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The Circulatory Changes Following Full Therapeutic Doses of Digitalis.

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It has been thoroughly established that digitalis diminishes cardiac output of normal animals. Recent observers have attributed this to a direct cardiac action of digitalis,[1, 2] but earlier workers[3, 4] showed that the action on the peripheral vessels was of greater importance. The relationship of the vascular changes to cardiac output in intact animals has not been clearly established or appreciated. We have measured the cardiac output of dogs by the Fick and cardiometric methods and have also observed the changes in arterial pressures, and peripheral organ volumes.

Full therapeutic doses of digitalis produce the following changes in the circulation of morphinized dogs: There is an immediate rise of arterial and venous pressures together with a vagal slowing of the heart, and a peripheral vasoconstriction. Within 5 minutes the venous pressure begins to fall, although arterial pressure may rise gradually for over half an hour. Severe operative procedures diminish the pressor responses. The diminution in cardiac output continues with the progressive fall in venous pressure for 2 hours or more. The vessels of the skin and intestine remain constricted, but the spleen and liver increase in volume. The latter change indicates a pooling of blood in this reservoir probably as the result of hepatic vein constriction which thus results in diminished venous return to the heart.

[1] Harrison, T. R., and Leonard, B. W., *J. Clin. Invest.*, 1926, iii, 1.

[2] Cohn, A. E., and Stewart, H. J., *J. Clin. Invest.*, 1928, vi, 53.

[3] Kaufmann, M., *Rev. d. Med.*, 1884, iv, 381.

[4] Tigerstedt, K., *Skand. Arch. Physiol.*, 1908, xx, 115.

It is therefore concluded that the diminution of cardiac output following digitalization of dogs is due to diminished filling of the heart, as the result of diminished venous return, which in turn is due to widespread peripheral vasoconstriction and redistribution of blood. There is no evidence that the reduced blood flow is due to a cardiac action of the drug.

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Relation of Protein Denaturization Rate to Specific Antibodies.

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Horse proteins injected in routine doses intravenously into normal dogs are so completely denatured by the end of about 4 days that they no longer call forth recognizable anaphylactic reactions on massive blood transfusion into partially exsanguinated horse-serum-hypersensitive dogs.[1] Representing this normal denaturization rate by the coefficient 1.0, the following approximate coefficients summarize our present data:

Horse protein denaturization rate in:

(a) Normal dogs	1.0
(b) Horse-serum-immune dogs[2]	0.7
(c) Cow-serum-hypersensitive dogs	0.5
(d) Horse-serum-hypersensitive dogs[1]	6.0 to 8.0
(e) Desensitized H.S. hypersensitive dogs	4.0

The rapid protein denaturization in hypersensitive dogs, therefore, is apparently due to some specific antibody which is absent or inoperative in immune dogs. This is best explained by the assumption that anaphylactic antibodies and immune antibodies are of different chemical compositions and of different physiological functions, both conceivably defensive in character.

[1] Manwaring, W. H., *et al.*, *J. Immunol.*, 1927, xiii, 357.

[2] Manwaring, W. H., *et al.*, *J. Immunol.*, 1928, xv, 351.