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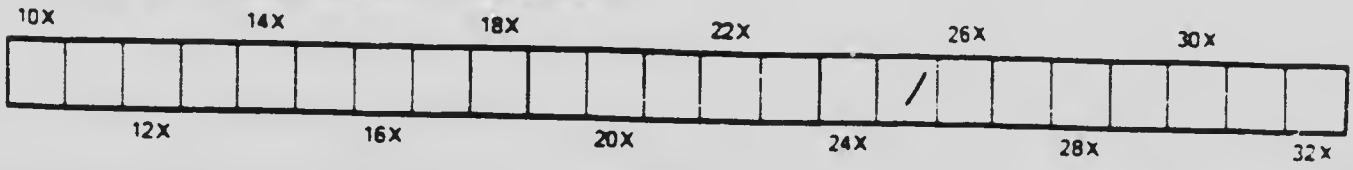

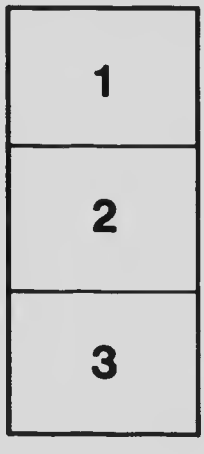

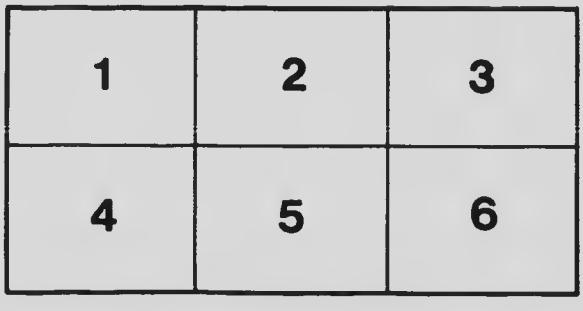

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PHYSIOLOGICAL SERIES

No. 26: DEATH PRODUCED BY TYING THE ADRENAL VEINS, BY F. A. HARTMAN and W. E. BLATZ

(REPRINTED FROM ENDOCRINOLOGY, VOL. 3)

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DEATH PRODUCED BY TYING THE ADRENAL VEINS

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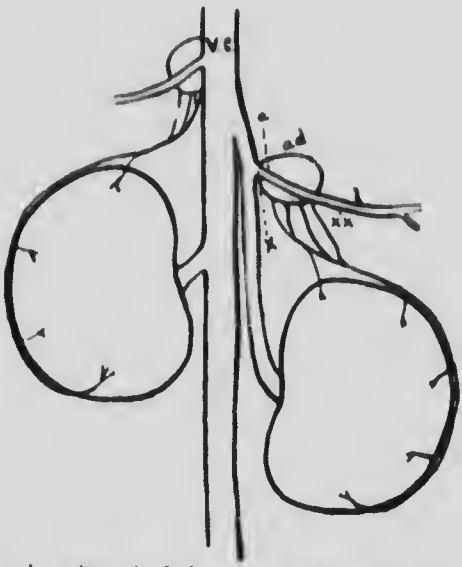
Since the discovery that Addison's Disease is due to disturbance of the adrenal apparatus, many attempts have been made to produce the disease artificially. Adrenal insufficiency is said to be the main cause, and hence epinephrectomy was thought to be the best method of producing the peculiar syndrome of the disease. This method is, however, too drastic, the animal succumbing more or less rapidly to the operation. Some method of reducing the adrenal function without completely destroying it, appeared to be required.

Certain infections diseases impair the function of the adrenals. Diphtheria (1) produces vacuolization and hemorrhage in the adrenals, and diphtheria toxin (2) is said to lessen the pupil dilating substance in the adrenal venous blood. In view of this we attempted to destroy a portion of each gland by the injection of sublethal doses of diphtheria toxin into the exposed gland. Evidently the toxin was either neutralized, or else washed away by the blood stream before it could cause much destruction of the adrenal tissue, because no symptoms could be noticed, following such injection. Although we experimented with only one cat and one guinea pig, the method was considered unsatisfactory.

The blood flow through the adrenals is relatively very large; therefore by hindering the blood supply we should be able to produce degenerative changes rather easily. If the blood flow could be almost stopped, the changes in the gland might be slow enough to produce merely a condition of hypo-secretion, such as we desired. The arteries break up into such fine branches before entering the capsule, that checking the inflow would be too difficult. On the other hand, the outflow is mainly through a large vein emptying into either the vena cava, or else the renal vein, so that by ligation the flow could easily be stopped. However, a small amount of blood escapes

through a rete of vessels connecting the adrenal with the kidney (3) so that occlusion of the adrenal vein does not produce complete stasis of blood in the gland. (See accompanying figure.)



Veins to the adrenal of the cat. The rete of vessels connecting the adrenal with the kidney, after the diagram of Cow.
ad., adrenal.
a., common lumbo-adrenal vein.
l., lumbar vein joining the adrenal vein.
v. c., vena cava.
x., position of ligature.
xx., ligature here in some experiments, in addition to position x.

