The Importance of the Brain in the Endocrine Response to Injury *

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EVERY SEVERE TRAUMA, in man or in the dog, is accompanied by a pituitary secretion of ACTH and, as a consequence of this, an increased output of adrenal corticosteroids. Failure of this response to occur results in the death of the individual. This paper deals with the mechanisms set in motion by trauma which lead to an increased release of anterior pituitary ACTH. The importance of the brain and other portions of the nervous system to this response will be emphasized.

Methods

Mongrel dogs were used for all experiments. Intermittent samples of adrenal venous blood were collected through an adrenal vein cannula by the method of Hume and Nelson.[14] The adrenal venous blood samples were analyzed for 17-hydroxycorticosteroids (17-OH CS) by the method of Nelson and Samuels.[26] Blood ACTH levels were assayed by the method of Nelson and Hume.[27] Cavernous sinus blood was obtained for ACTH measurements by the technic of Ganong and Hume.[9] Hypothalamic lesions were created by the method of Hume and Ganong.[16] Removal of the cortex of the brain, and the entire brain above the inferior colliculus, was carried out by the method of Egdahl and Jackson.[4] Removal of the hypothalamus from below was carried out by the method of Hume and Jackson.[23] Section of the pituitary stalk was carried out through a transbuccal approach by the method of Jackson, Egdahl, and Hume.[24] Cord section at C-7 and section of the medulla oblongata were carried out at open operation.

Results and Discussion

1. *Cord Section:* It was shown by Hume and Wittenstein [11] and by Hume [12, 13] that section of the spinal cord at C-7 in the dog abolished the usual eosinopenic response to trauma below the level of cord section. If a very severe scald was applied to the leg some eosinopenia occurred, but this was much less than normal. Gordon [10] also showed that denervation of the limb in rats abolished the adrenal ascorbic acid depletion which usually accompanied fractures of the femur. He noted, however, that a severe burn of the denervated leg did produce adrenal ascorbic acid depletion.

These studies were interpreted as showing that it was essential to have an intact afferent nerve supply from the area of the injury to the brain in order to stimulate the ACTH release normally seen following trauma. It was felt on the basis of the burn studies that a subnormal release of ACTH could occur following burn trauma, and that this might be on the basis of some humoral toxic agent released in the vicinity of the burn.[13]

These early studies utilized indirect methods to assess adrenal cortical function. They have therefore been repeated using adrenal venous blood corticosteroid secretion as a direct measure of adrenal activation, and a standard burn trauma as the

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TABLE 1

			Burn Denervated Leg							Burn above site of section					
Exp.	Dog	Control	5′	15′	30′	60′	90′	ACTH	Control	5′	10′	15′	30′	60′	ACTH
1	W-28	0.3	0.1	0.3	0.1	0.3	1.1	15.0							
2	W-25	1.5	0.9	0.5	0.6	0.8	1.6	29.0							
3	W-25	1.5	1.7	0	7.2	3.2			3.2	28.8	26.6	20.0	8.8	21.2	
4	W-31	0.1	0	0.6	0.4	0.2	0	13.8							
5	W-31	0.8	0.5	0.1	1.7	0.9	2.7								
6	W-32	1.0	2.6	0.4	3.2	0.4	1.0	19.0							
7	W-32	2.6	0	0	1.8	0.3		28.4							
8	PC-5	7.4	0	0.1	0.2	2.0			2.0			10.7	7.8	4.2	11.8
9	PC-6	1.2	3.0	1.4	0.4	0.8			0.8	20.8	10.8	1.4	0.4		21.8

stimulus. Nine experiments were carried out in six dogs. The results are summarized in Table 1. It may be seen that no increase in adrenal cortical secretion occurred in response to a severe burn of the denervated leg. It may be seen further that all dogs responded with markedly increased adrenal cortical secretion to injections of ACTH, indicating that the adrenal cortex was normally reactive. In three experiments (nos. 3, 8, 9), the animal received a burn on the neck—above the area of cord section—while under nembutal anesthesia. A good response occurred following the burn in the normally innervated portion of the body. A typical experiment is shown in Figure 1. These studies seem to indicate conclusively that an intact afferent nerve supply leading from the injured area is essential for the pituitary-adrenal activation which normally accompanies burn trauma. There is no evidence for any humoral factor arising in the burned area, as we thought at one time.[13] The minor degree of eosinopenia which had been seen following burns of the denervated extremity in the earlier work by

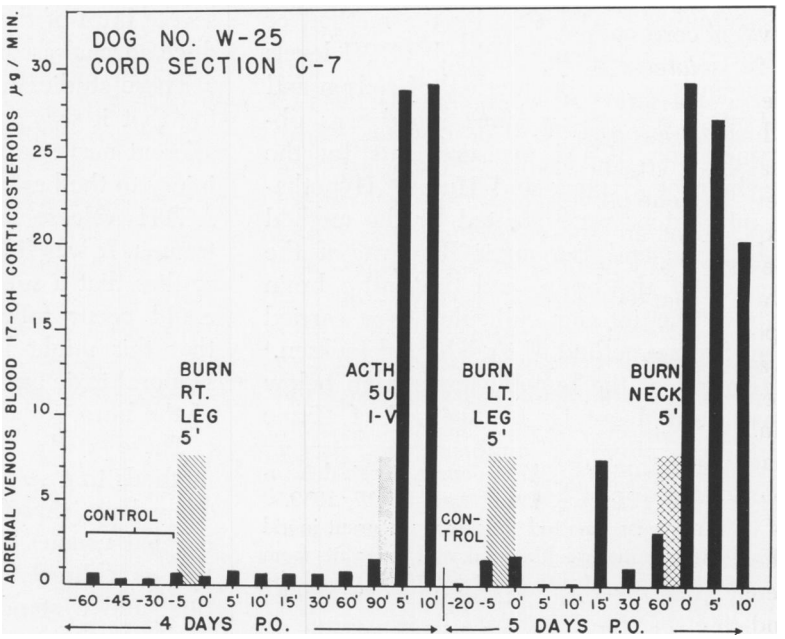

FIG. 1. The adrenocortical response to a burn following section of the cord at the level of C-7. A burn below the level of section produced no increase in adrenocorticosteroid secretion over the control values. Five units of ACTH intravenously produced an immediate marked rise in adrenocortical output. Under nembutal anesthesia, a burn of the left hind leg produced no significant increase in corticosteroid output. By contrast a burn of the neck above the level of cord section produced a marked and immediate increase in adrenocortical secretion.

