Mechanisms of Fluid and Electrolyte Retention in Experimental Preparations in Dogs

III. Effect of Adrenalectomy and Subsequent Desoxycorticosterone Acetate Administration on Ascites Formation

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with the surgical assistance of Alfred Casper

The role of the adrenal cortex in the pathogenesis of ascites has been studied in adrenalectomized dogs with thoracic inferior caval constriction. Discontinuation of hormone therapy resulted in a diuresis which demonstrates that adequate adrenocortical function or replacement therapy is essential for ascites formation during normal sodium (Na) intake. Evidence is presented in support of the thesis that sodium retention results from an excess of circulating adrenocortical salt-retaining hormones.

Previous studies of experimental ascites in dogs have failed to reveal the mechanism of salt and water retention by the kidney. Neither the rate of glomerular filtration (GFR) nor the level of cardiac output has been correlated with the marked reduction in sodium (Na) excretion. Evidence for a direct renal action of chronic venous hypertension is also lacking.

Many workers have proposed that an alteration in adrenocortical activity results in Na retention. The pattern of renal and fecal electrolyte excretion in dogs with ascites provided suggestive evidence for this hypothesis. Ascites formation in dogs is characterized by a reduction in fecal as well as urinary Na excretion; urinary potassium (K) excretion is also depressed whereas fecal K output is elevated. These findings indicate the need for further observations on the relation of the adrenal cortex to the pathogenesis of ascites. The present report includes (1) studies of renal function and metabolic balances following discontinuation of desoxycorticosterone acetate (DCA) therapy in bilaterally adrenalectomized dogs with ascites, (2) data on the efficacy of DCA in producing the characteristic pattern of urinary and fecal electrolyte excretion in adrenalectomized dogs with thoracic inferior caval constriction, and (3) observations during the diuresis which followed removal of the caval ligature in the same animals.

Methods

Studies were conducted on four trained female mongrel dogs weighing 16 to 18 Kg. Right adrenalectomy was performed before the thoracic inferior vena cava was constricted to produce ascites. The animals were then studied for a three to four week control period. Subsequently, the left adrenal gland was removed and observations were made during an experimental period of several months. Later, the caval ligature was removed and studies made during recovery. Dogs 1 and 2 were observed during all phases of the study but dogs 3 and 4 were studied only during administration of DCA to produce the pattern of electrolyte excretion which occurs in dogs with ascites and intact adrenal glands.

Determinations were made in the postabsorptive state and before daily hormone administration. The experimental procedures and chemical methods have been described previously; in addition, ascitic fluid volume was measured by T-1284 dye dilution.

The dogs were fed a synthetic diet containing 50 Calories per kilogram per day, 0.6 Gm. per kilogram per day of nitrogen and either 2 or 4 mEq. per kilogram per day of Na; K intake was 17.6 mEq. per day. Intake was constant during each experiment. Water was allowed ad libitum.

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RESULTS

The Effect of Discontinuation of DCA Therapy in Bilaterally Adrenalectomized Dogs with Ascites

During the control period following caval constriction, alterations in electrolyte balances and water exchange (fig. 1) were the same as those described previously. On a high protein diet and a Na intake of 2 mEq. per kilogram per day, the level of plasma protein and nitrogen balance did not vary appreciably (figs. 1 and 2) and reproducible values for C<sub>CR</sub> and C<sub>PAR</sub> were obtained. Twenty-five milligrams per day of cortisone and 3 mg. per day of DCA were administered before left adrenalectomy; renal function and electrolyte metabolism were not detectably altered. Following extirpation of the left adrenal gland, substitution therapy was given for 12 days (figs. 1 and 2). Ascites continued to accumulate and body weight increased at approximately the same rate as during the control period.

