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Comparison of Changes in Serum Glucose, Serum Potassium and Blood Pressure After Epinephrine.*

FOSTER N. MARTIN, JR. (Introduced by Ralph G. Smith.)
From the Departments of Pharmacology, University of Michigan and the Medical College of the State of South Carolina.

D'Silva[1] and Schwarz[2] described independently the effect of epinephrine in increasing serum potassium. Harrop and Benedict[3] had previously described a fall in serum potassium following insulin. They suggested that this fall in serum potassium was due to involvement of potassium in the formation of the phosphate carbohydrate compound. The fact that epinephrine increases the blood sugar as well as the serum potassium would seem to be support for this. The present work was undertaken to test this theory on the basis of the chronologic relationship of these actions.

Experimental. Cats were anesthetized with pentobarbital and atropinized. Blood samples were taken from a femoral artery before, and as rapidly as possible for the first two minutes after the injection of epinephrine. Further samples were taken at gradually increasing intervals up to periods of from one to 2 hours. Serum potassium was determined by the method of Hoffmann[4] using the Evelyn photoelectric colorimeter. Serum sugar was determined by a Folin micro method also involving the use of the photoelectric colorimeter. The carotid blood pressure was recorded with a mercury manometer. On the same record the time of blood sampling was also recorded. A dosage of 0.075 mg of epinephrine per kg of body weight by intravenous injection was used on 4 cats and in a fifth cat 0.025 mg per kg of epinephrine was used.

Results. The administration of 0.075 mg per kg of epinephrine gave essentially the same results on all animals. In Fig. 1 are recorded the average results obtained from the 4 cats. The same chronologic relationship between blood pressure and potassium changes occurred as previously reported when dosages

* This work was presented as partial fulfillment of the requirements for the Ph.D. degree in Pharmacology at the University of Michigan.

1 D'Silva, J. L., *J. Physiol.*, 1934, **82**, 393; 1936, **86**, 219.

2 Schwarz, H., *Archiv. f. d. Exp. Path. u. Pharm.*, 1935, **177**, 628.

3 Harrop, G. A., and Benedict, Ethel M., *J. Biol. Chem.*, 1924, **59**, 683.

4 Hoffmann, W. S., *J. Biol. Chem.*, 1937, **120**, 57.

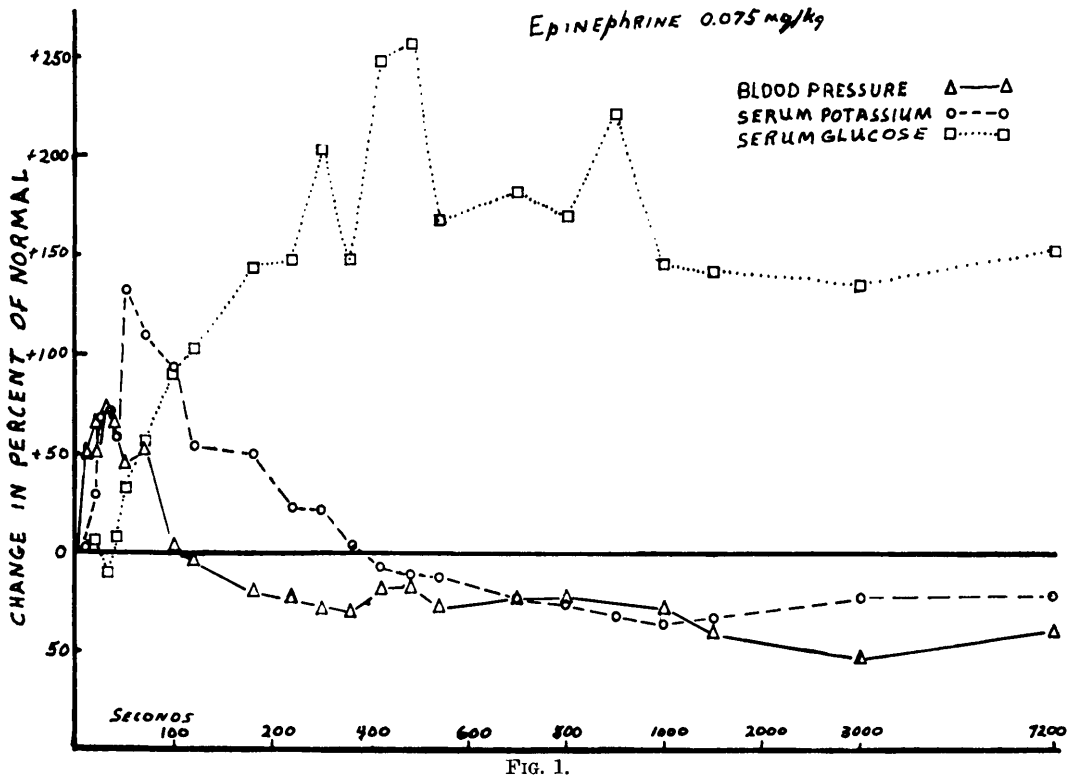

FIG. 1.