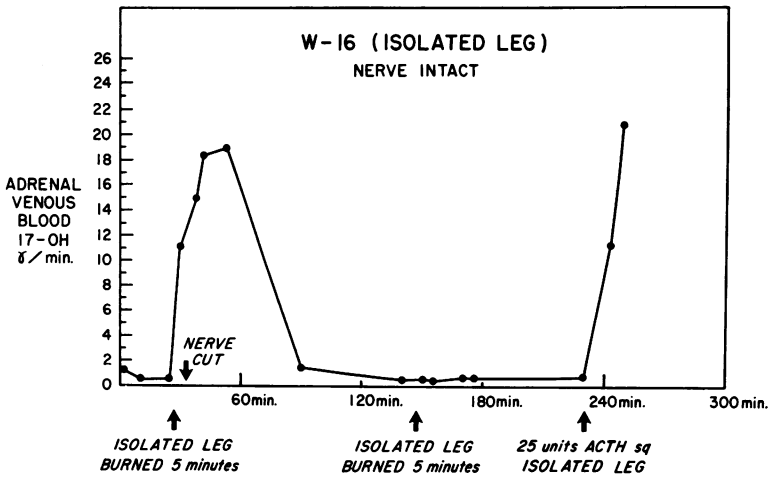

FIG. 2. The hind leg has been isolated so that it is attached to the body only by one artery, one vein and one nerve. A burn of the isolated leg produced a marked and immediate rise in adrenal venous blood corticosteroid output. During the height of the response the nerve was cut and the secretion dropped rather promptly to control levels. A second burn of the same leg now produced no adrenocortical response. ACTH injected subcutaneously into the isolated leg produced a prompt and marked increase in adrenocorticosteroid secretion. (From Egdahl: Pituitary-Adrenal Response Following Trauma to the Isolated Leg. Surgery, 1959. In press.)

Hume may have been due to destruction of circulating eosinophils passing through the burned area.

It has also been shown that no significant increase in adrenal secretion occurs as a consequence of operative trauma below the level of cord section in paraplegic humans.[17]

2. *Isolated-Leg Dogs:* Egdahl[5] has carried out a series of experiments in dogs in which he has isolated a leg from the body, leaving it attached only by one artery, one vein and one nerve. The results of a typical experiment are shown in Figure 2. It will be seen that when the leg was burned there was a marked adrenal corticosteroid response. After the response was well under way the nerve was cut, but the artery and vein were left undisturbed. In a very short time the adrenal cortiscosteroid response had ceased. When the leg was now reburned no response was seen. The injection of 25 units of ACTH subcutaneously into the isolated leg invoked an immediate adrenal corticosteroid response. These data indicate that the pituitary-adrenal response to trauma is normal as long as the afferent nerve from the injured area is intact, but that the response is completely absent when the nerve is cut, even though the artery and vein are still intact. The injection of ACTH subcutaneously into the leg provokes an immediate adrenal response, indicating (1) that the adrenal cortex is reactive and (2) that any humoral substance capable of initiating pituitary-adrenocortical stimulation—and present in the leg following the burn—could have evoked this response. One must conclude that there is no humoral stimulating substance formed in the burned area, and that the adrenocortical response following a severe burn depends entirely upon an intact nerve supply leading from the burned area. The appreciation of pain is not necessary for this response, since the entire experiment was performed under nembutal anesthesia, and a response is present even if the brain cortex is removed.

The cord section work and the isolated leg data taken together are important to our appreciation of the role of the brain in

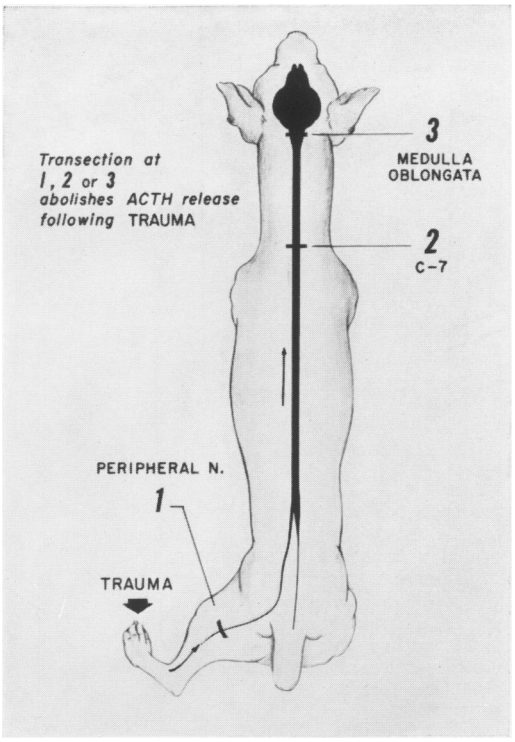

FIG. 3. Trauma to the hind leg no longer leads to the pituitary adrenocortical activation after transection at any of the three locations indicated in this diagram. It is thus apparent that an afferent nerve impulse has to reach the brain in order to produce pituitary ACTH release.

the control of ACTH secretion, since they indicate conclusively that ACTH release following trauma is not brought about through any mechanism capable of direct pituitary stimulation, but rather through central nervous system mediation.

3. *Section of the Medulla Oblongata:* A section was carried out through the lower portion of the medulla oblongata in three dogs. These animals failed to show an increased adrenocortical secretion following burns in the extremities. The level of section is shown in Figure 3. Transections at sites 1, 2, or 3 completely abolish the ACTH release usually seen following trauma below this area. An activation of brain centers is necessary for ACTH release following trauma.

4. *Chronic Hypothalamic Lesions:* It has been shown by us in several groups of experiments over the last 10 years that hypothalamic lesions located in the anterior portion of the median eminence and the postoptic area abolish the normal pituitary-adrenal activation seen following trauma. In the earlier experiments[11,12,13] the change in circulating eosinophils was used as an indirect measure of adrenocortical activity. In the later experiments[15, 17, 18, 20, 23] direct measurements were made of blood ACTH levels and adrenal venous blood corticosteroid secretion. The results are shown in Figure 4. Increased levels of circulating ACTH could easily be detected in the normal dog during an abdominal laparotomy. In animals tested one month after the production of a hypothalamic lesion in the median eminence no detectible amounts of ACTH were present in the arterial blood following trauma, and the adrenal corticosteroid secretion was markedly reduced.

An additional finding in the group of animals with hypothalamic lesions was that the adrenal cortex had become much less responsive than that of the normal dog to injections of ACTH.[15, 17] This occurred in spite of the fact that the adrenal was not atrophic, and appeared normal histologically. By contrast, following partial removal of the pituitary[7, 18] there was a marked adrenal atrophy after a month's time. In spite of this the pituitary-adrenal response to operative injury was nearly normal, and the adrenal was normally responsive to injections of exogenous ACTH. Total hypophysectomy totally abolished the adrenal response to operative trauma, and adrenal responsiveness to ACTH was all but absent after 48 hours (Fig. 11).

5. *Acute Hypothalamic Lesions:* The effect of the hypothalamic lesions mentioned in the paragraph above on adrenocortical secretion was tested from one month to two years after the production of the lesion. Another set of experiments was carried out in which acute lesions were made in the hypo-