Discontinuation of hormone therapy resulted in a diuresis (fig. 1). Renal loss of Na, chloride (Cl) and water occurred; K and nitrogen bal-
ances remained positive until near the end of the diuresis. A low Na and Cl and a high K pattern of plasma electrolytes was observed throughout the diuresis. Alterations in renal function and protein metabolism were not detected in both dogs (see fig. 2). Recovery from adrenal insufficiency was effected with adrenocortical extract, intravenous saline and DCA; ascites reappeared and all functions gradually returned to the prediuresis level (figs. 1 and 2).

**Fig. 2.** Renal function, plasma protein, cardiovascular pressures and heart rate during ascites accumulation following adrenalectomy and in the absence of DCA therapy. CCR, CPAH and plasma protein are plotted as solid columns from a line which represents the average control value. The stippled area shows femoral arterial pulse pressure. See figure 1 for other symbols and for the dose of DCA and cortisone.

In spite of the drop in arterial pressure during acute adrenal insufficiency, CPAH remained elevated (dog 1) or failed to fall below the control level (dog 2), but CCR declined mark-

**Comparative Na Retaining Action of Different Doses of DCA in Adrenalectomized Dogs with Ascites**

The minimal amount of DCA required to maintain adrenalectomized dogs in the presence of ascites and after removal of the caval ligation and disappearance of ascitic fluid was determined. The criteria for adequate maintenance included the attainment of electrolyte and nitrogen balance, stable body weight and normal arterial pressure. Under these circumstances the general appearance and vigor of the animals were excellent. After the con-
stricting ligature had been removed and ascites had disappeared, all physiologic evidence indicated that the animals were essentially the same as simple adrenalectomized dogs.* After the minimal maintenance dose was ascertained, DCA was administered in doses ranging from 1.0 to 3.0 mg. per day in dogs 1 and 2 and from 1.0 to 25.0 mg. per day in dogs 3 and 4. Consequently, this experiment provided comparative data on the dose of DCA required for maintenance and that necessary for salt and water retention and ascites formation.

1). Since others 7, 8 have also shown that simple adrenalectomized dogs can be maintained on 0.5 to 0.6 mg. per day of DCA with a lower Na intake than that employed in the present study, the maintenance dose of DCA was not determined in dogs 3 and 4 in the absence of caval constriction and ascites. The rate of glomerular filtration apparently did not influence the maintenance requirement of DCA; $C_{cr}$ was the same in the presence of the constriction and after the diuresis which followed removal of the caval ligature. Therefore, approximately 0.5 mg. per day of DCA was required to simulate a state of normal adrenocortical activity in regard to salt retaining hormones in the presence and in the absence of ascites. In order for ascitic fluid to accumulate, additional (more than 0.5 mg. per day) DCA was necessary (figs. 3 and 4 and table 1). The quantity of retained Na became progressively greater as the dose of DCA was increased. A daily dose of 1 to 2 mg. of DCA resulted in retention of 20 to 60 per cent of ingested Na, whereas with 3 mg. per day 70 to 80 per cent

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**Fig. 3.** Effect of DCA on Na balance in a bilaterally adrenalectomized dog with thoracic inferior caval constriction and after removal of the caval ligature and diuresis. See figure 1 for convention used in the plot of Na balance.

The DCA requirement for maintenance was not appreciably different in adrenalectomized dogs with ascites and in the same animals following removal of the constriction and diuresis. Approximately 0.5 mg. per day of DCA were required for maintenance of dogs 1 (fig. 3) and 2 before and after removal of the caval ligature, and for dogs 3 and 4 in the presence of caval constriction and ascites (fig. 4 and table...
Na retention occurred. Slightly more complete Na retention resulted with 10 mg. per day (83 to 85 per cent) and with 25 mg. per day (90 to 94 per cent). This degree of Na retention is comparable to that (88 and 94 per cent calculated from data in table 1 during intake of 60 to 64 mEq. per day of Na) observed in dogs A and B with thoracic inferior caval constriction and intact adrenal cortices. Since CCR remained the same or was slightly higher with the larger doses of DCA, the increased Na retention which resulted from the higher doses of DCA cannot be attributed to a low GFR.