This research is a preliminary study of the effects produced by disturbing the blood supply to the adrenals.

Methods

A lumbar vein from the dorsal musculature joins the adrenal vein as the latter leaves the gland (Fig.) so that their blood is carried by a common trunk into the vena cava. In some cases one adrenal was excised. In all of the experiments the common lumbo-adrenal vein was completely tied off (at *X* in Fig.) central to the adrenal or adrenals left in the body.

Because of the possibility of a back flow through the lumbar vein, this was also tied in a few animals (*XX*, Fig. VII

animals were anesthetized with ether and the operations conducted aseptically. Cats were used in a majority of cases, but dogs and rabbits occasionally.

After the operation the animals were studied at first daily, and later at longer intervals to see whether characteristic symptoms developed. They were examined for changes in rectal temperature, weight, heart rate and muscular weakness. In some cases the animal was killed, in others it was allowed to die following the natural course of events. The adrenals were then fixed and studied.

The glands were placed for twenty four hours in a mixture of 90 parts of 3.5 per cent $K_2Cr_2O_7$ with 10 parts of 40 per cent formaldehyde (4). They were then washed in running water for an equal time, after which they were immersed in a solution of gum Arabic for a few hours before sectioning.

Sections 5 micra to 30 micra in thickness were cut with a freezing microtome. After washing in tap water to remove the gum, the sections were stained 5 to 10 minutes with Delafield's haematoxylin, subsequent treatment with water removing the excess stain. They were finally left in a saturated 70 per cent alcoholic solution of Sudan III over night. After again washing with water they were mounted for study in Farrant's medium. The lipoids were stained red by Sudan III and chromaffin cells yellowish if they contained adrenalin.

Results

Experiment 1. The adrenal veins to both glands in a rat were tied off by ligating the vein coming from the lumbar muscles and the common vein as it entered the vena cava. The only possible outlet from the adrenals was the kidney rete. Forty-eight days later the animal died without developing any noticeable symptoms except muscular weakness just before death. Microscopic examination of the glands showed a slight vacuolization in the zona fasciculata and the presence of adrenalin in the medulla. Lipoids were plentiful in the cortex.

Experiment 2. The right adrenal was excised and both the lumbar vein and the common lumbo-adrenal vein tied off on the other side. The cat died two days later with no observed external change. The adrenal which had remained in the animal was much congested with blood. The superficial veins of

the kidney on the same side were also congested. The glands were compared microscopically. The appearance of left adrenal was very striking. Adrenalin instead of being limited to the medulla was disseminated throughout the gland being especially concentrated in the cells of the zona glomerulosa. Adrenalin in the zona fasciculata and zona reticularis was found between the cell columns, but was absent from the cells. The total quantity of adrenalin was much greater in the left adrenal than in the right, as indicated by the stain. There was considerable vacuolization in the zona fasciculata.

Experiment 3. The lumbar and lumbo-adrenal veins were tied on the left side, the right adrenal being left intact. The animal in this case was a dog. Eighteen days later the animal was killed, and the two adrenals fixed. No great difference was observed between the two glands. There was less lipoid in the ligated gland, there being great numbers of large lipoid bodies in the cortex of the normal gland, while these were largely absent from the ligated gland.

Experiment 4. The lumbo-adrenal vein where it enters the vena cava was tied off on both sides, but the veins to the lumbar muscles were not touched. This animal, a rabbit, gained in weight during the next thirty-two days. It died seventy-five days after the operation. Upon microscopic examination the presence of adrenalin was not found. Lipoids were present in amount.

Experiment 5. After removal of the right adrenal the lumbo-adrenal vein from the left gland was tied off, the veins from the lumbar muscles being left intact. The animal [illegible] was operated upon at 4 p. m.

At nine o'clock the next morning the pupils were [illegible] greatly dilated, and constricted much less than did those of a normal cat when exposed to a bright light. The most striking thing, however, was the marked pilomotor effect. The hair was erect all along the dorsal surface, and to a certain extent on the tail. The heart was beating at the rate of 140 per minute, whereas before the operation the rate was 250. The rectal temperature was 35.7° C.

Forty-one hours after the operation, the pupils had become nearly normal, while the pilomotor effect still persisted [illegible]

was not quite so marked. The heart rate was 184 beats per minute. The rectal temperature was 37.2° C.

In four days the cat appeared normal except for a slight adynamic effect. Later certain changes were apparent. The hair on the face was falling out. The hair on the ears had become quite scanty. There was a red coloration on the inner side of both forelegs. The cat began to cry incessantly and lost weight. Eruptions appeared on the skin of the face (46 days after the operation).

Sixty-eight days after the operation, the weight had been reduced from 2.500 kgm. to 2.060 kgm., in spite of its eating well. The rectal temperature was 39.1° C. The hair was very scraggy and unkempt. The cat was irritable, but weaker than normal. It was not so active, largely on account of muscular weakness, because it still appeared restless. The heart rate was normal (240). At this time there was considerable difficulty in micturating. It took several minutes to expel the urine.