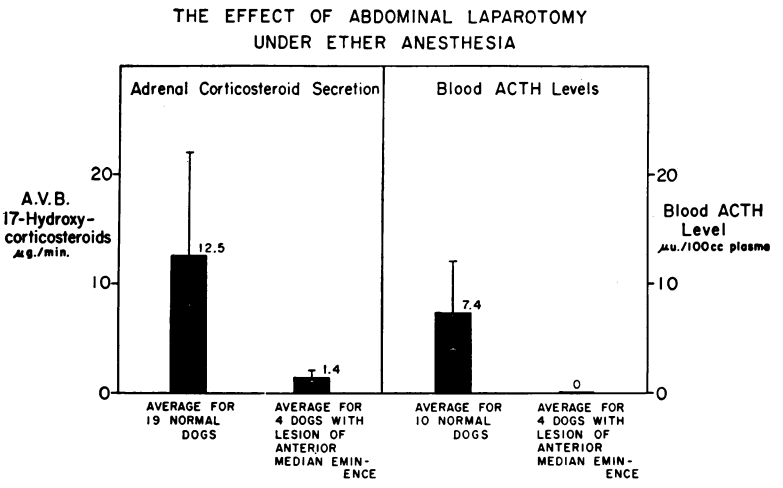

FIG. 4. The adrenocorticosteroid secretion and blood ACTH level in the normal dog subjected to operative trauma under ether anesthesia compared to that seen in dogs with lesions involving the anterior median eminence and postoptic area. An easily measurable blood ACTH level was found in all normal dogs subjected to operative trauma. No detectable ACTH was found in dogs with median eminence lesions when the same quantity of blood was used. Adrenocorticosteroid secretion in the animals with median eminence lesions was much less than that seen in normal dogs (reprinted from Hume: The Method of Hypothalamic Regulation of Pituitary and Adrenal Secretion in Response to Trauma. Pathophysiologia Diencephalica, International Symposium Milan, May 1956. Springer-Verlag, Vienna, 1958, Pg. 217).

thalamus and the animal's response to trauma was tested immediately after, and at various periods up to a week.[23] It was found that a lesion of the median eminence which leads to almost complete unresponsiveness of the pituitary and adrenal at the end of a month failed to block the response to trauma when tested in the first 24 hours after the production of the lesion. Two examples are shown in Figure 5. Because such profound changes in pituitary ACTH release and adrenal response had occurred a month after such a lesion it was postulated that this area might have something to do with the formation of ACTH in the pituitary, and with its periodic release throughout the day to maintain adrenal reactivity.

6. *Stalk Section:* In another series of animals the pituitary stalk was sectioned after exposing it through a transbuccal approach.[24] Pituitary-adrenal response to electrical stimulation of the sciatic nerve [1] and burns was tested. It was found that acute section of the stalk did not prevent release of ACTH from the pituitary following stimulation, either in the first 24 hours after the stalk section or several days later (Fig. 6).

7. *Removal of the Hypothalamus:* In another series of animals the stalk was sectioned exactly as in the animals referred to in the previous paragraph, and following this the tip of a very small sucker was inserted so as to remove large areas of the anterior hypothalamus and preoptic area. Another group of animals was treated in exactly the same fashion except that the hypothalamic removal involved the anterior-middle portion and did not extend as far anteriorly as in the first group. The stalk section and hypothalamic removals are diagrammed in Figure 7. In contrast to the animals with stalk section there was a complete failure of the animal with anterior hypothalamic removal to respond to stimuli in the first 24 hours after the lesion (Fig.

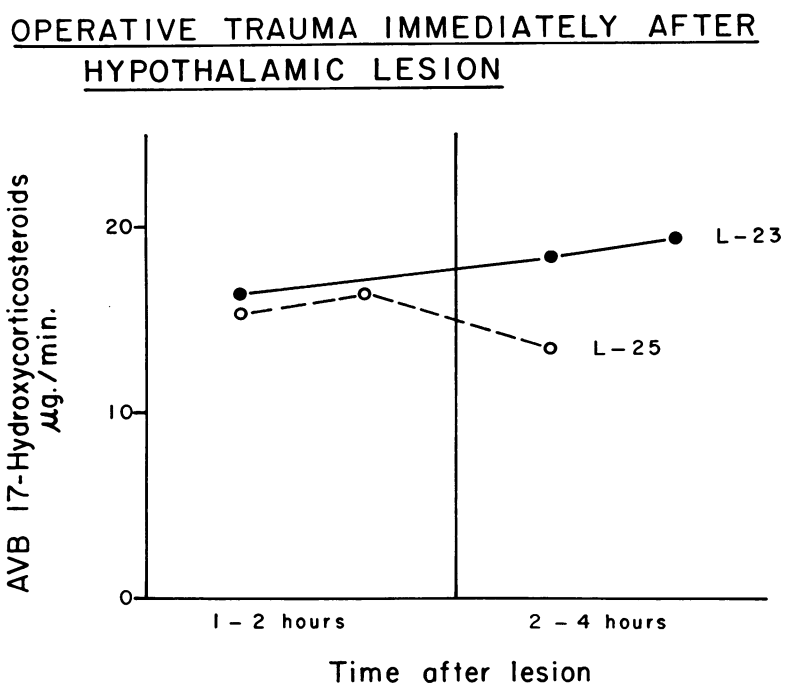

FIG. 5. Adrenocorticosteroid secretion in two dogs undergoing abdominal laparotomy during the first four hours after production of an electrolytic lesion destroying the anterior median eminence and postoptic area. A normal response is present. The animals shown in Figure 4 had lesions in exactly the same location, but were tested a month after the production of the lesion.

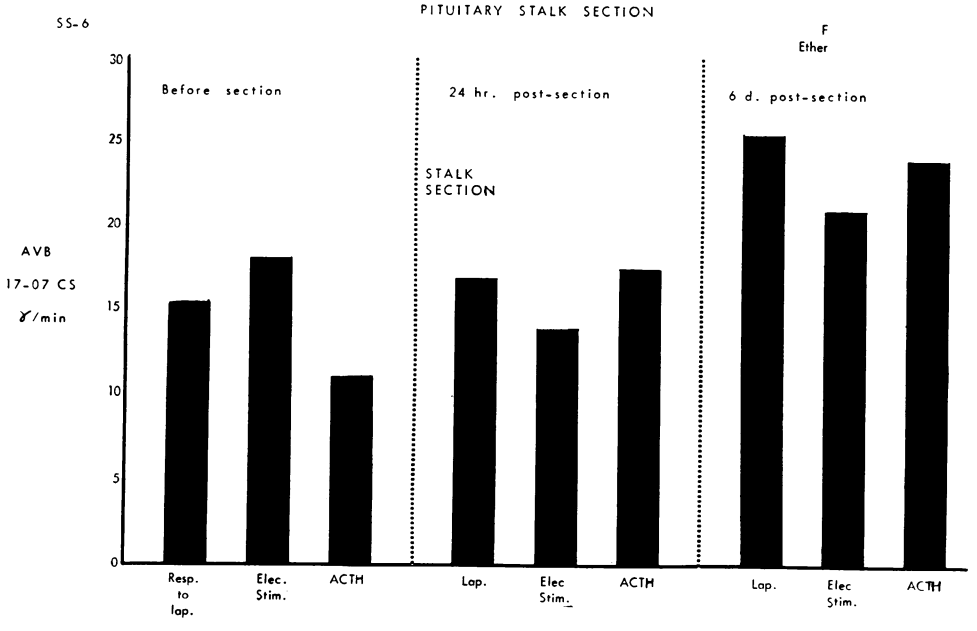

FIG. 6. The adrenocorticosteroid response to abdominal laparotomy, electrical stimulation of the sciatic nerve, and intravenous ACTH before section of the pituitary stalk, 24 hours after section of the stalk, and six days after section of the stalk. Ether anesthesia was used. Section of the pituitary stalk did not alter the normal response of the dog to trauma or to ACTH.

8). In some other animals (Fig. 9) there was a slight response to stimulation in the first 24 hours but this diminished with each successive stimulus and was far less than that seen with ACTH. It may be seen in Figure 10 that after five days there is nearly a complete absence of response to trauma, but still a very good response to ACTH.

