

## THE EFFECT OF ADRENALECTOMY ON THE BLOOD HISTAMINE OF RABBITS

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DALE & LAIDLAW [1912] first demonstrated that adrenalectomy greatly enhanced the sensitivity of animals to injections of histamine. Later, Dale [1920] showed that the adrenalectomized cat was extremely sensitive to histamine, but recognized that it was impossible by his experiments to determine whether the absence of the medulla or of the cortex was responsible for the decreased resistance of the adrenalectomized animals to histamine. Perla & Gottesman [1929] regarded the protective action of adrenaline as a hormonal effect and not entirely dependent on the pharmacological antagonistic action of adrenaline to histamine. They showed that the resistance of adrenalectomized animals to histamine can be increased if adrenaline is administered, but this obtains only if adrenaline has been administered repeatedly for some time before the injection of histamine. Indeed, they later [1931] suggested the increased susceptibility of adrenalectomized rats to histamine as a basis for the assay of cortical extract. On the other hand, Wyman [1932], experimenting on rats, claimed that the decreased resistance to histamine was due to the removal of the medulla. Ingle [1937] stressed the importance of adrenal cortex in maintaining normal resistance to injections of histamine, and pointed out that while removal of the medulla alone lowered resistance to histamine, a much lower resistance resulted from complete adrenalectomy. He further observed that adrenaline increased the resistance of rats in which the medulla had been destroyed, but that cortical extract did not have a similar effect. Rose & Browne [1938] showed that in adrenalectomized rats the rate of disappearance from the blood and tissues of histamine injected intravenously was much slower than in normal animals.

As no study appeared to have been made of the effect of the adrenal cortex on the blood histamine of animals, it seemed important to determine whether histamine could be formed in the absence of the adrenal cortex, and to ascertain the influence of cortical extract on the blood histamine level of adrenalectomized animals.

### METHODS

Male rabbits 3–4 months old were adrenalectomized in a one-stage operation by the abdominal route. The anaesthetic was ether. Immediately after operation the animals were given 3.5 c.c. 5% NaCl intravenously and 1 c.c. cortical extract subcutaneously. The rabbits were maintained for 2 days after operation on a diet of cabbage, oats and bran with 2–3 c.c. cortical extract subcutaneously daily. The cortical extract used was "Cortin Organon", 1 c.c. extract equivalent to 50 g. fresh suprarenal gland. Samples of blood (2–2.5 c.c.) were taken by cardiac puncture from the left side of the heart. Whole blood, using no anticoagulant, was extracted by the method of Anrep, Barsoum, Talaat & Weininger [1939].

The histamine was assayed on the isolated gut of the guinea-pig according to Code's [1937] modification of the method of Barsoum & Gaddum. The arterial blood pressure in the ear vessels was determined by the method of Grant & Rothschild [1934].

### RESULTS

#### I. *The effect of adrenalectomy on the blood histamine*

Twelve hours after withdrawal of cortical extract all the rabbits showed signs of adrenal insufficiency, namely, thirst, anorexia, weakness and diarrhoea. Control animals which were subjected to the same operative technique, but without removal of the suprarenal glands, were given the same treatment. The blood pressure recording showed considerable variation (Table I) but in each case the blood pressure fell after adrenalectomy, and the histamine content of the blood was raised.

#### II. *The effect of cortical extract on the blood histamine level of adrenalectomized rabbits*

The effect of cortical extract was observed on six rabbits which had been adrenalectomized, and had received no cortical extract for at least 12 hr. Blood was withdrawn at the intervals specified in Table II. 1 c.c. cortical extract was given subcutaneously immediately after taking

TABLE I. The effect of adrenalectomy on the blood histamine and blood pressure (rabbit)

Animal no.	Blood histamine ( $\mu\text{g./c.c.}$ )			Blood pressure (mm./Hg)	
	Before adrenalectomy	After adrenalectomy	% Difference	Before adrenalectomy	After adrenalectomy
41	4.6	16.7	+263	76-78	70-72
51	4.7	6.2	+32	82-84	70-74
501	5.0	6.4	+28	64	45
231	1.9	2.3	+21	66-68	46-48
251	0.9	2.2	+145	82-84	16-20
401	2.7	11.5	+326	—	—
Controls	Before operation	After operation		Before operation	After operation
483	3.3	2.9	-12	68-70	68-70
493	2.9	2.5	-14	70	68
473	3.8	3.8	—	70	70

TABLE II. The effect of cortical extract on the blood histamine level of adrenalectomized rabbits

