diminished in the experimental and the thymectomized control groups. They were present and within normal limits in sham-thymectomized irradiated controls. The depression in the thymectomized irradiated mice characteristically involved the small mononuclear cells. 4. It is concluded that recovery of the immune mechanism following total body irradiation takes place by means of a thymus-dependent mechanism.

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Effect of Removal of Various Parts of the Brain on ACTH Secretion in Dogs.* (28171)

B. L. WISE, E. E. VAN BRUNT† AND W. F. GANONG
Division of Neurological Surgery and Department of Physiology, University of California School of Medicine, San Francisco

The increase in adrenal glucocorticoid secretion produced by surgical trauma in dogs is blocked by lesions of the median eminence of the hypothalamus(1). However, Egdahl has reported(2) that glucocorticoid secretion is elevated after removal of the entire hypothalamus and cerebrum. He has postulated that a circulating factor from the hind brain which stimulates the pituitary to release ACTH is responsible for this elevated level of adrenocortical activity. If this hypothesis is correct, removal of the hind brain in addition to the hypothalamus should lower the level of adrenocortical secretion to that seen in animals with lesions of the median eminence. In the present studies, the effect on adrenocortical secretion of removal of the entire brain in dogs has been determined, and compared to the effects of removal of parts of the brain.

Methods. Brain operations were performed under pentobarbital anesthesia in male mongrel dogs weighing 7.5 to 16.8 kg. The operations were as follows: *Group 1.* Bilateral craniotomy with opening of the dura only (4 dogs); *Group 2.* Removal of all brain tissue

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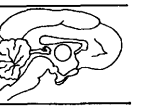
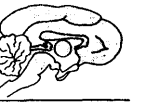
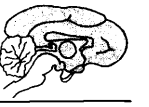
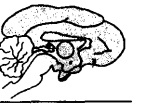
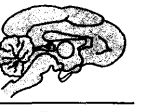
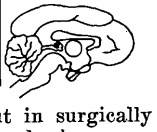
† Postdoctoral Research Fellow of U.S.P.H.S.

above and lateral to the hypothalamus and a wedge of tissue between the posterior hypothalamus and the pons (hypothalamic island —5 dogs); *Group 3.* Removal of all brain tissue rostral to the pons, including the hypothalamus, leaving the pituitary in place (isolated pituitary, hind brain in—4 dogs); *Group 4.* Same operation as Group 3 plus removal of the pituitary (2 dogs); *Group 5.* Removal of the entire brain to the level of the first cervical spinal segment, leaving the pituitary in place (isolated pituitary, hind brain out—6 dogs); *Group 6.* Section of the pituitary stalk *via* the transtemporal approach (5 dogs).

Four hours after completion of the brain operation, the adrenocortical response to surgical trauma was tested by cannulating the right lumboadrenal vein and collecting adrenal venous blood in heparinized tubes by the technique of Hume and Nelson(3). The dogs were then given 10 mU of ACTH (Upjohn) intravenously and another sample of adrenal venous blood collected starting 4 minutes later. All samples were promptly centrifuged and the plasma stored in the frozen state for subsequent determination of 17-hydroxycorticoid content by the method of Silber and Porter(4). 17-Hydroxycorticoid output was calculated by multiplying the hormone concentration by the adrenal venous plasma flow per minute. Body temperature was monitored throughout the experiment with a thermistor probe in the rectum, and blood pressure was monitored, using a cannula in the femoral artery, a Statham strain gauge, and a Grass model 5 polygraph. Body temperature was maintained by the use of heating pads and lamps as necessary. Blood from hypophysectomized donor dogs was infused to replace all blood loss. In the total brain removal experiments, the dogs were maintained on a respirator and received a constant infusion of isotonic saline. Vasopressor drugs were not used.

In most of the dogs in Groups 2, 3, and 5, India ink was infused through one carotid artery just before the animals were sacrificed. All brain and pituitary tissue above the midbrain was removed at autopsy, fixed in formalin, serially sectioned, and examined microscopically.