Ninety-five days after the operation, the heart was still normal in rate, the temperature still high (39.0° C.) and the weight partly regained (2.350 kgm.). It appeared a little stronger, but still walked with a stiff-legged gait. The fur was still in a poor condition, the longer hairs, such as the vibrissae, being broken and scraggy.

The cat died 128 days after the operation. It had been gradually losing weight so that it was reduced to two-thirds the original, viz., to 1.750 kgm. The day before death it appeared very much as it had for weeks. (Death was hastened the last two or three days by a marked fall in the room temperature.)

Upon post mortem everything was found well healed. The lumbar vein to the left adrenal was much enlarged. The adrenal weighed 0.426 gm. Lipoids were fairly plentiful in the gland, but did not seem to be entirely confined to the cortex. Some adrenalin was present, as shown by the yellow stain.

The kidney on the same side had been fixed and stained in the same manner as the adrenal. Many of the blood vessels in the outer zone were stained yellow. Scattered here and there tubules and glomeruli were found similarly stained. It appeared that adrenalin brought to the kidney directly from

the adrenal was being excreted in the kidney. However, this observation needs further confirmation.

Experiment 6. A second cat was operated upon in the same way as in the preceding experiment. Within two hours after the operation the pupil had become normal. Eight hours later there was a decided pilomotor reaction along the back. In 13 hours the pilomotor effect had become slight. No other changes appeared. The animal died 18 days later. It had been eating well up to that time.

There were only slight traces of lipoid in the cortex of the adrenal which had been left in the animal. There were also traces of lipoid in the medulla. Adrenalin if present at all was extremely scant.

Experiment 7. The adrenals of a third cat were treated as in the two foregoing cases. Three hours after, there was a marked pilomotor effect, but no dilatation of the pupil.

The pilomotor effect persisted for 38 days. At that time the animal appeared weaker. The temperature and heart rate remained about normal. The animal died 59 days after the operation. It had fallen off slightly in weight, from 1.34 kgm. to 1.22 kgm.

Histologically, the adrenal which had remained in the animal was almost devoid of lipoids, the small amount present being in the cortex. No trace of adrenalin was found.

Experiment 8. A dog was operated upon as in the preceding experiments. It recovered without showing any decided symptoms. The rectal temperature 10 days after the operation was 39.2° C. The animal was killed 83 days after the operation. Its weight had fallen from 5.1 kgm. to 4.5 kgm. Histologically, the adrenal gland which had remained in the animal differed very little from normal.

Experiment 9. In order to determine how much pressure might be produced in the lumbar vein when the lumbo-adrenal vein was tied, we fastened a cannula into the former vein immediately after the latter had been tied. A large dog (18 kgm.) was used while under ether anesthesia. The cannula was connected with a long vertical glass tube containing a little half saturated Na_2SO_4 solution.

The pressure in the tube gradually rose as follows:

Time in minutes	Increase mm. ½ sat. Na_2SO_4 Sol.	Total pressure mm. ½ sat. Na_2SO_4 Sol.
1	155	155
2	109	264
3	93	357
4	81	438
5	71	509
6	60	569
7	47	616
8	38	654
9	30	684
10	26	710
11	19	729
12	19	748
13	12	760
14	9	769
15	6	775

The final pressure attained in the glass tube was 775 mm. or 73.25 mm. in terms of Hg. Arterial pressure at the same time was 77 mm. of Hg.

Discussion

The method which we have used does not produce death nearly so quickly as does the removal of both adrenals. In that case death occurs in a few hours to a few days (5). Six of the seven animals, in which the veins from the adrenals had been tied, died in 2, 18, 48, 59, 75 and 128 days respectively. Experiment No. 3 should not be included because one gland was left intact in the animal. Experiment No. 8, on a dog, was the exception, the animal being killed after 83 days. At the time of death, however, it was losing weight.

Three of the animals which died of their own accord, showed symptoms of weakness some time before death; in the other three, no changes were observed. In regard to the histological changes, three of the animals showed no presence of adrenalin, and only a trace of lipoid in the adrenal after death, while three others showed both adrenalin and lipoid in larger amount. Of course, the absence of adrenalin in a gland which

is not fixed immediately at death indicates little, for adrenal disappears very soon. But in any case, judging from the lipoid with the exception of experiment No. 5, the adrenal functi was much below normal.

Cat No. 5 was very exceptional and may have been a cas of hyperactivity of the adrenal. Many of the symptoms ten to indicate that. It is quite possible that in this instance th increased pressure produced by tying the common lumba adrenal vein stimulated the cells of the adrenal to greate activity. The increased pressure may also have produced back-flow of blood through the lumbar vein and thus through anastomoses into the general circulation. In fact, this was possible in all the animals where the lumbar vein was not tie because the pressure attained is nearly as great as arterial pressure (experiment No. 9).

Summary

1. After having the veins to the adrenal glands tied an animal lives much longer than after double epinephrectomy, but eventually dies.

2. There is evidence that the adrenals function for a con siderable time after such an operation, the secretion escaping through the rete of vessels leading to the kidney, and possibly by back flow through the lumbar vein, when that is left open

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