The results seen in removal of the anterior hypothalamus are thus much different than those seen in total hypophysectomy. In Figure 11 it may be seen that 24 hours after hypophysectomy there is no response at all to trauma, and the response to ACTH is diminished when compared with the response prior to hypophysectomy. By 48 hours even the response to ACTH is virtually absent.

8. *Removal of the Brain:* It has been shown by Egdahl [2-4] that removal of the brain does not alter the ability of the animal to respond to operative injury with an increased pituitary-adrenocortical secretion. The three different levels of brain removal are shown in Figures 12 and 13. In the first group the cortex alone was removed, in the second the cortex and thalamus were removed, and in the third all the brain above the level of the inferior colliculus was removed, leaving only the cerebellum, pons and medulla behind. Adrenal cortical responses occurred following operative trauma in all animals in Groups I and II. It may be seen in Figure 14 that the Group III animals with isolated pituitaries, having no connections to any other portion of the brain, were capable of showing a marked increase in ACTH secretion in response to operative trauma in many instances. Furthermore, it was noted that the animals of all three groups showed high resting levels of corticosteroid secretion in contrast to the normal animals, or the animal with a hypothalamic lesion. This suggested that an inhibitory effect of the cortex had been removed, permitting the brain stem to stimulate the pituitary to secrete higher resting levels of ACTH than it normally would.

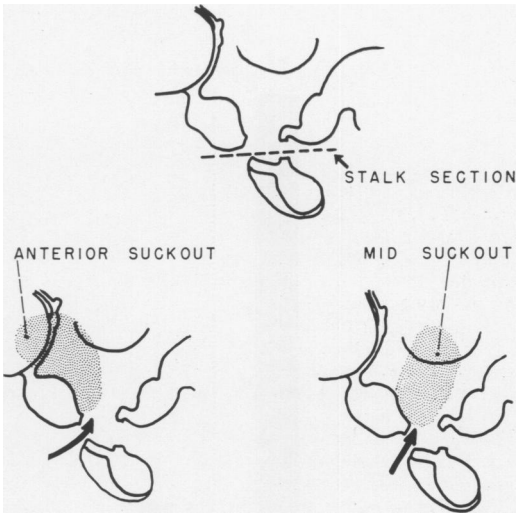

FIG. 7. In these diagrammatic sectional views of the hypothalamus of the dog the defects created by a stalk section, anterior suck-out, and mid-hypothalamic suck-out are illustrated. For the removal of the hypothalamus the suction tip is inserted in the direction indicated by the arrow. For the anterior suck-out the suction tip is bent back in a hook.

9. *The Stimuli to Adrenal Secretion Encountered During Operative Injury:* In other experiments which will not be discussed in detail here it has been shown that acute blood loss alone, without any other type of trauma, can lead to a marked stimulation of pituitary ACTH release and adrenocortical activation.[22] It has also been shown that psychic stimulation as a consequence of emotional trauma occurring during injury can by itself produce a marked stimulus to pituitary ACTH release and adrenocortical secretion.[8, 22] Some types of anesthesia, particularly ether, can themselves cause pituitary ACTH release and adrenocortical stimulation.[19] Others, such as nembutal, on the other hand, do not lead to pituitary stimulation.[19] Fever alone can lead to increased adrenocortical activity.[28] Bacterial toxins are also strong stimuli to pituitary adrenal activation.[6, 25] It has been shown that in mild shock there is an increased adrenal sensitivity to ACTH and therefore an increased adrenal cortical secretion.[14] It has further been shown that

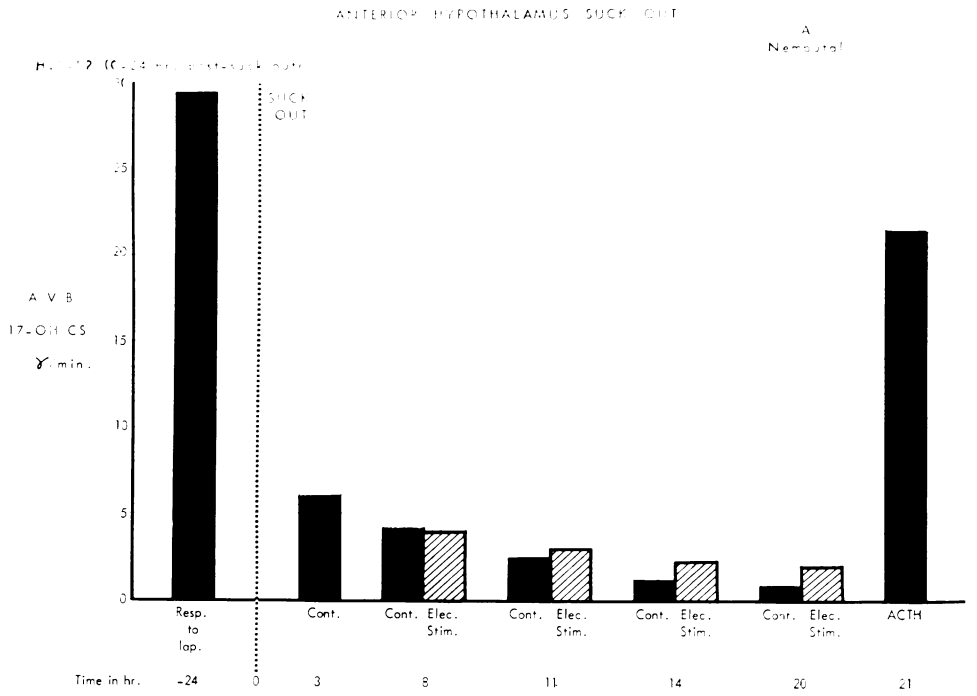

FIG. 8. The adrenocorticosteroid response to electrical stimulation of the sciatic nerve in the first 24 hours after removal of the anterior hypothalamus and preoptic area. The corticosteroid response to abdominal laparotomy 24 hours prior to the removal of the hypothalamus is also shown, as well as the ACTH response at the end of the stimulation. While the response to electrical stimulation was virtually absent, the response to ACTH was nearly normal.

small doses of ADH (antidiuretic hormone) can increase adrenal sensitivity to ACTH.[21] Large doses of ADH, whether naturally occurring, highly purified, or synthetic, can produce adrenocorticosteroid secretion even in the absence of the pituitary.[17, 21] This never occurs, however, from the amounts of ADH present in the body.[17] Afferent nerve impulses of course, constitute the major pathway for pituitary-adrenal stimulation following trauma. Presumably all the other stimulating factors except ADH, act through the brain.

