THE EFFECT OF PARTIAL ADRENAEL DEFICIENCY 
UPON SYMPATHETIC IRRITABILITY

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Received for publication January 14, 1915

In 1904 Elliott (1) reported the observation that in a cat moribund after complete adrenal extirpation the pressor reaction to nicotine was abolished and concluded that under such circumstances the irritability of the sympathetic system is lost. He offered the suggestion that adrenal deficiency results in a corresponding deficiency in circulating epinephrin which in turn renders the sympathetic myoneural junctions incapable of transmitting impulses. In 1909 Gautrelet and Thomas (2) reported results obtained in a dog and a rabbit that supported Elliott’s conclusion. Last year Hoskins and Wheelon (3) further investigated the matter. They thought that animals near the point of death are scarcely capable of giving significant information. Accordingly they studied the condition of the vasomotor mechanism in dogs during the earlier hours after ligation of both adrenals. They hoped thereby to detect the primary effect of adrenal deficiency before secondary results had obscured the picture. In such experiments they were unable to find any evidence of sympathetic depression at a time when the animals were showing marked muscular and cardial weakness. Their method of attacking the problem was based upon a supposition that the organism is not significantly affected by the loss of any quantity of adrenal tissue short of that which causes death. That idea receives a certain amount of support from such experiments as those recently reported by Crowe and Wislocki (4). These investigators found that glycosuria is caused by the manipulation of any fragment of adrenal tissue that is sufficient to maintain life,
but that equal irritation in the adrenal region in the absence of the gland tissue is without effect.

Whipple and Christman (5), however, have recently shown that partial adrenal deficiency causes a decrease in the amount of phenoltetrachlorphthalein excreted into the intestine, a result which they attribute to hepatic depression.

In the light of these results it seemed desirable to study the effect of partial adrenal deficiency upon vasomotor irritability. In order to obtain results as well marked as possible an attempt was made in the earlier experiments to reduce the adrenal tissue to the lowest amount compatible with survival. In a series of seventeen dogs one adrenal—usually the right—was destroyed completely, and at the same operation one-half to three-fifths of the other gland was similarly treated. An epidemic of distemper, added to the severity of the operation, gave a high mortality in the series but five of the animals survived. This series was supplemented by six successful cases in which the left adrenal only was destroyed.

The general methods employed in the research were the same as those previously described by Hoskins and Wheelon (6). Blood pressure from a femoral or carotid artery was recorded by means of a mercury manometer, using a reservoir cannula filled with 10 per cent sodium citrate. The reaction to a standard dose of adrenalin gave an index of the condition of the peripheral vascular structures. Similarly the reaction to nicotin indicated the degree of irritability of the sympathetic system proper. After the reactions to adrenalin and nicotin were obtained the vessels were ligated and the incision closed and dressed with a piece of gauze saturated with flexible collodion. In view of the fact that the whole procedure of setting the cannulas and closing the wound requires less than 10 minutes it did not seem worth while to attempt to surmount the difficulties of a "bloodless" technique. Aseptic precautions were taken throughout. Various methods of destroying the adrenal tissue were tried: excision, actual cautery, interstitial injections of chloroform or chromic acid and simple ligation. The injection methods were unsatisfactory in that they were hard to control. The liability to hemorrhage
and danger of injury to splanchnic nerve trunks rendered the cautery unsatisfactory. Excision of the adrenals without undue injury to nearby structures is notably difficult and time consuming. Ligation, on the other hand, is easily accomplished and is equally effective. This statement is based upon two observed facts: the reaction of the animal to ligation is characteristic of adrenal destruction and subsequent examination of the ligated glands shows that they have undergone destructive degeneration. In both these respects the present research has confirmed the observations of earlier investigators (7). The technique employed in isolating the glands was the following: The peritoneum over the adrenal was torn loose and by blunt dissection the organ was partially loosened from contiguous structures. Particularly it was sufficiently separated from the sympathetic trunks that subsequent tightening of the ligatures would not injure these. Two strands of strong linen thread were then passed together longitudinally under the gland. These were brought up, one on either side, and tied. The gland was thus completely isolated. This procedure is especially advantageous in case of the right adrenal which in the dog usually lies well under the vena cava. A bit of the dorso-lateral wall of the cava was grasped in a hemostat. Lateral traction then rolled the vein off the gland and left it fairly accessible, while offering no serious impediment to the circulation.

Parenthetically, it may be permissible to allude again to the advantages of the reservoir cannula method in routine blood pressure work. The cannula we have finally come to use with dogs is one of the ordinary arterial type in which is blown a bulb holding about 15 cc. This is filled with 10 per cent sodium citrate solution and attached directly to the manometer. The method avoids the inconvenience of developing an initial positive pressure in the system and of maintaining a cumbersome "wash-out" arrangement. When the artery clip is released an outflow of blood forces the citrate from the central stem of the cannula and partially displaces that in the bulb until pressure equilibrium is reached. The animal is thereby protected from a not uncommon accident—an intravascular injection of the anti-coagulant
when the artery is opened. Before coagulation has had time to occur, the citrate makes its way back against the blood column in adequate quantity to prevent clotting, but not enough reaches the circulation to cause any perceptible effect. This is true even though a considerable fall of blood pressure occur. It is rarely necessary to remove the cannula and dispose of a clot even in experiments lasting two hours or longer. The simplicity of the method renders it particularly advantageous for students’ use in conventional blood pressure experiments. The only precaution we have found necessary is to avoid the use of too large a reservoir.

