Effect of Hypophysectomy on Electrolyte Excretion in Dogs with Ascites Produced by Thoracic Inferior Vena Cava Constriction

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With the surgical assistance of ALFRED CASPER

Following complete or nearly complete hypophysectomy in dogs with thoracic inferior vena cava constriction, a striking increase in sodium (Na) excretion occurred concomitant with a fall in femoral venous pressure. The previously high venous pressure and renal Na retention were restored by administration of thyrotropin (TSH), growth hormone injection or further constriction of the thoracic inferior vena cava, but adrenocorticotropic hormone (ACTH) was without effect on these functions. The data indicate that pituitary hormones influence the accumulation of ascitic fluid by contributing to the maintenance of an adequate level of venous hypertension.

DOGS with ascites produced by constriction of the thoracic inferior vena cava characteristically show severe Na retention by the kidneys and a low ratio of Na and potassium (K) excretion in the feces. A more recent study suggested that this pattern of electrolyte excretion depends upon an increased level of circulating adrenocortical salt retaining hormones. As a working hypothesis, it was proposed that increased secretion of adrenocortical Na retaining steroids results, rather than a slow rate of metabolism of these hormones. Since ACTH influences the rate of secretion of hormones by the adrenal cortex, the present observations were undertaken to determine the effect of hypophysectomy and subsequent therapy with pituitary and adrenocortical hormones on ascites formation.

METHODS

Hypophysectomy was performed in 8 female mongrel dogs (dogs 1 to 3 and 5 to 9) in which the thoracic inferior vena cava had been constricted previously and ascites was present. A ninth animal (dog 4) was hypophysectomized 7 months before thoracic inferior vena cava constriction. In dog 5, thyroidectomy was performed before hypophysectomy. In dogs 7 and 8, the thoracic inferior vena cava was reconstructed late in the course of the study.

Metabolic balances of Na and K were measured during a control interval of 7 to 21 days and for 41 to 140 days after hypophysectomy (dogs 1 to 3 and 5 to 9); balance studies were conducted before and after production of ascites in dog 4. Postabsorptive renal clearances of creatinine (CCR) and para-aminohippurate (CPAH) were employed as measures of glomerular filtration rate (GFR) and effective renal plasma flow (RPF) respectively. Renal hemodynamic function and femoral arterial and venous pressures were determined at 2 to 10 day intervals throughout the study in all except dog 6 in which measurements were begun after hypophysectomy.

Cardiac output was measured in dog 1 only. The chemical methods and experimental procedures have been described elsewhere.

After hypophysectomy, hormone preparations were administered by intramuscular injection with the exception of thyroid which was given orally. Dogs 1, 2 and 5 received 30 mg. of ACTH (ACTHAR-Gel*) twice daily for 10 to 31 days; subsequently, dogs 1 and 2 were given 100 mg. of cortisone acetate once daily for 16 to 24 days. Dogs 5 and 6 received 1, 10 and 25 mg. per day of desoxycorticosterone acetate (DCA) in oil for periods of 5 to 10 days at each dosage level. A TSH preparation† was given

* Adrenocorticotropic hormone in gelatin with 30% propylene glycol.
† The authors wish to express their sincere thanks to Dr. I. M. Bunding of Armour Laboratories for the generous supply of TSH (Lot R49080) and growth hormone (Lot 990208B). The effects of these hormone preparations on renal function, water exchange and K balance have been reported previously. The growth hormone preparation contained less than 0.02 units of TSH per mg. of growth hormone (Armour's assay).
### Table 1.—Relation of Pathological Findings to the Effect of Hypophysectomy on Electrolyte Excretion in Dogs with Thoracic Inferior Vena Cava Constriction and Ascites.