Average changes in blood pressure, serum potassium and serum glucose following the intravenous injection of epinephrine in cats.

of 0.1 and 0.05 mg per kg of epinephrine were used.[5] The potassium effect was later by many seconds and was proportionately greater than the blood pressure rise. The peak of the potassium rise occurred after the blood pressure had begun to fall and remained high after the blood pressure had fallen below normal. The rise in blood sugar was slower even than the potassium effect since the rise did not begin until 50 seconds after injection as compared with 20 seconds for potassium. The curve did not reach a maximum until after the blood pressure and potassium had returned to normal or below normal and was still elevated at the end of the experimental period. The results were qualitatively the same with a dose of 0.025 mg per kg of epinephrine (Fig. 2).

Discussion. The delay of the glucose effect suggests the possibility that some decomposition product of epinephrine is responsible for this action rather than the unaltered drug, as suggested by Bacq[6] for the inhibitory effects of epinephrine. Supplementary experiments were carried out in an attempt to test this suggestion. The "adrenoxine" of Bacq[6] (Bacq and Heirman)[7] has not been obtained in sufficient amounts to make its use in such an experiment feasible so attempts were made to produce adrenochrome by oxidation of epinephrine. Enzymatic oxidation of epinephrine (Green and Richter)[8] produces adrenochrome which may be crystallized as a pure compound. Two atoms of oxygen are used for each molecule of epinephrine when the process is carried out in a Warburg apparatus. Since the enzymes and apparatus for such oxidation were unavailable a cruder method of oxidation with potassium permanganate was tried. Attempts to isolate the

[5] Martin, F. N., *J. Pharm. and Exp. Therap.*, 1942, **76**, 270.

[6] Bacq, Z. M., *J. Physiol.*, 1938, **92**, 28P.

[7] Bacq, Z. M., and Heirman, P., *Arch. Int. de Physiol.*, 1940, **50**, 129.

[8] Green, D. E., and Richter, D., *Biochem. J.*, 1937, **31**, 596.

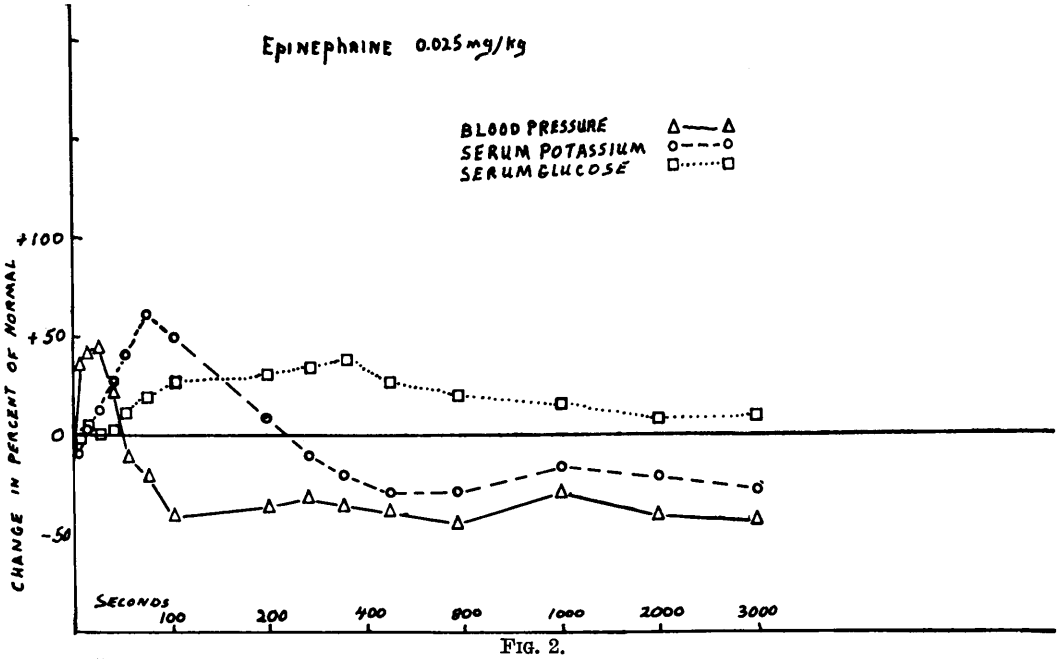

FIG. 2.

Changes in blood pressure, serum potassium and serum glucose following the intravenous injection of 0.025 mg/kg of epinephrine in a cat.