Discussion and Conclusion

It is possible to provide at least one hypothesis to explain all of the observations discussed in this paper. Admittedly other hypotheses may be equally good or even better, but for the sake of discussing data it is sometimes convenient to have a working hypothesis, and we have illustrated ours in Figure 15. It is postulated that stimulatory nerve impulses are sent toward the brain from the injured area, probably through the reticular formation. These impulses reach centers in the lower brain stem and in the hypothalamus. Psychic stimuli from the cortex of the brain also are transmitted down to the hypothalamus. A center in the anterior hypothalamus and preoptic area releases a humoral substance in response to in-coming stimuli which leads to ACTH release by the pituitary. The production of ACTH by the pituitary and its cyclic release in small quantities from day to day in order to maintain adrenal reactivity, is controlled by another center in the hypothalamus located in the anterior median eminence and postoptic area. When this center is removed the pituitary is still capable of responding from the stores of

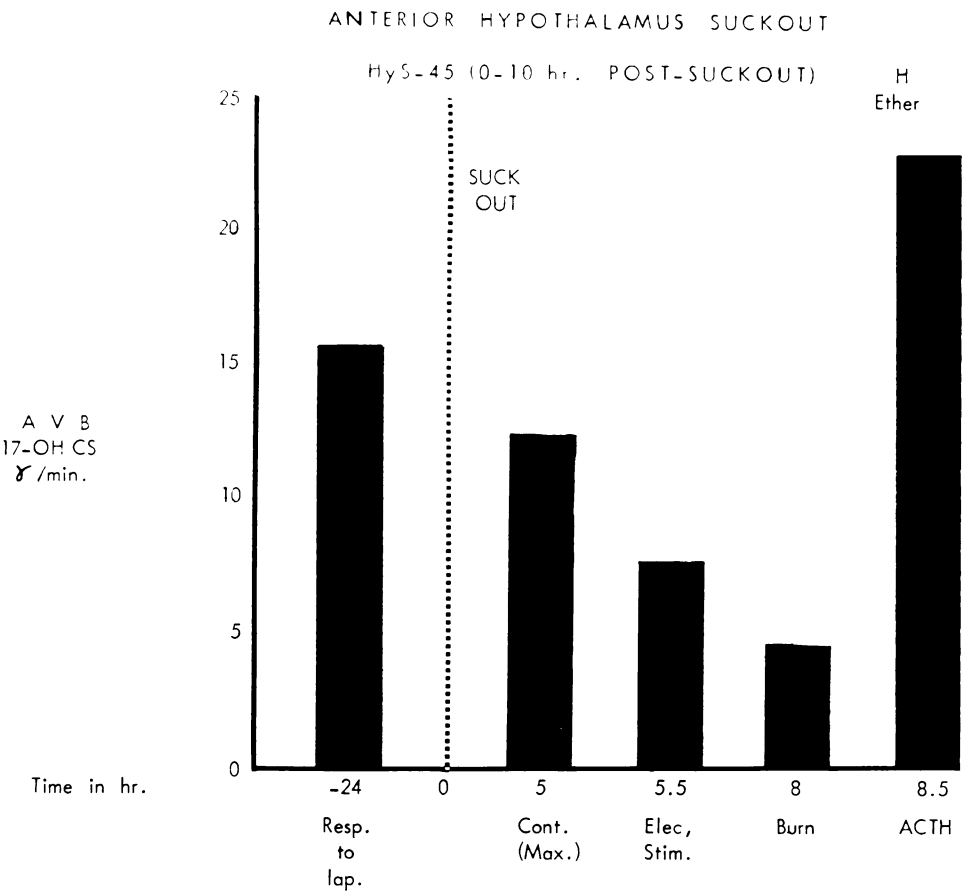

FIG. 9. The adrenocorticosteroid response to electrical stimulation of the sciatic nerve and a standard burn are shown in the 10-hour period after removal of the anterior hypothalamus and post-optic area. There was a steadily diminishing and markedly reduced response to trauma, while the response to ACTH remained normal. Since the entire experiment was carried out under ether anesthesia there was also a reduced response to ether anesthesia which normally acts as a stimulant.

ACTH which it maintains. However after a period of many days ACTH production lags, due to the absence of the hypothalamic center. Adrenal reactivity is lost because the adrenal is not being constantly stimulated by release of small amounts of corticosteroidogenic ACTH. Thus when the animal is traumatized a month after the destruction of this center there is a failure to release ACTH, and a failure of the adrenal to respond. There is also a loss of normal sensitivity of the adrenal to exogenous ACTH, although the adrenal is not atrophic.[17, 18] When the stimulatory center in the anterior hypothalamus and preoptic area is removed operatively there is a failure of ACTH release mechanisms, so that adrenal response to injury is absent or reduced immediately after. It should be stated that other experiments are underway to make absolutely certain that none of these observed changes are due to damage to the pituitary.

There is also thought to be a growth type of ACTH manufactured in the pituitary and not under the control of the hypothalamus. This substance controls adrenal size. Because it continues to be secreted following hypothalamic destruction, there is no atrophy of the adrenal cortex. When partial

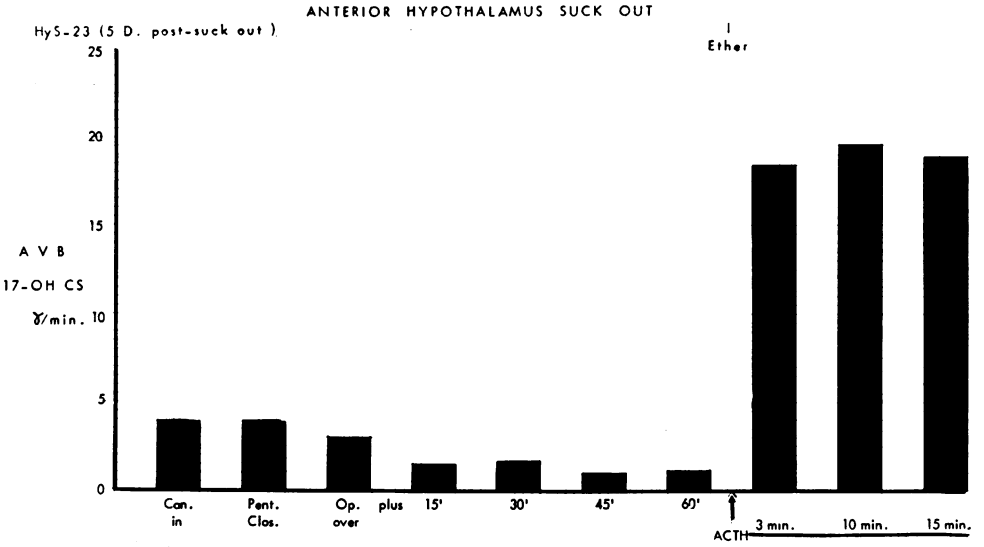

FIG. 10. An adrenal cannulation was carried out under ether anesthesia five days after the removal of the anterior hypothalamus and pre-optic area. Values were obtained just after the cannula was placed in the adrenal vein, after closure of the peritoneum, and at the end of operation. Several samples were obtained in the postoperative period. Responses to the operation and to ether anesthesia were markedly subnormal. By contrast, the response to exogenous ACTH is excellent and prompt.