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Total Na Excretion mEq./day</th>
<th>Fecal Excretion Na (mEq./day)</th>
<th>K (mEq./day)</th>
<th>Days After Hypophysectomy</th>
<th>Histologic Findings in Autopsy Material</th>
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<tbody>
<tr>
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<td>Control Period</td>
<td>Posthypophysectomy Period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weeks 1-2</td>
<td>Weeks 1 and 2</td>
<td>Weeks 3 and 4</td>
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<td>4.7</td>
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<td>6.8</td>
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<td>31.1</td>
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<td>.33</td>
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<td>4.2</td>
<td>2.9</td>
<td>54.5</td>
<td>.14</td>
<td>.20</td>
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</table>

* Dog 4 was hypophysectomized before the inferior vena cava was constricted and consequently the data are not comparable to that of dogs 1-3 and 5-9.
† All values are averaged for the entire period specified. Na intake = 30 mEq./day; K intake = 17.6 mEq./day.
‡ Dogs 5 and 6 received a course of 25 mg./day of DCA shortly before death.
§ Dog 8 received ACTH for 10 days.
to dog 7 in doses of 7.5 and 10 units per day for 10 and 4 days respectively. Desiccated thyroid (33 gr. daily) was given to dog 9 for 15 days. A growth hormone preparation† was administered in a dose of 12.5 mg. twice daily to dog 9 for 5 days.

The dogs weighed 15-25 Kg. They were fed once daily a synthetic diet which contained 1600 Calories; the intake of electrolytes was constant except during vomiting. Water was allowed ad libitum.

Hypophysectomy was performed by an oral route; the infundibular stalk was divided at its base and removal of the pars anterior, intermedia, nervosa and infundibularis‡ was attempted. After sacrifice, the hypothalamus and the contents of the sella turcica were sectioned serially and observations were made for pituitary remnants. The adrenal and thyroid glands and the ovaries were examined histologically to determine the degree of atrophy.

†The term pars infundibularis is used in preference to pars tuberalis in the dog because this part of the anterior lobe extends only to the sulcus infundibularis.

RESULTS

Effect of Hypophysectomy on Electrolyte Excretion. Data on total Na excretion and the ratio of Na and K output in the feces of dogs 1 to 3 and 5 to 9 are summarized in table 1. Individual responses in renal and fecal electrolyte excretion of dogs 6 to 9 are presented in figures 1 to 4. During the control period total Na excretion and the ratio of fecal Na and K output were very low. Following hypophysectomy, a marked increase in Na excretion occurred in dogs 5 to 9 but the increase was negligible in dogs 1 to 3. In dogs 7 and 8 the natriuresis became evident during the first two weeks after hypophysectomy whereas in dogs 5, 6 and 9, Na excretion did not increase appreciably until the third or fourth posthypophysectomy week. The low ratio of fecal Na and K excretion increased after hypophysectomy in all
dogs (table 1) but the change was greatest in dogs 5 to 9. The increase resulted from both an elevation in fecal Na and a drop in fecal K excretion (figs. 1 and 4). The decrease in fecal K output was associated with a concurrent elevation in urinary excretion which occurred in all animals (see figures 1 and 4); in dogs 1 and 6, K balance became slightly negative.

Effects of Pituitary and Adrenocortical Hormones on Electrolyte Excretion Following Hypophysectomy. ACTH failed to produce a change in urinary or fecal Na excretion in dogs 1, 2 and 8 (see fig. 3) although a marked drop in eosinophils occurred (see figures 3 and 5) and renal hemodynamic function increased toward (fig. 3) or returned to the control level (fig. 5). A transient kaliuresis resulted in dog 8 only during ACTH therapy. On TSH therapy, dog 7 showed a striking reduction in renal Na excretion (fig. 2) but fecal Na and K output and urinary K excretion were unaltered. A slight decrease in Na output occurred during administration of desiccated thyroid to dog 9 (fig. 4) but the change was of questionable significance. In dog 9, growth hormone resulted in a marked reduction in urinary Na and K output (fig. 4); fecal electrolyte excretion was unchanged.