At intervals of one to eight days in various cases, after adrenal operation the blood pressure and reactions to adrenalin and nicotin were again determined. The results indicate that partial adrenal deficiency does result in sympathetic depression. Experiment No. 4 which illustrates the general outcome of the series will be described:

November 24, 1914. Dog, Female adult. Weight, 7 kilos. Cannulas set in right femoral artery and vein. Reactions determined to adrenalin 2 cc. 1-200000, nicotin 0.8 cc., 1:4000, pilocarpin 0.5 cc. 1-10000.

Laparotomy. Abdomen opened in median line. Right adrenal gland exposed and ligatures placed so as to isolate posterior half of gland—circulation of anterior half apparently not harmed. Right gland exposed and completely isolated with two ligatures. Incision closed in three layers. Excellent recovery.

November 27. Dog somewhat weak as judged by resistance to anesthetizing. Incisions in leg and belly wall clean. Cannulas set in left femoral artery and vein. Reaction to adrenalin, nicotin and pilocarpin obtained as before.


Post mortem findings: Right adrenal: Anterior half of gland apparently normal: Posterior half degenerated, largely replaced by sclerotic tissue. Left adrenal: Marked central liquifaction necrosis leaving thin superficial layer of soft brownish yellow tissue.
Right and left splanchnic nerve trunks traced through operative fields. No evidence of their having been injured in the operation.

Subsequent measurement of the tracings in this experiment showed that the original blood pressure was 146 mm. Three days later at the time of the second determination it was 132. Nine days after the adrenal ligation it was still lower, 110 mm. The nicotin reactions were respectively 50, 22 and 14 mm. The pressor reaction to adrenalin was unusually constant being exactly 40 mm. in each case.

In several instances the blood pressure reactions to small doses of pilocarpin were determined, before and after adrenal ligation. No significant differences were observed. Apparently, therefore, the lessened irritability of the sympathetic system is not shared by the para-sympathetics.

A possible source of error in such experiments is the nearness of the splanchnic nerve trunks to the adrenal glands. Injury to these nerves might well cause perturbations in the vasomotor reactions. Elliott has shown, however, that decentralization of sympathetic paths results in heightened irritability to adrenalin. If, therefore, injury to the splanchnic trunks were a significant factor in our results depression of the nicotin reaction should be accompanied by augmentation of the adrenalin reaction—a condition that ordinarily did not maintain.

No attempt was made to determine exactly the minimal quantity of adrenal tissue that must be removed to cause an appreciable loss of sympathetic irritability. Owing to individual variability in this respect a large series of experiments would probably be required to settle the point. In some cases we noted, however, that removal of one gland only was without effect, while in others a depression resulted. It is probable, therefore, that the "margin of safety" is about 50 per cent.

Considering that the vasomotor depression resulting from adrenal deficiency might conceivably be due to a reduction in the amount of circulating epinephrin the effect of slowly supplying adrenalin to the blood stream seemed worthy of investigation. Accordingly in two animals that showed well marked depression
in the reaction to nicotine dilute adrenalin was infused for half an hour into a vein. The results were surprising. Even though the infused adrenalin was producing little or no effect upon blood pressure the reaction to nicotine soon became smaller and when the rate of infusion was increased to cause a minimal pressor effect the nicotine reaction was abolished. These results tend to indicate that epinephrin deficiency is not the cause of the sympathetic depression resulting from adrenal deficiency. The phenomenon is being further investigated and results will be reported in a later communication.

For the apparent discrepancy between the previous results of Hoskins and Wheelon and those herein reported no definite explanation is offered. It would seem, however, that in their experiments the overwhelming severity of a laparotomy added to the immediate effects of total deprivation of adrenal tissue caused a primary failure of the cardiac metabolism before the sympathetic system had time to be significantly affected. Also the possibility exists that the depression of sympathetic irritability observed in the experiments herein reported is not at all specific, but merely one phase of general depression of vitality, such as occurs in Addison’s disease. The sum total of available evidence seems to indicate that the essential feature of adrenal deficiency is an interference with fundamental metabolism—possibly oxidation—in which the more active tissues of the body suffer first.

SUMMARY AND CONCLUSION

From one-half to seven-tenths of the adrenal tissue was removed from dogs in various cases, at a single operation. At intervals of one to eight days after the operation the blood pressure and the vasomotor reaction to nicotine were decreased. The reaction to adrenalin was not similarly affected. Partial adrenal deficiency therefore results in a depression of the irritability of the sympathetic nervous system proper. This depression is probably only one phase of a generalized interference with fundamental metabolism.
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