Effect of Adrenalectomy and Subsequent DCA Administration on Fecal Electrolyte Excretion in Dogs with Ascites

In normal dogs mean values for fecal Na and K excretion were 6.3 and 1.4 mEq. per day respectively with a Na:K ratio of 4.4 (table 2). In dogs with intact adrenal cortices and ascites, a low Na (1.2 mEq. per day) and a high K (7.9 mEq. per day) pattern of fecal electrolyte excretion was present; the fecal Na:K ratio was 0.16. In three of the four animals with unilateral adrenalectomy and ascites (table 2), the Na:K ratio ranged from 0.8 to 3.2; in another dog with ascites (not included in table 2), the fecal ratio increased from 0.20 to 1.9 following right adrenalectomy. On the other hand, in dog 2 (table 2) and in one other unilaterally adrenalectomized dog with ascites (not included in the table) the fecal ratio was low (0.1 to 0.2). Therefore, four of the six unilaterally adrenalectomized animals with ascites showed a Na:K ratio of fecal excretion significantly higher than the low level present in dogs with both adrenal glands.

Following bilateral adrenalectomy, all four dogs (table 2) showed a further elevation in the fecal Na:K ratio (range 1.7 to 5.0) which was frequently within normal limits during maintenance on 0.5 to 3.0 mg. per day of DCA.

![Figure 4](http://circres.ahajournals.org/) Effect of DCA on urinary and fecal Na excretion in bilaterally adrenalectomized dogs 3 and 4 with thoracic inferior caval constriction. See figure 1 for the convention used in the plot of Na balance. The cross hatched areas show fecal Na excretion. Cumulative balance data and other measurements demonstrating the efficacy of small doses of DCA for maintenance of dogs 3 and 4 are shown in table 1.
TABLE 1.—Sodium Excretion Following Thoracic Inferior Vena Cava Constriction in Adrenalectomized Dogs on DCA and in Dogs with Intact Adrenal Glands

<table>
<thead>
<tr>
<th>Date</th>
<th>DCA Therapy</th>
<th>Na Intake</th>
<th>Na Excretion</th>
<th>Plasma Na</th>
<th>Plasma K</th>
<th>Ccr</th>
<th>GPAH</th>
<th>Femoral Arterial Pressure</th>
<th>Femoral Venous Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adrenalectomized Dog 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nov. 11</td>
<td>3.0*</td>
<td>30</td>
<td>2.7†</td>
<td>3.0</td>
<td>144</td>
<td>4.5</td>
<td>48</td>
<td>108</td>
<td>151/94</td>
</tr>
<tr>
<td>Nov. 19</td>
<td>10.0</td>
<td>30</td>
<td>1.0</td>
<td>3.5</td>
<td>144</td>
<td>4.0</td>
<td>50</td>
<td>116</td>
<td>148/96</td>
</tr>
<tr>
<td>Nov. 28</td>
<td>25.0</td>
<td>30</td>
<td>1.3</td>
<td>1.2</td>
<td>140</td>
<td>4.8</td>
<td>43</td>
<td>93</td>
<td>151/92</td>
</tr>
<tr>
<td>Dec. 6</td>
<td>0.5</td>
<td>30</td>
<td>30.1</td>
<td>5.5</td>
<td>143</td>
<td>4.6</td>
<td>37</td>
<td>91</td>
<td>142/89</td>
</tr>
<tr>
<td>Dec. 16</td>
<td>1.0</td>
<td>30</td>
<td>18.7</td>
<td>4.8</td>
<td>140</td>
<td>3.7</td>
<td>41</td>
<td>91</td>
<td>153/94</td>
</tr>
<tr>
<td><strong>Adrenalectomized Dog 4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nov. 5</td>
<td>3.0</td>
<td>30</td>
<td>4.6†</td>
<td>3.6</td>
<td>148</td>
<td>4.2</td>
<td>52</td>
<td>124</td>
<td>158/91</td>
</tr>
<tr>
<td>Nov. 13</td>
<td>0.5</td>
<td>30</td>
<td>23.8</td>
<td>4.9</td>
<td>139</td>
<td>4.0</td>
<td>63</td>
<td>142</td>
<td>104/65</td>
</tr>
<tr>
<td>Nov. 21</td>
<td>1.0</td>
<td>30</td>
<td>24.9</td>
<td>4.5</td>
<td>140</td>
<td>4.4</td>
<td>49</td>
<td>121</td>
<td>102/56</td>
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<tr>
<td>Nov. 29</td>
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<td>30</td>
<td>5.9</td>
<td>2.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dec. 1</td>
<td>2.0</td>
<td>30</td>
<td>13.1</td>
<td>2.4</td>
<td>140</td>
<td>4.3</td>
<td>45</td>
<td>127</td>
<td>98/53</td>
</tr>
<tr>
<td>Dec. 5</td>
<td>2.5</td>
<td>30</td>
<td>8.5</td>
<td>2.4</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dec. 10</td>
<td>10.0†</td>
<td>30</td>
<td>2.5</td>
<td>2.6</td>
<td>140</td>
<td>4.6</td>
<td>50</td>
<td>106</td>
<td>130/80</td>
</tr>
<tr>
<td>Dec. 17</td>
<td>25.0</td>
<td>30</td>
<td>0.9</td>
<td>0.8</td>
<td>146</td>
<td>4.1</td>
<td>50</td>
<td>103</td>
<td>189/112</td>
</tr>
</tbody>
</table>