The effect of DCA on electrolyte excretion was studied in dogs 5 and 6 (fig. 1). Total Na

Fig. 2. Effects of hypophysectomy, subsequent therapy with thyrotropin (TSH) and reconstruction of the thoracic inferior vena cava (ivc) on Na excretion, femoral venous pressure and glomerular filtration rate (GFR) in a dog with ascites produced by thoracic inferior vena cava constriction. On July 27, 210 mEq. of Na were given intraperitoneally (I.P.) in addition to the oral intake of 30 mEq. Femoral venous pressures are plotted as solid bars from the horizontal line representing the control level before hypophysectomy. The cross-hatched bars show the volume of ascitic fluid present (measured by T-1824 dye dilution) whereas the solid bar is indicative of ascitic fluid removed by paracentesis.
Fus. 3. Effects of thyroidectomy, hypophysectomy, subsequent ACTH and subsequent reconstruction of the thoracic inferior vena cava (IVC) on Na excretion, femoral venous pressure and glomerular filtration rate (CCR) in a dog with ascites produced by partial ligation of the thoracic inferior vena cava. Femoral venous pressures are plotted as solid bars from the horizontal line which represents the average control value.

Excretion was reduced in both animals to 30 to 50 per cent of the intake on a dose of 10-25 mg./day of DCA; electrolyte excretion was apparently unaffected by 1 mg./day of this steroid. The low Na and high K pattern of fecal excretion, which disappeared following hypophysectomy, reappeared on DCA therapy in dog 6 (Fig. 1), but in dog 5 a high fecal K output resulted without depression of fecal Na excretion. After discontinuation of DCA, a large negative Na balance resulted in dog 5 but Na retention continued for 10 days in dog 6. Thereafter, both urinary and fecal Na excretion increased in dog 6. After DCA was discontinued, a prompt decline in fecal K output occurred in both dogs. A 15 to 16 day course of cortisone was given to dogs 1 and 2 with the result that a striking transient increase in renal Na and K output occurred but fecal Na and K excretion was unaffected. In dog 8, cortisone was given for 2 days in preparation for surgery (reconstruction of the vena cava) and the characteristic natriuresis and kaliuresis resulted.

Effects of Hypophysectomy and Subsequent Hormone Therapy on Femoral Venous and Arterial Pressures, Cardiac Output and Renal Hemodynamic Function. Following hypophysectomy, femoral venous pressure fell during the period of increased Na excretion in dogs 5 to 9 (see Figs. 1 to 4); in the 3 animals in which a natriuresis failed to occur, femoral venous pressure declined in one dog only (Fig. 3). Subsequently, dog 7 received TSH and dog 9 was given a course of growth hormone and a course of desiccated thyroid. Growth
hormone and TSH resulted in an increase in femoral venous pressure and a concurrent drop in renal Na excretion but the effect of thyroid was equivocal. Discontinuation of TSH and growth hormone was followed by return of venous pressure and Na excretion to the posthypophysectomy levels. Because of the efficacy of TSH in increasing venous pressure, dog 8 was subjected to thyroidectomy before hypophysectomy (fig. 3). A substantial drop in femoral venous pressure resulted but apparently the final level reached was not low enough for a natriuresis to occur. No detectable change in femoral venous pressure was observed during administration of ACTH, DCA or cortisone.

Cardiac output decreased markedly following hypophysectomy in dog 1 (fig. 5); oxygen consumption decreased but the arteriovenous oxygen difference was unaltered. Both ACTH and cortisone were without effect on cardiac output. Femoral arterial pressure remained within normal limits throughout the observations.

A striking fall in GFR and RPF occurred during the first 2 to 4 weeks after hypophysectomy (figs. 1 to 5). ACTH, TSH and growth hormone resulted in a substantial rise in GFR (figs. 1, 3 and 4) and RPF toward or to the control levels, and hormone withdrawal was followed by a prompt decline in renal function to the low posthypophysectomy level. The slight increase in GFR observed during thyroid therapy (fig. 4) is of questionable significance. On the large doses of DCA (10–25 mg./day), GFR and RPF appeared to increase slightly in dog 5 but remained low in dog 6 (fig. 1).