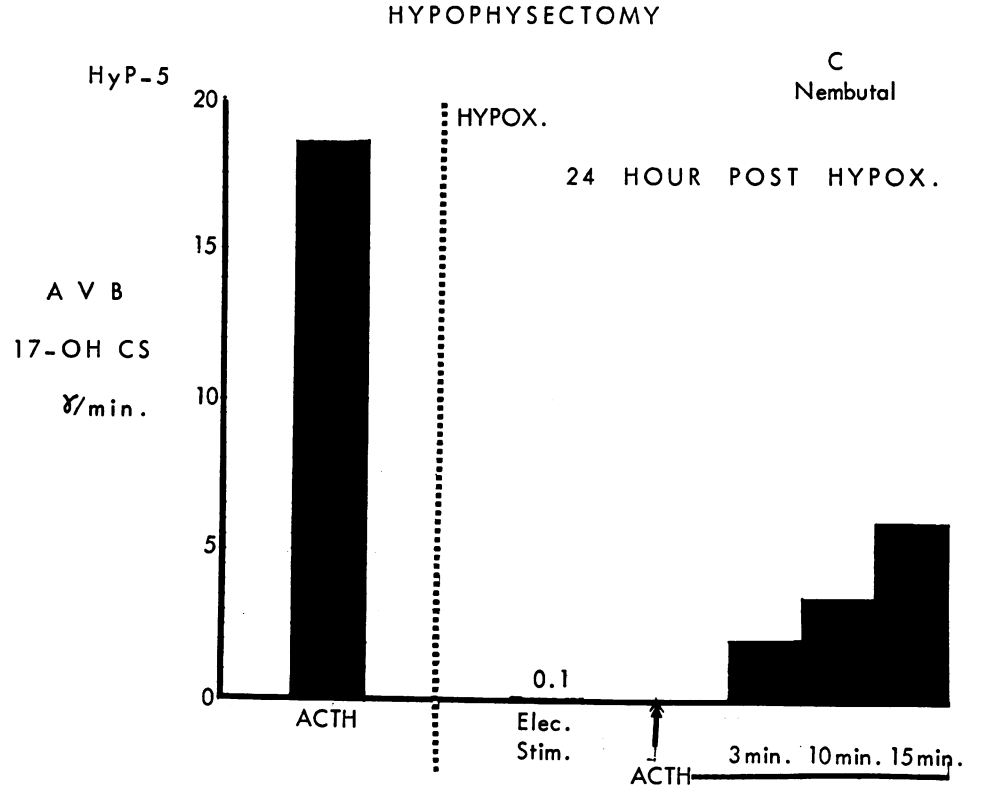

FIG. 11A. Electrical stimulation of the sciatic nerve produces no output of adrenocorticosteroids 24 hours after hypophysectomy. A dose of exogenous ACTH at this time shows a much smaller response than the ACTH response just prior to hypophysectomy.

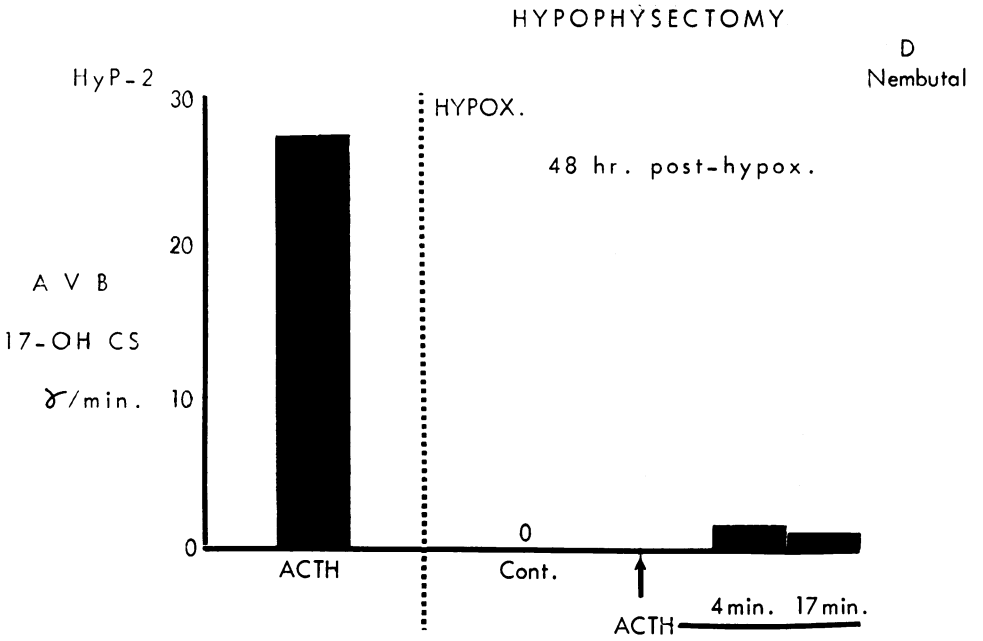

FIG. 11B. The response to exogenous ACTH 48 hours after hypophysectomy is very markedly reduced. This response should be contrasted to that seen five days after removal of the anterior hypothalamus and illustrated in Figure 10.

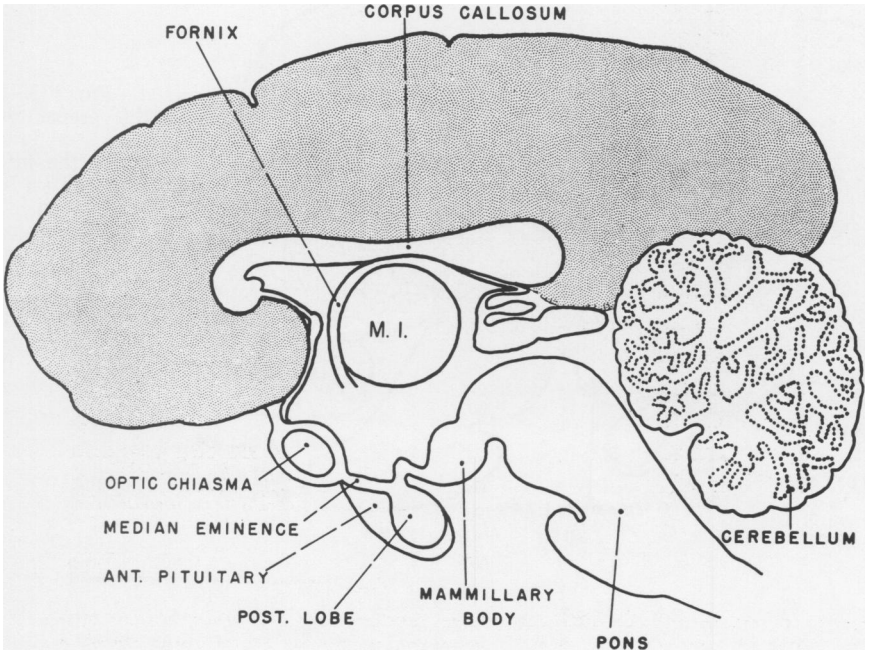

FIG. 12A. A diagrammatic sagittal section of the dog brain. The stippled area representing the cortex, has been removed in this preparation, leaving the remaining structures of the brain intact.

