

We have not seen nearly as great a degree of exhaustion in this animal as in the cat. This might be interpreted as in favor of Elliott's view, since signs of "emotional" disturbance are also less marked in the rabbit, although great dilatation of the pupil, increased respiration and other symptoms are present, which, according to Mutch and Pembrey¹ "give the impression that the drug produces a state of increased psychic activity accompanied by muscular action appropriate to the emotions." It seems to us, however, more natural, considering our results with morphin and "frightening" without drugs to interpret the greater effect on the epinephrin content in the cat as due to some other action of the drug than the hypothetical emotional disturbance.

We determined the epinephrin content by the colorimetric method of Folin, Cannon and Denis, which we found to agree sufficiently well with blood pressure observations on the pithed cat.

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The liberation of epinephrin from the adrenals.

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The solution of the question of the liberation of epinephrin into the adrenal veins and the estimation of the amount so liberated in the absence of artificial stimulation of the splanchnics are complicated by the fact that after withdrawal of blood pressor substances are quickly developed in it, which give the same effect as epinephrin on such objects as the vessels of a frog's legs.² It is therefore desirable to demonstrate the fact of its liberation and to assay its amount without the necessity of withdrawing blood. We have done this (in the cat) by means of the denervated eye reactions (of Meltzer),³ and by the effect on the blood pressure curve.

¹ *J. of Physiology*, 1911, 43, p. 109.

² Cf. Trendelenburg, *Archiv f. Exper. Path. u. Pharmacol.*, 1915, 79, p. 154.

³ Experiments on the liberation of epinephrin by stimulation of the splanchnics, in which the eye reactions were used, have been described by us elsewhere, *Journal of Pharmacology and Experimental Therapeutics*, 1916, 8, p. 205.

1. For the eye reactions all that is necessary is to clamp off temporarily a pocket of the inferior vena cava so that only adrenal vein blood enters it. A clamp is applied just above the iliac veins. The renal veins are then clamped and the segment of cava emptied of blood by gently stripping it upwards. Finally a clamp is put on the cava above the adrenal veins. Only a few seconds are occupied in the adjustment of these clamps. Small branches of the segment of cava have been previously tied. The pocket is allowed to fill with blood from the adrenals. When the clamps are removed, the eye reactions are elicited at practically the same time interval as when the splanchnics are stimulated with the vessels free.

2. After section of both splanchnics (above the diaphragm) the reactions can no longer be obtained. Section of the splanchnics has therefore greatly diminished, if not abolished, the liberation of epinephrin. This is not due to the low blood pressure caused by division of the nerves. For if only the right splanchnic is cut there is little, if any, fall of blood pressure. Nevertheless when the cava pocket is closed off as described, and in addition a clamp is put on the left adrenal vein, the right being free, no eye reaction is elicited on allowing the pocket to empty itself. When the experiment is repeated with the left adrenal vein free the reaction is obtained, although of course less strongly than with both splanchnics intact and both adrenal veins open, since only half the amount of epinephrin is discharged.

3. To demonstrate the effect of epinephrin liberated into a cava pocket upon the blood pressure of the same animal, a somewhat different procedure must be adopted, in order to avoid undue disturbance of the blood pressure curve on forming and on releasing the pocket. The lower end of the cava segment is tied permanently after previous ligation of the abdominal aorta and squeezing of blood from the legs. The renal arteries and veins are also tied. When the eye reactions are available to compare with the blood-pressure curve and manipulation of the intestines is avoided during the application of the upper clamp to the cava segment, it is not always necessary that the circulation through the intestines and liver should be interfered with. Even when the blood pressure curve is somewhat irregular the rise of pres-

sure caused by the liberated epinephrin, occurring at a definite interval after release of the pocket, can be identified by the fact that the eye reaction also commences at or about this moment. However, to further strengthen the evidence we have made experiments in which the celiac and superior mesenteric arteries are first tied off, then the renal arteries, and then the abdominal aorta just below the kidneys. As much blood as possible is got into the anterior end of the animal, and then the inferior cava is tied above the iliacs. The renal veins are then ligated, and the cava pocket now represents only a blind pouch upon the circulation, the filling of which from the adrenal veins, or the emptying of which after removal of the upper clamp produces relatively little mechanical effect upon the blood pressure. The lower end of the animal is kept raised throughout the experiment. This facilitates emptying of the pocket without manipulation.

4. In different experiments we have assayed, by the injection of known quantities of adrenalin, the amount of epinephrin liberated without artificial stimulation of the splanchnics, under our experimental conditions (narcosis with urethane alone, and with urethane supplemented with ether). For example, in one experiment we found 0.0005 mg. and in another 0.0009 mg. per kg. of animal, per minute. When the pocket is allowed to fill during stimulation of the splanchnics, with intervals of rest, the effect on release is distinctly greater than when it is allowed to fill for the same time without artificial stimulation of the nerves.

5. We have endeavored to measure the amount of blood collected in the pocket, without bringing it into contact with any foreign substance, in the following way: One of the iliac veins is tied near its distal end and the other near the cava. Both iliacs are then divided distal to the ligatures. By means of the ligature on the first iliac it is suspended vertically, while the greater part of the cava segment lies undisturbed. The iliac vein thus serves as the neck of a measuring flask, so to say, the body of which is composed of the cava segment. It is not difficult to determine the moment when the blood, entering the pocket practically without resistance, the walls of the vein being scarcely at all distended so long as the vertical portion of the pocket is empty, just reaches the proximal end of the iliac. If undue exposure of

the vein is prevented, a comparison of the flow from the adrenals in successive observations is made possible by noting the intervals of time necessary for the pocket to fill up to this point. The quantity of blood required to fill the pocket can be determined once for all in each animal. The vertical position of a portion of the pocket helps to empty it without manipulation when the clamp is removed.

6. The sensitiveness of the eye-reactions to epinephrin discharged from the adrenals, for example in response to stimulation of the splanchnics, can be increased notably by temporarily clamping off alternative arterial paths. This must be done at such an interval of time after the beginning of stimulation as is not more than sufficient to allow the epinephrin to reach the beginning of the aorta. A larger proportion of the blood containing the epinephrin is thus forced to take the path to the eye whose reactions are being studied. If, for instance, the left iris is the denervated one, clamping at the proper moment of the thoracic aorta and the innominate markedly increases the reaction. It can be further increased by tying off all accessible branches of the left carotid except those through which the eye must obtain its blood supply.

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Attenuation of the living agents of cyanolophia.

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Paschen¹ (1911) says that leucocytes must play an important part in the process of immunization. This remark seems partly justified in the attenuation process of cyanolophia. The living agents of cyanolophia are differently affected in tissue cultures of *red* bone marrow from *white* bone marrow.

¹ Paschen, O., "Handbuch der Technik und Methodik der Immunitätsforschung," 1911.