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Effect of Adrenal-Demedullation on Acceleration of Denervated Heart by Acetylcholine Hypotension.*

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Evidence has been presented that adrenaline and sympathin are liberated reflexly in unanesthetized dogs as a result of the brief hypotension produced by intravenous injection of acetylcholine.[1] The diphasic action of acetylcholine on intestinal motility was interpreted as resulting from a direct stimulatory effect of the compound on the intestinal smooth muscle followed by inhibition of the intestine by sympathomimetic substances. Adrenal demedullation prolonged the direct excitatory phase and reduced the inhibitory phase. It was considered that the inhibition that still resulted after adrenal demedullation was caused by sympathin liberated at the endings of adrenergic nerves activated reflexly by the fall in blood pressure.

Wiggers and Green have suggested that the evidence that a part of the acceleration of the denervated heart after acetylcholine injection is caused by adrenalin would have been more convincing had it been shown that the acceleration is reduced after excision of the adrenal medullae.[2] Such an experiment should also determine the cardiac effects of the sympathin produced during acetylcholine hypotension. The effect of a given dose of acetylcholine on the rate of the denervated heart can not be readily determined for the same dog before and after adrenal-demedullation, because the nutritional state of the animals with denervated hearts does not permit carrying them through additional operations. However, records have been obtained from 2 series of dogs with denervated hearts, one series having intact adrenal glands and the other series having the adrenals demedullated prior to the cardiac denervation.

Data obtained by the methods previously described[1] show that adrenal demedullation greatly reduces, but does not entirely eliminate, the acceleration of the denervated heart following acetylcholine in-

* Aided by a grant from the John and Mary R. Markle Foundation.

1 Youmans, W. B., Aumann, K. W., Haney, H. F., and Wynia, F., *Am. J. Physiol.*, 1940, **128**, 467.

2 Wiggers, C. J., and Green, H. D., *Annual Rev. Physiol.*, 1941, **3**, 313.

jections. These facts provide additional evidence that acetylcholine causes the liberation of sympathomimetic substances from both adrenal and extra-adrenal sources. The lower curves in the figure show a comparison of the average effect of intravenous acetylcholine on the rates of the denervated hearts of otherwise normal dogs (solid line) and of dogs with the adrenal glands demedullated (broken line). The former curve is based on 28 experiments on

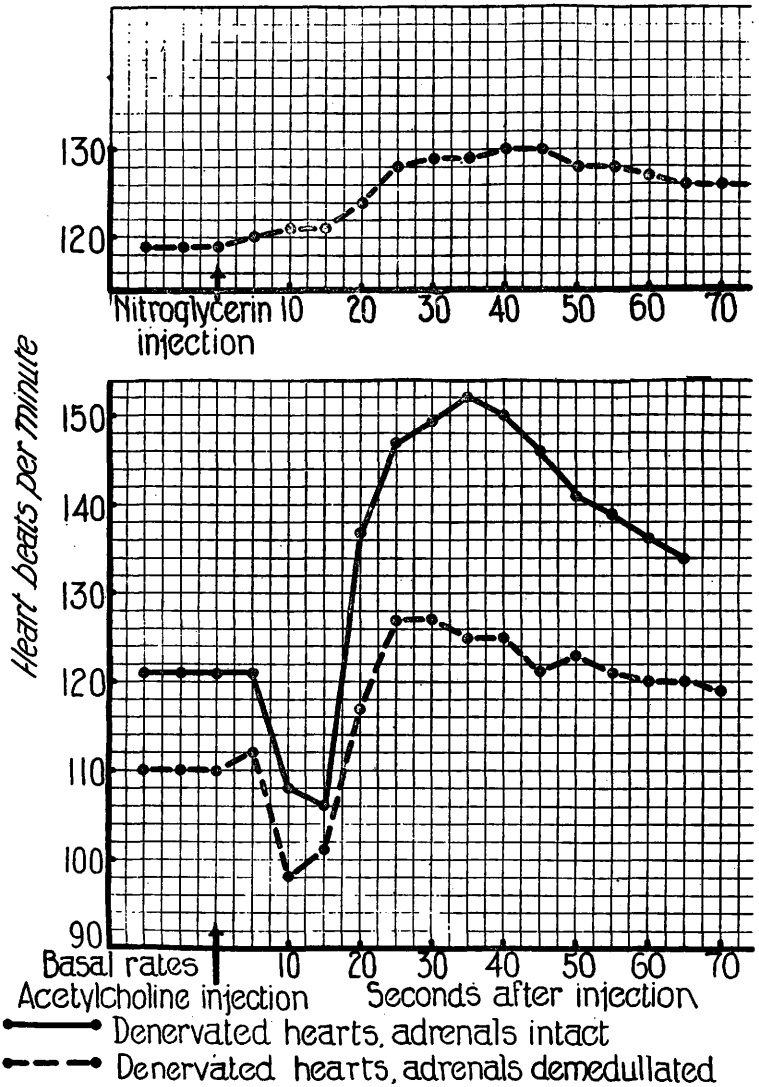

FIG. 1.

9 dogs, and the latter is based on 15 experiments on 5 dogs. Analysis of individual records showed that the denervated hearts of adrenal-demedullated animals were accelerated to rates 10% to 35% above the pre-injection level. The denervated hearts of animals with adrenals intact were accelerated, with comparable doses, to as high as 100% above the pre-injection level, and half of these were accelerated more than 35%. Hearts were considered to be completely denervated if they showed no reflex slowing from a rise in blood pressure produced by neosynephrin and if early acceleration was not obtained following a sharp fall in blood pressure. Eight dogs were discarded because they failed to meet these requirements.

It is possible that a part of the sympathin production during acetylcholine hypotension may have resulted from ganglionic stimulation. Therefore, it was desirable to produce hypotension by a drug lacking nicotinic action. A dose of nitroglycerin was determined which upon intravenous injection produced a severe lowering of blood pressure. The effect of this dosage (1 cc of 1 to 2500 solution) on the rate of the denervated heart as determined in 3 adrenal-demedullated dogs is shown in the upper part of the figure. The late appearance of the cardiac acceleration and its duration indicate that the acceleration is not caused by the direct action of the nitroglycerin. The animals showed no external signs of being disturbed by the injection.

The data obtained in this study when combined with those of the previous paper[1] indicate that a sharp lowering of the blood pressure produced by mild procedures in unanesthetized dogs under near-basal conditions is opposed by reflex liberation of adrenalin. When the adrenals are demedullated a lesser amount of a substance acting qualitatively and quantitatively like adrenalin on both the denervated heart and the denervated intestine still enters circulation. This substance is probably sympathin produced primarily by excitatory adrenergic nerves which are reflexly activated to compensate for the low blood pressure. However, this sympathomimetic substance does not possess the peculiar properties attributed to excitatory sympathin by the theory of Cannon and Rosenblueth;[3] it can not be distinguished from adrenalin itself by the test objects used.

[3] Cannon, W. B., and Rosenblueth, A., *Autonomic Neuro-effector Systems*, pp. 98-109, Macmillan & Co., 1937.