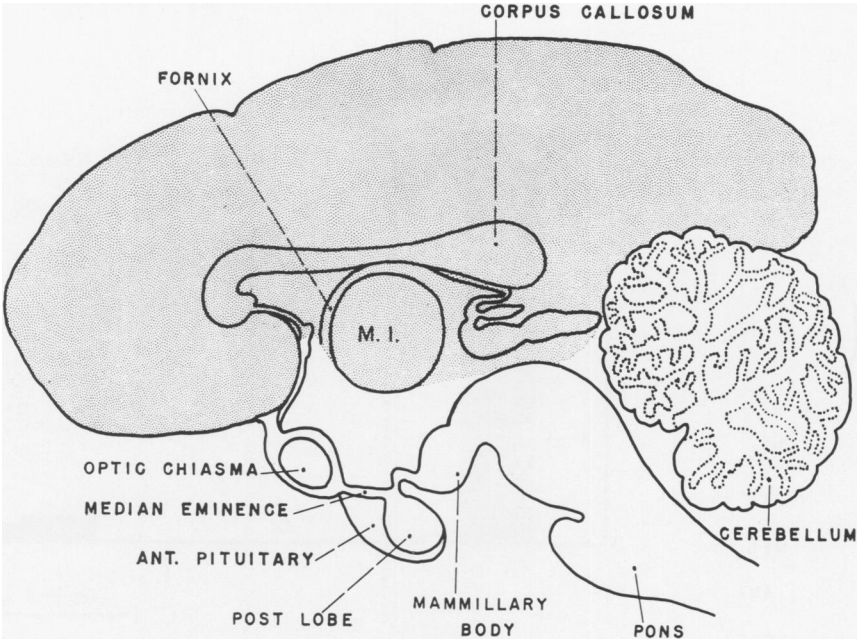

FIG. 12B. In this preparation the cortex, corpus callosum, thalamus and corpora quadrigemina have been removed, leaving the cerebellum, pons, cerebral peduncles, hypothalamus and pituitary.

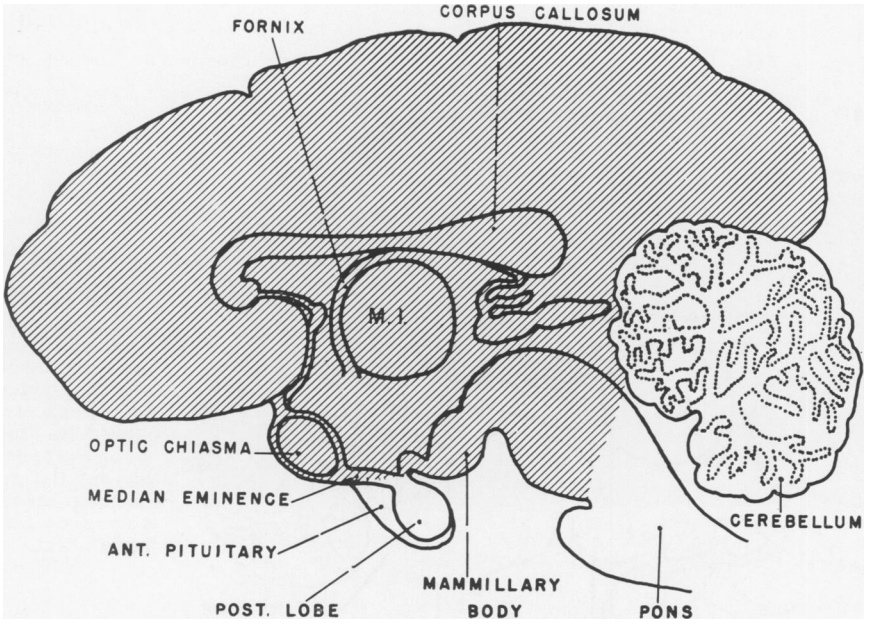

FIG. 13A. In this preparation the entire brain above the inferior colliculus has been removed, leaving only the medulla, pons and cerebellum. The pituitary has been left behind.

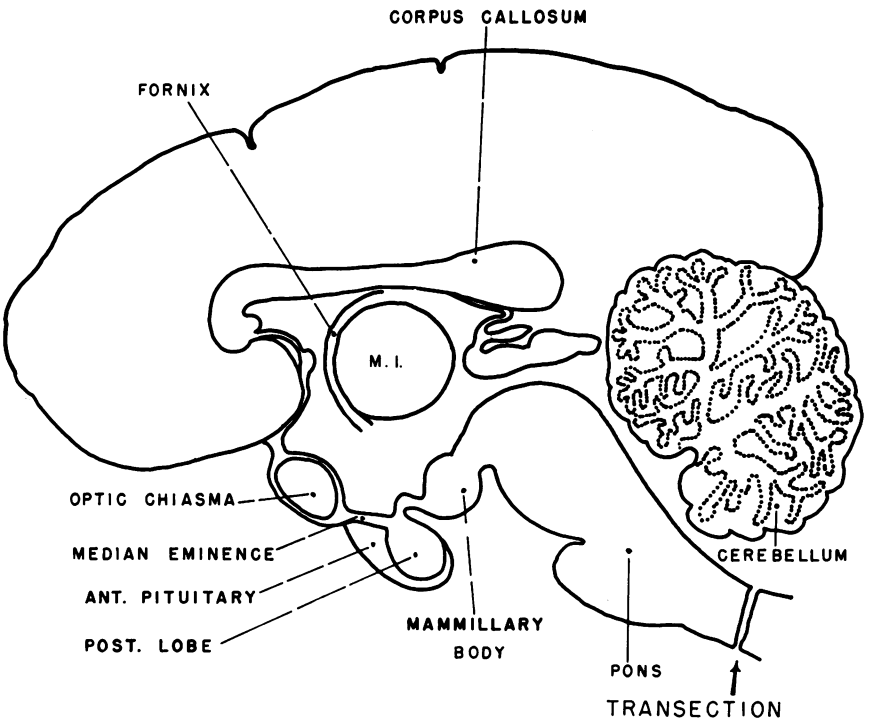

FIG. 13B. In this preparation the brain is intact, but the medulla has been transected at the point shown on the diagram.

removal of the pituitary is carried out [7, 15] there is a decreased amount of growth ACTH present and the adrenal cortex becomes atrophic. The hypothalamic mechanism for the release of corticosteroidogenic ACTH is still present however, so that the animal responds to operative trauma with an increased secretion of ACTH and adrenal corticosteroids.

Superimposed upon this mechanism is another stimulatory center located in the lower brain stem. In the intact animal this stimulatory center is inhibited by impulses arising in the cortex of the brain. Therefore when the anterior hypothalamus and preoptic areas are removed no ACTH release occurs in response to trauma, because the lower brain stem center is completely inhibited by the cortex of the brain. When the cortex of the brain, or for that matter the entire brain above the inferior colliculus, is removed the inhibition of the lower brain stem is gone. The stimulatory center in the medulla or pons is therefore capable of stimulating ACTH release from the anterior pituitary. With the removal of cortical inhibition this center continually fires off, leading to high resting levels of corticosteroid secretion. Even higher levels of secretion are triggered off by trauma. The effect of the lower brain stem on the pituitary, and the effect of the hypothalamus on the pituitary must come about through humoral mechanisms, because there are no nervous connections between these areas and the pituitary. The inhibitory effect of the brain cortex upon the lower brain stem center is probably by means of a direct nervous connection between the two, but may be through a humoral mechanism.

Conclusions

The secretion of ACTH and adrenal corticosteroid following trauma are under the control of a complex neurohumoral mechanism located in various areas of the brain.

