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Experiments on the Supposed Relation of Epinephrine Secretion to Hypertension.

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Cannon and de la Paz[1] suggested that, in emotional excitement, "some of the adrenal secretion set free by nervous stimulation returns to the glands in the blood stream, and, within limits, stimulates them to further activity." If this occurs, it is conceivable that it might play a significant rôle in the production of a persistent elevation of blood pressure. However, such an "autogenous continuance of adrenal secretion," assumed to be important as an emergency function, would at the same time constitute a serious potential menace.

We made quantitative determinations of the rate of epinephrine secretion from the adrenals in dogs after intravenous administration of epinephrine. Ten to 500 times the average amount of epinephrine ordinarily secreted per minute (Stewart and Rogoff[2]) was injected. Epinephrine concentrations were determined with segments of rabbits' intestine. Some of the results were confirmed by the method described by Rogoff.[3] In some experiments the epinephrine was administered at a constant rate, in others it was given in a single injection to simulate an "outburst" from the adrenals as is alleged to occur during emotional excitement. Injection of 0.002 mg. per kg. body weight per minute caused an elevation of blood pressure in anesthetized dogs; striking effects were produced by the larger doses.

Constant injection of epinephrine in doses equal to 10, 20, and 50 times the average normal rate of liberation from the adrenals, did not influence the rate of epinephrine secretion from the glands; nor did such quantities measurably alter the epinephrine concentration in the adrenal vein blood. Similar results were obtained with doses up to 500 times the normal output although in some cases the epinephrine concentration in the adrenal vein blood was increased by the circulating epinephrine. Such increased concentration in the

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1 Cannon, W. B., and de la Paz, D., *Am. J. Physiol.*, 1911, **28**, 64.

2 Stewart, G. N., and Rogoff, J. M., *Am. J. Physiol.*, 1923, **66**, 235.

3 Rogoff, J. M., PROC. SOC. EXP. BIOL. AND MED., 1937, **36**, 441.

adrenal blood closely corresponds with the epinephrine concentration in the systemic circulation and does not necessarily indicate increased secretion. If an increase does occur it is small and transient; when pressor response of a massive dose subsides, a transient diminution in the adrenal output is observed.

These tremendous doses of epinephrine are much greater than the amounts liberated from the adrenals under powerful stimulation. Stewart and Rogoff[4] observed increases up to 20 or 30 times the initial epinephrine output under the influence of certain drugs or electrical excitation of the splanchnic. This would correspond with the smaller amounts employed in the present experiments. We can confirm the observations of Dragstedt, *et al.*,[5] that constant injection of epinephrine in quantities corresponding to 10 times the normal average rate of secretion from the adrenals, or more, cannot be continued for long without serious consequences.

Following a single injection of a quantity equal to 25 to 50 times the amount ordinarily secreted per minute by the adrenals, epinephrine can no longer be detected in the systemic blood about 2 minutes after the injection. Approximately half of the injected epinephrine may be detected in the arterial blood if it is obtained within 30 seconds after injection. These observations on dogs agree with unpublished results on cats obtained in 1931 by Rogoff and Wasserman at Western Reserve University.

The much larger doses of epinephrine yielded similar results, although presence of detectable amounts of epinephrine in the blood sometimes persisted a little longer when large amounts were injected constantly for long periods. We found a loss of epinephrine from the blood in passing from the arterial to the venous course of the circulation. A similar loss was observed in the pulmonary circulation. In quantities that are within the limits of possible experimental increase of secretion by the adrenals, injected epinephrine very rapidly disappears from the circulation.

A few experiments were done in some of which acute hypertension was produced by renal ischemia following firm application of Goldblatt clamps, in others by ligation of the renal arteries. In none of the animals was the rate of epinephrine secretion from the adrenals different from that ordinarily found in normal dogs. Goldblatt[6]

[4] Stewart, G. N., and Rogoff, J. M., *J. Pharm. Exp. Therap.*, 1919, **13**, 95, 183; *Am. J. Physiol.*, 1924, **69**, 605.

[5] Dragstedt, L. R., Prohaska, J. V., and Harms, H. P., *Am. J. Physiol.* (proc.), 1937, **119**, 298.

[6] Goldblatt, H., Lynch, J., Hanzal, R. F., and Summerville, W. W., *J. Exp. Med.*, 1934, **59**, 347.

was able to produce chronic hypertension by renal ischemia after excision of one adrenal, denervation of the other and mechanical destruction of its medulla. This type of hypertension, therefore, apparently is independent of epinephrine secretion from the adrenals. Rogoff and Wasserman tested bloods from a small group of patients with hypertension (obtained through the courtesy of Dr. R. W. Scott at Cleveland City Hospital) and were unable to detect epinephrine in the specimens. Stewart[7] had previously reported a similar negative result.

These experiments lead to the conclusion that increased secretion of epinephrine from the adrenals, as a probable factor in causing persistent hypertension, lacks support of adequate quantitative experimental evidence. Our evidence is against the physiological concept which is a basis for the clinical procedure of surgical interference with the adrenal glands as a therapeutic measure for the relief of hypertension.

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Effects of Thyroxin and Female Hormone on One Phase of Saddle Feather Development.

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The c-isochrone has been defined by Fraps and Juhn[1] as the locus of points in the regenerated feather representing a given level of cell division around the annular collar of the feather germ. This locus appears as a constant configuration in each vane-half of the grown feather and is symmetrical with respect to a common transverse shaft level. If the barbs of either vane-half are in parallel array (at any uniform angle with the shaft), the c-isochrone is a straight line from shaft to margin, equidistant on shaft and a given barb from the point of union of that barb with the shaft. In Fig. 1, for example, barbs are laid out at right angles to the shaft, AB (apex of the feather at A), and the c-isochrone must form in this particular construction an angle of 45° with the shaft. Since the apex of the

[7] Stewart, G. N., *J. Exp. Med.*, 1911, **16**, 502.

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[1] Fraps, Richard M., and Juhn, Mary, *Phys. Zool.*, 1936, **9**, 319.