 571.

6 Ueda, S., *Acta Scholæ Med. Univ. Kioto*, 1924, **6**, 193.

7 Cattell, J. M., and Gold, H., *J. Pharm. and Exp. Therap.*, 1938, **62**, 116.

* We are indebted to the Sandoz Chemical Works, Inc., for supplies of this and other material.

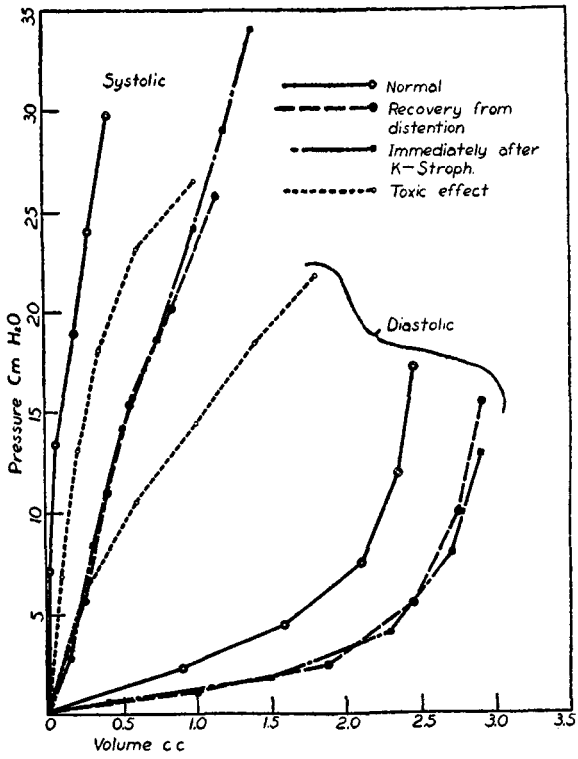

FIG. 1.

these factors. The method of measurement was essentially that employed previously,[8] and consisted in a device for measuring ventricular volume at various pressures in the normally beating ventricle in systole and diastole. Graded doses of the drug were used in different experiments.

The general result of all experiments is seen in Fig. 1, in which is shown the time course of changes following addition of 0.036 mg K-Strophanthosid to 180 cc of perfusion fluid, making a concentration of 1 part in 5 million. The observed changes are: (a) There is no change in diastolic elasticity over the first 10 minutes, while there was a great increase in work performed and tension set up. The pulse pressure at 2 cc diastolic volume before the drug was 10 cm H_2O and after it was 19 cm H_2O, an increase of 90%. The work performed increased in proportion. In experiments in which smaller doses were administered no further change occurred, other

[8] Kabat, H., and Visscher, M. B., 1939, Submitted for publication in the *American Journal of Physiology.*

than the progressive decline in elasticity and work over time, reported elsewhere[8] in the absence of any drug. (b) However, when relatively large doses of glucoside were administered, (greater than 1 part in 7 million) the ventricle showed a progressive increase in diastolic and systolic elasticity, the former increasing more than the latter, so that the pulse pressure and the work fell off greatly. In this experiment, in curve 4 the pulse pressure diminished to 4 cm H_2O at the diastolic volume 1.8 cc. This is to be compared with the 19 cm H_2O figure during the early stage of the glucoside action. All gradations between the 2 occur during the toxic phase, and under the influence of varying doses. In complete contracture the pulse pressure became zero. (c) The most important result noted was that whenever a dose of drug increased the diastolic elasticity, the pulse pressure fell off and the work done declined. The increased work capacity of the heart muscle produced by this glucoside was not associated with a change in elasticity (or tonus).

The further positive fact that, when increases in elasticity were produced by toxic doses, the work done fell off, indicates decisively that the theory, previously held, that the improvement in cardiac efficiency by digitalis glucosides is due even in part to changes in diastolic tonus, is without critical experimental foundation. This theory has been developed from experiments on mammalian heart where it is extremely difficult to dissociate effects of increased work capacity from direct effects upon elasticity. Improved oxygen supply to the myocardium increases elasticity directly[8] and since digitalis increases efficiency of doing work,[1] the oxygen balance is improved by it. An increase in ventricular elasticity in the failing heart after digitalis therefore need not be due to an effect on the physical property of elasticity by the drug, at all, but could be due simply to the indirect effect of improved work capacity. It is obvious that these two effects must be dissociated, which is accomplished readily in the case of the tortoise ventricle.

Summary. The cardiac glucoside K-Strophanthosid has no effect on the diastolic elasticity of tortoise ventricle with doses and within times which result in very large increases in tension set up and work done. Larger doses produce after a time great increases in diastolic elasticity, up to the point of contracture, but when such increases occur the work and tension production fall off. The increase in work capacity of tortoise ventricular muscle produced by this glucoside is not positively correlated with diastolic elasticity changes.

Inferences from observations on the failing mammalian heart are

confused by the fact that anoxia itself alters elasticity, and therefore the increased efficiency produced by digitalis would in itself be expected to increase diastolic elasticity. Such an indirect effect is a secondary result of the primary action of the drug upon work performance.

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Liver Regeneration in Rats Protected with Xanthine Against Carbon Tetrachloride Poisoning.

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Many investigators have attempted to prevent liver necrosis which may arise from the industrial or medical use of carbon tetrachloride or chloroform. Sato[1] described a liver hormone, "Yakriton," prepared from ox livers. Since that time Sato and his collaborators, in a series of nearly a hundred papers, have reported excellent results from the use of this detoxicating hormone. Among the more important claims for "Yakriton" has been the prevention of chloroform necrosis. Recently, Forbes and Neale[2] and Forbes, Neale, and Scherer[3] prepared a liquid extract of hog livers, which, when administered to albino rats prior to acute poisoning with carbon tetrachloride or chloroform, gave a protective action against these drugs. This protective agent was later crystallized from the crude extract by Forbes and McConnell.[4] Neale and Winter,[5] continuing these investigations, were able to identify as xanthine or sodium xanthine the crystalline material that protected against carbon tetrachloride and chloroform. The protective action of liver extract, as well as of sodium xanthine, has been further confirmed by Barrett, MacLean, and McHenry.[6]

Because of the observations made in this laboratory on calcium

1 Sato, A., *Tohoku J. Exp. Med.*, 1926, **8**, 232.

2 Forbes, J. C., and Neale, R. C., PROC. SOC. EXP. BIOL. AND MED., 1936, **34**, 319.

3 Forbes, J. C., Neale, R. C., and Scherer, J. H., *J. Pharm. and Exp. Therap.*, 1936, **58**, 402.

4 Forbes, J. C., and McConnell, J. S., PROC. SOC. EXP. BIOL. AND MED., 1937, **36**, 359.

5 Neale, R. C., and Winter, H. C., *J. Pharm. and Exp. Therap.*, 1938, **62**, 127.

6 Barrett, H. M., MacLean, D. L., and McHenry, E. W., *J. Pharm. and Exp. Therap.*, 1938, **64**, 131.