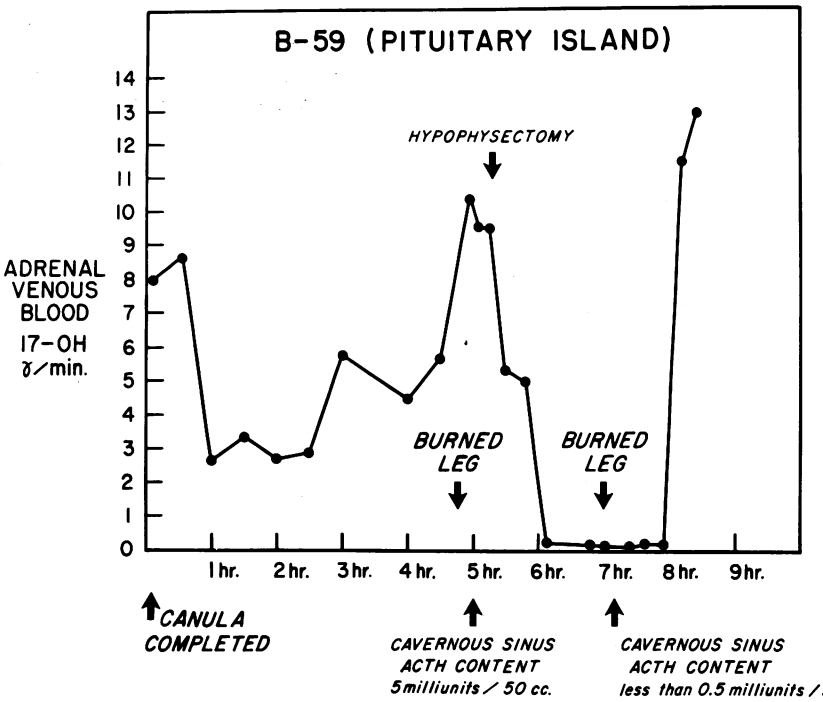

FIG. 14. An adrenal venous cannula has been performed in a dog who has had all of the brain removed above the inferior colliculus, with the exception of the cerebellum. The pituitary has been left behind as an isolated island. The animal had high resting corticoid levels, and the adrenal corticosteroid output increased sharply following the production of a burn on the hind leg. There was an easily measurable amount of ACTH present in the cavernous sinus blood. Following hypophysectomy adrenocorticosteroid secretion fell to zero. When the leg was reburned there was no response noted. The cavernous sinus ACTH content was too low to measure. Although it is not indicated on this diagram, ACTH was given at the 8 hour mark and a rapid and marked increase in adrenal corticosteroid output occurred. (From Egdahl and Jackson: Pituitary-Adrenal Cortical Function in Dogs with Isolated Pituitaries. In press.)

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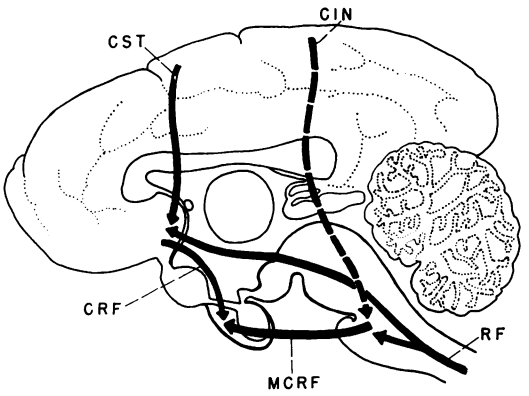

FIG. 15A. A diagram to indicate one possible hypothesis for the mechanism of ACTH control which is consistent with the observed facts. Afferent impulses ascend from the injured area, probably via the reticular formation (RF). These impulses are capable of stimulating cells in the lower brain stem and in the hypothalamus. Descending stimulatory psychic impulses from the cortex of the brain (CST) are also capable of exciting the hypothalamic control centers. As a consequence of these and other stimuli the hypothalamic-preoptic center secretes a corticotrophin releasing factor (CRF) which leads to ACTH release from the anterior pituitary. Cortical inhibitory influences (CIN) are also present, and these normally totally inhibit the release of the lower brain stem corticotrophin releasing factor (MCRF). In the absence of the cortex of the brain, the inhibitory mechanism is gone and MCRF is released, causing ACTH secretion from the pituitary even when the hypothalamus is absent.

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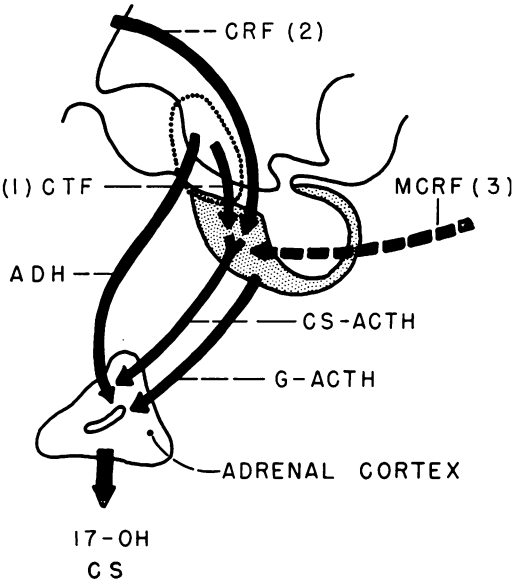

FIG. 15B. Several hypothalamic influences are postulated as working toward effective adrenal cortical secretion. (1) A corticotrophin trophic factor (CTF) is released into the blood stream from the median eminence and postoptic areas. This substance acts as a catalyst to ACTH production by the anterior pituitary. In the absence of this area corticosteroidogenic ACTH (CS–ACTH) is not produced and released in normal amounts, and the adrenal cortex loses its responsiveness to ACTH. (2) Corticotrophin releasing factor (CRF) is produced in more anterior parts of the hypothalamus and leads to the release of ACTH in response to trauma. The antidiuretic hormone (ADH) is secreted in the supraoptic nucleus and acts directly on the adrenal cortex to increase adrenal sensitivity to ACTH. (3) The lower brain stem corticotrophin releasing factor (MCRF) plays a role in ACTH release only when the inhibition of the brain cortex has been removed. A growth type of ACTH (G–ACTH) is released by the pituitary for the purpose of maintaining adrenal size. It is not under neural control.

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Discussion

Dr. Oliver Cope: Dr. Ravdin, Members and Guests: It is an honor to open the discussion of this paper. Dr. Hume deserves enormous credit. He is the surgical pioneer in bringing the endocrine system into the body. The gastro-intestinal tract, the cardiac mechanism, vascular control, muscular activity, have all been oriented to the brain—even thinking. But the endocrine system has been floating around in the body like the yolk in an egg, unattached. Up until now all we have managed is to relate the thyroid, let's say, or the adrenal to the anterior pituitary, but not to the rest of the body.

Such detachment, of course, was wholly unreasonable. There has to be a master somewhere, and it should, in terms of the rest of the systems that we know about, lie somewhere in the brain.

Dr. Hume has persisted in orienting us to this problem with his ingenious experimentation. His findings fit with what we know clinically. Dr. Phemister long ago made a determined effort—I wish he were here today to hear this—to relate traumatic shock and the nervous system. Dr. Hume has related them today, and that is tremendously important. But the wider implications of this relation he summed up in the last few words. He didn't have time to go on to all the other endocrine glands.

So it is to Dr. Hume, the surgical pioneer in this field, to whom we all owe so much.

Dr. David M. Hume (closing): I should like to thank Dr. Cope for his very kind words and to point out again what I think is the most interesting and important new chapter in this work; that is, the results of the brain removal experiments that have been added by my co-author, Dr. Egdahl. Thank you.