**Dogs with Intact Adrenal Glands**

<table>
<thead>
<tr>
<th>Date</th>
<th>Na Intake</th>
<th>Na Excretion</th>
<th>Date</th>
<th>Na Intake</th>
<th>Na Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mEq./day</td>
<td>mEq./day</td>
<td></td>
<td>mEq./day</td>
<td>mEq./day</td>
</tr>
<tr>
<td></td>
<td>Urine</td>
<td>Feces</td>
<td></td>
<td>Urine</td>
<td>Feces</td>
</tr>
<tr>
<td>March 22</td>
<td>64</td>
<td>2.1†</td>
<td>March 8</td>
<td>60</td>
<td>2.7†</td>
</tr>
<tr>
<td>April 12</td>
<td>1.4</td>
<td></td>
<td>April 18</td>
<td>60</td>
<td>1.1</td>
</tr>
<tr>
<td>April 13</td>
<td>0.7</td>
<td></td>
<td>April 19</td>
<td>9</td>
<td>0.9</td>
</tr>
</tbody>
</table>

* The daily dose of DCA for each cumulative balance period is indicated on the first day of the period.
† Each cumulative period of urinary and fecal Na excretion begins with the preceding date.
‡ In addition to DCA, 50 mg. per day of cortisone was given; arterial pressure returned to normal two days after onset of cortisone administration.

-low Na:K ratio of fecal excretion reappeared in both unilaterally and bilaterally adrenalectomized dogs with large doses (10 to 25 mg. per day) of DCA. An alteration in fecal K excretion was always accompanied by a corresponding reciprocal change in urinary K.
output.* Data on urinary Na excretion have also been included in Table 2 to show the rate of ascites formation; Na intake was constant. The lowest Na:K ratios of fecal excretion were associated with the most marked reductions in urinary Na excretion, and the slowest rates of ascites formation were accompanied by high fecal ratios. The highest fecal ratio (3.2) observed in the unilaterally adrenalectomized animals occurred in dog 4 during a temporary spontaneous diuresis. The results indicate that excessive amounts of adrenocortical hormones are necessary to