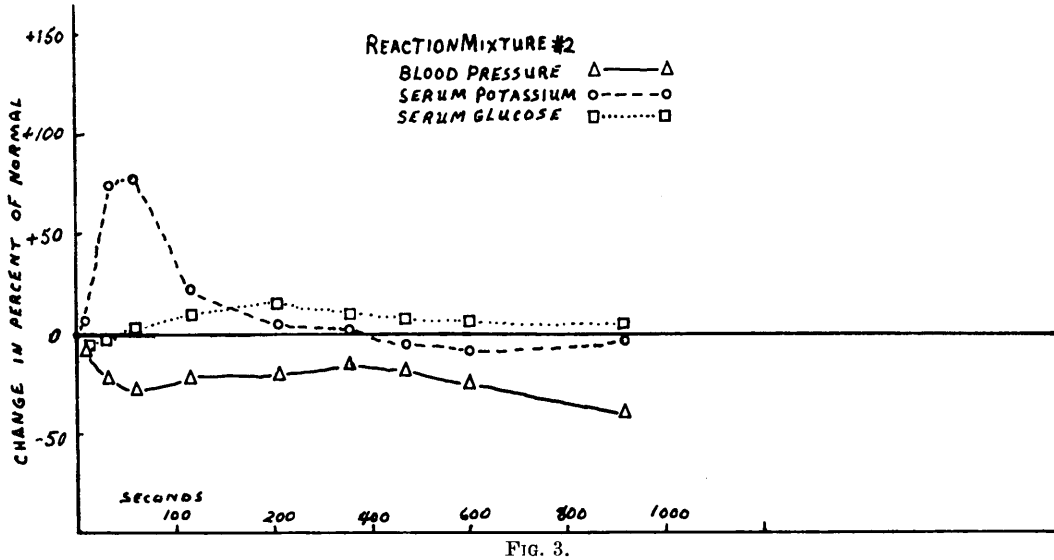

FIG. 3.

Changes in blood pressure, serum potassium and serum glucose following the intravenous injection of an oxidation product of epinephrine in the cat.

resulting adrenochrome as a pure crystalline compound from the reaction mixture failed, as they have for others (Green and Richter)[8]; because on concentration the ruby red color, presumably due to adrenochrome, disappears leaving a brown substance, probably melanin.

The crude reaction mixtures used in these experiments were prepared in each case just before use. In the first cat a reaction mixture No. 1 (which resulted from adding potassium permanganate calculated to supply 2 atoms of oxygen for each epinephrine molecule) in a dose of 5 mg per kg of original epinephrine resulted in a very marked diminution of the serum glucose rise, so that practically no change occurred. On the contrary the

increases in blood pressure and serum potassium were comparable with those shown in Fig. 1. In consideration of the large dose, however, these increases were slight since greater effects are obtained even with 0.1 mg per kg of epinephrine.[5] Two samples of reaction mixture No. 2 were prepared in which potassium permanganate was added to supply 2½ atoms of oxygen per molecule of epinephrine. Each was tested on a cat. The serum glucose was little affected as with reaction mixture No. 1. The blood pressure however showed a fall instead of a rise in both animals. In one animal the serum potassium rose (Fig. 3) as it did with reaction mixture No. 1 but in the other it showed no change. These experiments although few in number gain significance by the fact that the regularity and degree of blood pressure and serum potassium changes produced by epinephrine have been previously established,[5] the same being true for the serum glucose changes as reported in the first part of this paper. Consequently any deviation from this constant effect is striking. These results suggest an independence of the three effects since in the oxidation of epinephrine they are not modified in parallel. The elimination of the serum glucose effect even before those of blood pressure and serum potassium would not support the postulation made above that this action is due to a decomposition product of epinephrine.

Summary. In a series of experiments on cats the changes in serum glucose, serum potassium and blood pressure produced by epinephrine were compared chronologically. The rise in serum potassium occurs later than the rise in blood pressure while the rise in serum glucose begins still later and is much more prolonged than the other 2 effects. This indicates that epinephrine hyperglycemia is independent of the serum potassium increase. As further evidence it is shown that in the oxidation of epinephrine by potassium permanganate the above actions are not modified in parallel.

14958

Tumor of Rat Testis Produced by Heterotransplantation of Infantile Testis to Spleen of Adult Castrate.

MORTON S. BISKIND* AND GERSON R. BISKIND.

From the Endocrine Laboratory, Beth Israel Hospital, New York, and the Departments of Pathology, Mount Zion Hospital and the University of California Medical School, San Francisco.

In a previous report,[1] we have described the development of granulosa cell tumors of the rat ovary after transplantation of one ovary to the spleen and removal of the other. With this technic, the estrogen produced by the transplanted ovary is secreted into the portal circulation and inactivated in the liver. The estrogen is thus prevented from exerting its normal cyclic inhibiting effect on the pituitary. The excessive secretion of pituitary gonadotrophin which thus results is enabled to act continuously on the transplanted gonad.

The present communication is concerned with application of this technic to the production of neoplasm of the rat testis. Implantation of an entire adult testis into the spleen of the same rat is impossible owing to the comparatively large size of the former organ; only small amounts of testicular tissue can thus be implanted. However, heterotransplantation of the testis of an infantile rat, from 9 to 14 days old, into the adult spleen, is comparatively as simple as similar ovarian

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1 Biskind, M. S., and Biskind, G. R., PROC. SOC. EXP. BIOL. AND MED., 1944, **55**, 176.