Time (hr.)	0	1	3	5	8	12	15	24	Death
Animal no.	Blood histamine ( $\mu\text{g./c.c.}$ )								
52	6.2	3.4	—	—	4.5	—	—	—	5.9
23	2.3	1.4	—	—	—	—	1.6	—	4.3
25	2.2	2.3	—	—	—	—	2.7	—	4.5
03	6.0	—	4.3	6.9	—	—	—	—	6.1
05	8.6	—	6.5	—	—	—	—	6.8	4.2
06	3.4	3.0	—	—	—	2.8	—	—	4.1

zero-hour samples of blood. The level of blood histamine was lowered within 1 hr. in all cases except in animal 25. The duration of fall varied, in the observations made, from 3 to 24 hr. The histamine level at death was increased in four animals, while in animal 05 there was a marked decrease, though the animal died in typical convulsions. Animal 52 remained alive for 7 days, but at autopsy no accessory glands were apparent. The effect of cortical extract on the blood pressure varied considerably. In all animals there was an increase in blood pressure after cortical extract had been given, but in no animal did the blood pressure attain the value recorded before adrenalectomy.

A further series of experiments was made to determine whether cortical extract could prevent a rise in blood histamine, if given immediately after adrenalectomy. Five rabbits immediately after adrenalectomy were given 3.5 c.c. 5% saline intravenously, and 1 c.c. cortical extract subcutaneously. Blood was withdrawn 6 hr. after completing the operation. This period was considered sufficient to allow the animals to recover

from the anaesthetic. The blood histamine in all animals which had received cortical extract after adrenalectomy was decreased 6 hr. after adrenalectomy (Table III).

TABLE III. The effect of cortical extract on blood histamine  
6 hr. after adrenalectomy

Animal no.	Blood histamine ( $\mu\text{g./c.c.}$ )		
	Before operation	After operation	% difference
38	4.30	2.3	-46.5
39	2.90	1.8	-37.9
41	2.23	1.7	-23.8
42	1.65	1.6	-3.0
44	1.60	1.3	-18.8

### DISCUSSION

Much attention has been paid to the protective mechanism against the action of histamine. The inactivation of histamine by the enzyme histaminase has been studied by Best & McHenry [1930] and others. On the other hand, Anrep, Barsoum & Talaat [1936], following the observations of Weiss, Ellis & Robb [1929], and of Jacobs & Mason [1936], have shown that "when histamine is given by slow intravenous injection to dogs it does not remain in active form in the plasma". They stated that the histamine is, in part, rendered physiologically inactive by being taken up by the red blood cells. Later, Code [1938] pointed out that, while the white blood cells carry the major part of the blood histamine during anaphylactic shock in dogs, the plasma contains the greater part of histamine at the peak of reaction. In their experiments with rats, Rose & Browne [1938] made interesting comparisons on the fate of intravenously injected histamine in normal and adrenalectomized animals. They found that at the end of 3 hr. the amount of histamine in the blood of the normal rat was  $0.2 \mu\text{g./c.c.}$ , whereas in the adrenalectomized animal it was  $7.0 \mu\text{g./c.c.}$  While they stated that the initial blood histamine level in the normal rat is  $0.5 \mu\text{g./c.c.}$ , they do not appear to have determined the corresponding level in the adrenalectomized animal. The evidence produced by the experiments here described indicates that an explanation of the decrease in the rate of disappearance of histamine injected into the adrenalectomized rats may be due in part to an increase in the initial blood histamine level. The use of cortical extract in the treatment of "shock" has been advocated by Swingle, Parkins, Taylor & Hays [1938] who stated that in circulatory collapse the cortical hormone exerts a beneficial effect on the control of capillary tone. Moon [1939] has pro-

vided interesting evidence of the pathological changes in viscera in burns, and has pointed out the haemorrhagic appearance of the suprarenal glands in such cases. He suggested the use of cortical extract in the treatment of burns. Barsoum & Gaddum [1936] have shown that in burns the blood histamine is increased, and suggested that this increase may be secondary to pathological changes in organs such as the liver and kidneys. The experiments here described suggest the use of cortical extract where the blood histamine is raised, and further that the cortical extract should be administered as soon as possible. It is realized that estimations of plasma histamine as well as whole blood histamine are desirable but, as Code [1937] points out, there are technical difficulties associated with the separation of plasma in rabbit's blood. Investigations are proceeding on the effect of cortical extract on whole blood and plasma histamine in cases of burning and in Addison's Disease.

#### SUMMARY

Adrenalectomy produces a rise in the blood histamine of rabbits. Cortical extract given subcutaneously reduces the blood histamine level of adrenalectomized rabbits within 1 hr. This effect is maintained for a period of from 3 to 24 hr.

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