### Table 2.—Effect of Adrenalectomy and Subsequent DCA Therapy on Fecal Electrolyte Excretion in Dogs with Ascites

<table>
<thead>
<tr>
<th>Dogs with Ascites after Right Adrenalectomy</th>
<th>Same Dogs after Bilateral Adrenalectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DCA Therapy</strong></td>
<td><strong>Fecal Excretion</strong></td>
</tr>
<tr>
<td><strong>Na mEq./day</strong></td>
<td><strong>K mEq./day</strong></td>
</tr>
<tr>
<td>Dog 1</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>3.0f</td>
</tr>
<tr>
<td></td>
<td>3.0f</td>
</tr>
<tr>
<td>Dog 2</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>3.0f</td>
</tr>
<tr>
<td></td>
<td>3.0f</td>
</tr>
<tr>
<td>Dog 3</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>25.0</td>
</tr>
<tr>
<td></td>
<td>25.0</td>
</tr>
<tr>
<td>Dog 4</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>25.0</td>
</tr>
<tr>
<td></td>
<td>25.0</td>
</tr>
<tr>
<td>Normal dogs</td>
<td>None</td>
</tr>
<tr>
<td>(N = 12)</td>
<td>2.92</td>
</tr>
</tbody>
</table>

* Each value for dogs 1 to 4 represents a collection period of 5 to 8 days; Na intake = 30 mEq. per day, except in dog 1 after bilateral adrenalectomy Na intake = 57.5 mEq. per day. K intake = 17.6 mEq. per day.
† 25 mg. per day of cortisone were also given.
‡ 50 mg. per day of cortisone were also given.
§ X = Mean.
|| Na intake = 4.0 mEq. per kilogram per day; K intake = 1.0 mEq. per kilogram per day.

* The marked K depletion resulting from administration of large doses of DCA to normal dogs on a high salt intake does not occur in dogs on a low salt diet or in animals forming ascites presumably because of the marked decrease in electrolyte excretion.
produce the low Na and high K pattern of
fecal electrolyte excretion during ascites for-
amation.

Observations during the Diuresis which Followed Removal of the Caval Ligature

After removal of the caval ligature diuresis occurred during administration of 3 mg. per
day of DCA (fig. 5). Na, K, Cl and water
ascites formation has been demonstrated; dis-
continuation of hormone therapy resulted in a
diuresis in adrenalectomized dogs with thoracic
inferior vena cava constriction during normal
Na intake. The data indicate that diuresis re-
sulted from a reduction in renal tubular reab-
sorption of Na, Cl and water; postabsorptive
C\text{CR} remained at the control level until the
end of the diuresis. The duration of the diuresis
balances were negative until all ascites had
disappeared. A marked elevation in GFR and
renal plasma flow (RPF) accompanied the
diuresis. Femoral venous pressure returned to
the control level and arterial pressure re-
mained unchanged.

Discussion

The necessity of functional adrenocortical
tissue or adequate substitution therapy for
and the excellent appearance of the dogs until
ascites disappeared distinguish this prepara-
tion from the simple adrenalectomized dog.
The ascites, which provided a continuous
source of Na and water for maintenance of
plasma volume, probably accounts for the
excellent appearance and vigor of the animals
during the prolonged diuresis.

Additional data on the role of adrenocortical
hormones in the pathogenesis of ascites were
ADRENALECTOMY AND DCA ON ASCITES FORMATION

provided by study of the Na retaining effect of different doses of DCA. The DCA requirement for maintenance of adrenalectomized dogs was essentially the same before and after the disappearance of ascites (0.5 mg. per day) but additional DCA was necessary for ascitic fluid accumulation. Retained Na increased progressively as the dose of DCA was increased. The marked degree of Na retention occurring in dogs with caval constriction and intact adrenal glands was observed during administration of 10 to 25 mg. per day of DCA. The data suggest that an excess of circulating adrenocortical salt retaining hormones is present in the dog with ascites and intact adrenal cortices.

Evidence for a hormonal mechanism has also been reported in certain clinical states with edema and ascites. In congestive heart failure and decompensated hepatic cirrhosis, the concentration of Na is reduced in feces, sweat, and saliva. In dogs with experimental ascites a humoral mechanism was suggested by the finding that fecal as well as urinary Na excretion was markedly reduced. Since adrenocortical hormones influence the intestinal mucosal transport of Na and K, it was proposed that the low Na and high K pattern of fecal electrolyte excretion in dogs with ascites is a reflection of altered adrenocortical activity.