	17 HYDROXYCORTICOID OUTPUT (μg/min)		
	TRAUMA	AFTER ACTH	
(1) CRANIOTOMY (4 DOGS)	10.8±2.0	13.1±3.0	
(2) HYPOTHALAMIC ISLAND (5 DOGS)	6.8±1.5	9.2±1.3	
(3) ISOLATED PITUITARY, HIND BRAIN IN (4 DOGS)	5.4±0.6*	8.4±1.2	
(4) HYPOPHYSECTOMIZED (2 DOGS)	0.2*	6.6	
(5) ISOLATED PITUITARY, HIND BRAIN OUT (6 DOGS)	3.6±0.8*	8.2±1.4	
(6) STALK SECTION (5 DOGS)	5.9±1.6	10.6±1.1	

* Value significantly different from group (1), $p<0.01$

FIG. 1. 17-Hydroxycorticoid output in surgically traumatized dogs 4 hr after various brain operations. Shaded areas in the diagrams of sagittal sections of the dog brain on the right show extent of brain removal in each group.

Results. The mean 17-hydroxycorticoid outputs in each group of dogs following the trauma of cannulation, and after 10 mU of ACTH, are shown in Fig. 1. The output following the trauma of adrenal vein cannulation was at least 3.6 μg/min in all groups except that in which the pituitary was removed. However, the output was significantly lower in both of the groups with isolated pituitaries than it was in the craniotomy control group ($P<0.01$). In the isolated pituitary group with the hindbrain removed, the mean output was slightly but not significantly lower than it was in the group in which the hindbrain was not removed ($P>0.3$). There was some variation in the mean ACTH response from group to group, probably due to chance variation in adrenal size(5), but the differences between groups were not statistically significant. The 10 mU dose of ACTH is sufficient to produce maximal glu-

cocorticoid output in hypophysectomized dogs(6). The blood pressure in the total brain removal group of animals averaged 88/45 mm Hg at the time the first adrenal venous specimen was collected. It was higher in the other groups of animals. The slightly lower 17-hydroxycorticoid output value in the brain removal group may have been due to hypotension.

Histologically, the isolated pituitaries were found to contain India ink in appreciable quantities. There were scattered areas of infarction in the anterior lobes in many animals. In the few animals in which these areas were extensive, 17-hydroxycorticoid output was generally low. There were no pituitary infarcts in the animals with hypothalamic islands, but the hypothalamic tissue was disrupted and hemorrhagic.

Discussion. These results confirm Egdahl's reports (2,7) that there are appreciable numbers of patent blood vessels supplying the pituitary after removal of the hypothalamus in the dog, and that the output of 17-hydroxycorticoids in such animals is considerably above the value of approximately 1 to 3 μg/min found in surgically stressed dogs with lesions of the median eminence. The high hormone output is due to a factor secreted from the pituitary, presumably ACTH, since removal of the pituitary reduces the 17-hydroxycorticoid output to less than 1 μg/min. It should be noted that although the 17-hydroxycorticoid output is not reduced to low levels, it is not as high in animals with isolated pituitaries as it is in the control group with intact hypothalami. Removal of the hindbrain fails to produce a statistically significant lowering of the response, making it unlikely that a factor secreted by the hindbrain is responsible for the relatively high level of ACTH secretion. Egdahl has recently confirmed this observation(8), and he has also reported that removal of the whole brain and the spinal cord does not depress 17-hydroxycorticoid output to basal levels in traumatized dogs with isolated pituitaries. On this basis, he has now retracted his original hypothesis, and agrees that the hindbrain is not the source of an ACTH-stimulating neurohumor.