**Effect of Reconstriction of the Thoracic Inferior Vena Cava on Electrolyte Excretion.**

Femoral venous pressure was increased by further constriction of the thoracic inferior vena cava.
in dogs 7 and 8 (figs. 2 and 3). In both instances the elevation in femoral venous pressure was followed by marked Na retention. Both renal and fecal Na excretion decreased but K excretion remained unchanged. In dog 4, which was hypophysectomized before caval constriction, it was necessary to constrict the inferior vena cava on 3 occasions before Na retention and ascites occurred.

Pathologic Findings

In dogs 1 to 4, hypophysectomy was incomplete; a small fragment of pars anterior or intermedia was present in each dog and the adrenal cortex was normal in histologic appearance in all 4 animals. In dogs 5 to 9, hypophysectomy was complete or nearly complete; no evidence of the pars anterior was found in dogs 7 to 9. In dogs 5 to 9, the adrenal cortex and thyroid glands (except in dog 8 in which the thyroid glands were removed before hypophysectomy) were atrophic and the ovaries appeared inactive. The adrenal cortex showed differential atrophy; advanced atrophy of the two inner zones was present but the zona glomerulosa appeared normal or only slightly atrophic. Attention is called to the fact that the histologic appearance of the adrenal cortex may have been influenced by previous DCA therapy in dogs 5 and 6 and ACTH in dog 8.

Discussion

Observations on the effect of hypophysectomy on ascites formation have been reported previously\textsuperscript{4-6} but the mechanisms responsible for altered electrolyte excretion were not determined. In the present study the first possibility considered to explain the striking increase in Na excretion following hypophy-
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sectomy was the loss of ACTH with a subsequent decline in the level of circulating adrenocortical salt retaining hormones. The evidence, however, shows that this is not the correct explanation for the following reasons: ACTH, in doses sufficient to cause an eosinopenia and to return GFR and RPF to normal, had no effect on electrolyte excretion, Na retention recurred during TSH therapy in dog 7 and during growth hormone administration in dog 9, and reconstriction of the thoracic inferior vena cava in dogs 7 and 8 resulted in marked Na retention. This finding demonstrates that adequate Na retaining hormones were present since dogs with caval constriction diurese when adrenalectomized if therapy is inadequate.

The present results are consistent with data from other recent reports on the effect of ACTH and cortisone on Na excretion. In normal dogs neither ACTH nor cortisone produced Na retention. Cortisone showed a very weak Na retaining action in adrenalectomized dogs. Also, in adrenalectomized dogs with thoracic inferior vena cava constriction, ascites disappeared when therapy was changed from DCA to cortisone. In studies of nephrosis with edema, Luetscher and Johnson have reported the presence of a highly active Na retaining corticoid in urine; therapy with ACTH depressed rather than augmented the Na retaining activity of urine extracts.

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The close reciprocal relationship between femoral venous pressure and renal Na excretion suggests that the fall in venous pressure following hypophysectomy resulted in the natriuresis. It has been shown previously that Na retention in dogs with constriction of the thoracic inferior vena cava depends upon sufficient elevation of venous pressure and is unrelated to the level of cardiac output. Failure of Na excretion to increase after hypophysectomy in dog 1 may be related to an inadequate fall in femoral venous pressure. The close association of reciprocal changes in venous pressure and urinary Na excretion was also found under the following circumstances: during growth hormone and TSH administration, after discontinuation of these hormones, and following reconstriction of the thoracic inferior vena cava. Growth hormone and TSH resulted in an elevation of femoral venous pressure, and Na retention again ensued; discontinuation of hormone therapy was followed by a drop in venous pressure and a concurrent elevation in Na excretion by the kidney. Further partial ligation of the thoracic inferior vena cava resulted in an elevation of venous pressure and severe Na retention. It is concluded that the pituitary gland is essential for ascites formation in dogs with thoracic caval constriction only in so far as it is required to maintain an adequate level of venous hypertension. The effects of thyroidectomy, thyrotropin and growth hormone indicate that loss of either or both TSH and growth hormone may be involved.