The present observations provide more conclusive data on the significance of the low Na:K ratio of fecal excretion in dogs with experimental ascites. The ratio of fecal Na and K excretion was markedly elevated above this low level in four of six unilaterally adrenalectomized dogs and was frequently within normal limits in all four bilaterally adrenalectomized dogs on 0.5 to 3.0 mg. per day of DCA. On 10 to 25 mg. per day of DCA, the elevated ratio returned to the low level characteristic of dogs with ascites and intact adrenal glands. These findings suggest that the low fecal ratio is indicative of increased adrenocortical hormones which regulate the transfer of electrolytes across the intestinal mucosa. Since ascites formed in unilaterally adrenalectomized dogs without hormone therapy and in bilaterally adrenalectomized animals on 1.0 to 3.0 mg. per day of DCA in the absence of the low Na and high K pattern of fecal excretion, it appears that a higher level of circulating hormone is necessary for the fecal pattern than for ascites formation.

Disappearance of ascites following removal of the caval ligature shows that elevated venous pressure is also essential for the accumulation of ascitic fluid. It seems likely that the marked elevation in GFR contributed to the diuresis. The data are in agreement with previous reports that the simple adrenalectomized dog does not retain Na and form edema even with large doses (10 to 25 mg. per day) of DCA. It appears, therefore, that at least two factors are essential for Na retention by the kidney in dogs with thoracic inferior caval constriction, namely, (1) elevated venous pressure and (2) an excess of circulating adrenocortical hormones.

The present data do not distinguish between altered secretion and decreased inactivation of adrenocortical hormones. Until more information is available on the metabolism of adrenocortical compounds, it seems more plausible to proceed on the basis that altered secretion occurs. The possibility that the renal tubules and intestinal mucosa are highly sensitive to a normal level of circulating hormone cannot be completely excluded; however, large doses of DCA were necessary for complete replacement in adrenalectomized dogs with caval constriction.

On the basis of available evidence, a working hypothesis is presented to explain the pathogenesis of ascites. The basic concepts of this hypothesis were proposed by Peters several years ago, and current developments supporting the theory have been reviewed recently. In dogs with experimental pericarditis or with constriction of the thoracic inferior vena cava, an elevation in hepatic venous pressure can be inferred from the finding of femoral venous hypertension. An elevated hepatic venous pressure results in the localization of fluid in the peritoneal cavity. The appearance of ascites seems to precede the onset of salt and water retention by the kidney. Ascitic fluid (300 to
This observation suggests that plasma volume was decreased in these dogs; however, later in the experimental period, dogs showing Na retention have always had a normal or elevated T-1824 dye space. More complete renal tubular reabsorption of salt and water may be explained on the basis of an alteration in adrenocortical secretion which favors salt retention. Accordingly, a receptor-effector system is activated by loss of fluid and electrolytes from plasma to the peritoneal cavity. Since evidence is lacking for the concept that a volume receptor responds to a generalized decrease in plasma volume, it has been suggested that a local decrease in plasma volume occurs in the region of the receptor.

SUMMARY AND CONCLUSIONS

1. The effect of adrenalectomy and subsequent DCA administration on renal function, cardiovascular pressures, electrolyte and nitrogen balances and plasma electrolytes has been studied in dogs with experimental ascites.

2. During normal Na intake, discontinuation of hormone therapy resulted in a diuresis which demonstrates that adequate adrenocortical function or substitution therapy is necessary for ascites formation.

3. Two lines of evidence have been adduced in favor of the thesis that an excess of circulating adrenocortical salt retaining hormones results in Na retention during ascites formation. First, the degree of Na retention was proportional to the amount of DCA administered and the marked Na retention characteristic of dogs with ascites and intact adrenal cortices was present only with large doses of DCA in adrenalectomized animals with caval constriction. Secondly, the low Na:K ratio of fecal excretion and the low urinary K output disappeared following adrenalectomy and reappeared only during administration of large quantities of DCA.

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REFERENCES


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