There remains the problem of why ACTH output is elevated after trauma in the hypothalamic island and isolated pituitary preparations. It is possible that the damaged adenohypophyseal tissue liberates ACTH autonomously, and this possibility cannot be ruled out in the present study. However, Egdahl has kept dogs with isolated pituitaries alive for 5 days(2,7) and found that their 17-hydroxycorticoid output remains elevated. Although there are no experimental data on the point, it seems unlikely that ACTH release due to pituitary hypoxia or ischemia would continue for this length of time.

Three other possible explanations of the elevated ACTH secretion deserve consideration. There could be a substance, or "wound hormone," liberated during trauma into the circulation from some part of the body other than the brain that stimulates the hypothalamus to release corticotropin-releasing factor (CRF). Alternatively, there could be a "wound hormone" that stimulates the anterior pituitary directly. A third possibility is that in all these preparations, traumatized and degenerating neural elements liberate CRF autonomously. It is impossible at present to choose among these alternatives. The fact that actual removal of the hypothalamus does not lower the 17-hydroxycorticoid output to low levels does not necessarily mean that a postulated circulating factor must work directly on the anterior pituitary, because in all the present isolated pituitary preparations, the posterior pituitary was present, and this tissue is known to contain CRF and to resemble median eminence tissue(9). Egdahl has reported that removal of the posterior pituitary as well as the hypothalamus does not reduce the level of corticoid secretion(8). However, the removal of all neural tissue could be proved only by examining serial sections of the pituitary remnants, and it would be extremely difficult to remove all shreds of neural tissue without severely damaging the anterior pituitary.

The responses of the isolated pituitary dogs might be due to autonomous release of CRF from damaged hypothalamic or neurohypophyseal remnants, and the responses in

the animals with hypothalamic islands could also be explained on this basis because these islands were extensively disrupted and hemorrhagic. The 17-hydroxycorticoid output in dogs in which the pituitary stalk had been sectioned acutely, interrupting the portal vessels and producing a degree of pituitary damage similar to brain removal, but leaving the brain intact, was similar to the output in isolated pituitary preparations.

If the hypothalamus or pituitary is activated by a humoral factor liberated from some portion of the body during trauma, the output of 17-hydroxycorticoids in dogs with hypothalamic islands or isolated pituitaries should be low in the absence of stress, while if the release of ACTH is autonomous, the rate should be high. It has been reported that in non-stressed rats with hypothalamic islands, the circulating corticosterone levels are low(10). However, there are no data on the output of 17-hydroxycorticoids in the absence of stress in dogs after similar operations, and a truly unstressed state after such extensive surgery would be difficult to achieve.

Summary. The adrenocortical response to the trauma of cannulating the adrenal vein has been tested in dogs 4 hours after removal of various parts of the brain. Compared to controls, 17-hydroxycorticoid output in adrenal venous blood is slightly decreased in dogs in which all brain tissue above the pons except the hypothalamus has been removed. Output was significantly lower, but still definitely above basal levels in dogs in which the entire brain above the pons had been removed. It was in the same range when the entire brain had been removed. Acute section of the pituitary stalk decreased the adrenocortical response to an approximately equal degree. Removal of the pituitary as well as the brain reduced output to low levels. These data do not support the hypothesis that the hindbrain secretes a factor which stimulates the pituitary to secrete ACTH. Other possible explanations of the results are discussed.

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Influence of Aldosterone and Angiotensin II on Endotoxin Shock in the Primate.* (28172)

WESLEY W. SPINK, JAMES A. VICK, JAMES C. MELBY AND JOANNE FINSTAD
Departments of Medicine, University of Minnesota Medical School, Minneapolis and University of Arkansas, Little Rock

Canine endotoxin shock has been successfully reversed with aldosterone and angiotensin II(1).¶ Because endotoxin shock in the monkey corresponds more closely to the hemodynamic and metabolic alterations occurring in human patients, studies were extended to the primate. Features of endotoxin shock in the monkey are hypotension, oliguria or anuria, hyperkalemia and terminal acidosis.

The main objectives of the present investi-

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