Although the natriuresis following hypophysectomy is attributable to the fall in venous pressure, no correlation was found between the rate of fecal Na and K excretion and the level of venous pressure. The low Na to K ratio of fecal excretion characteristic of ascites formation in the presence of an intact endocrine system failed to reappear when venous pressure increased during TSH and growth hormone therapy and after reconstriction of the thoracic inferior vena cava.

When the effect of loss of pituitary hormones was overcome by further constriction
of the thoracic inferior vena cava, Na retention recurred and ascites reaccumulated although the adrenal cortex was atrophic. Of particular interest was the finding of differential atrophy; the two inner zones of the adrenal cortex were markedly atrophic whereas the zona glomerulosa was normal or only slightly atrophic. Lane and de Bodo also found a striking difference in the atrophic changes of the outer and inner layers of the adrenal cortex following hypophysectomy of normal dogs. They reported that the zona glomerulosa and outer zona fasciculata showed atrophic changes later and were less severely atrophied than the inner fasciculata and reticular zones; in some of their long term (75 to 750 days) hypophysectomized animals, the only surviving tissue was an atrophic zona glomerulosa and outer zona fasciculata. Of further significance is the capacity of the hypophysectomized dog with an atrophic adrenal cortex (may be entirely zona glomerulosa and outer zona fasciculata) to conserve Na during severe prolonged salt restriction. In connection with electrolyte excretion, attention is called to previous work in adrenalectomized dogs with caval constriction in which 3-5 mg./day of DCA were required to produce the degree of Na retention observed in the present hypophysectomized dogs after resection of the thoracic inferior vena cava; this dose of DCA is 6 to 10 times the minimal maintenance dose of DCA for adrenalectomized dogs with caval constriction. Therefore, hypophysectomized dogs with sufficient elevation in femoral venous pressure showed marked Na retaining activity in the presence of an atrophic adrenal cortex in which the zona glomerulosa was normal or only slightly atrophic.

Summary and Conclusions

The effect of hypophysectomy on ascites formation has been studied in dogs with constriction of the thoracic inferior vena cava. In animals in which hypophysectomy was complete or nearly complete, Na excretion increased strikingly from the previous low level. The abnormally low ratio of fecal Na and K excretion increased in all dogs. Changes in electrolyte excretion were accompanied by decreases in femoral venous pressure (except in two dogs in which hypophysectomy was incomplete), cardiac output, GFR and RPF. Replacement therapy with ACTH was without effect on electrolyte excretion, femoral venous pressure and cardiac output but GFR and RPF returned toward or to control levels and an eosinopenia resulted. Both growth hormone and TSH produced an elevation in femoral venous pressure and a concurrent drop in renal Na excretion; discontinuation of these hormones was followed by a fall in femoral venous pressure and the reappearance of a negative Na balance. Reconstriction of the thoracic inferior vena cava and return of venous pressure to the high prehypophysectomy level was followed by marked Na retention again. It is concluded that pituitary hormones contribute to the maintenance of an adequate level of venous hypertension which is essential for ascites formation.

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References

4. —, Howell, D. S., Laquere, G. L. and Peirce,
HYPOPHYSECTOMY AND ELECTROLYTE EXCRETION


Registration of Pulmonary Arterial Pressures by Transbronchial Puncture

The technic for recording left atrial and pulmonary arterial pressures in man by passing a needle through the walls of a bronchus has been described previously (Euler, 1949; Allison and Linden, 1953; Epps and Adler, 1953). The procedure is said to be safe and can be repeated even on ambulatory patients in the upright position. It is claimed that artifacts which so often distort records obtained by catheterization technics can more easily be avoided.

Nevertheless, most of the previously published pressure pulses obtained with this technic were obviously distorted in some manner. This was due to the necessity of placing recording manometers at the ends of long fluid columns. This difficulty has been circumvented by placing a miniature counter-induction manometer in close proximity to the puncture needle. The manometer and needle can then be introduced into a bronchus by the usual bronchoscopic technics.

Records published indicate that pressure fluctuations in the pulmonary artery of man can be accurately recorded by this apparatus.

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