Renal Hilar Lymph

EFFECTS OF DIURESIS ON FLOW AND COMPOSITION IN DOGS

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ABSTRACT

Renal lymph was collected from single hilar lymphatics in 58 anesthetized dogs (1) to study the mechanism by which lymph production is affected during diuresis and (2) to determine whether a medullary contribution to renal lymph could be defined by changes in the electrolyte concentration of hilar lymph with concomitant alterations in the concentration gradient of the renal medulla. When diuresis was induced by a solute load (mannitol), lymph flow increased by 25 to 300%. On the other hand, when diuresis was induced without such a solute load, lymph flow was either unaffected (mersalyl) or slightly reduced (furosemide). It was concluded that the effect of mannitol on renal lymph flow was mediated primarily through its general effect on extracellular fluid rather than through any specific intrarenal consequence of the diuresis itself.

Control hilar lymph-to-plasma concentration ratios for Na⁺ (1.057 ± 0.040), Cl⁻ (1.129 ± 0.040) and Ca²⁺ (0.770 ± 0.048) but not K⁺ (0.986 ± 0.086) were found to be significantly different from 1.0. Failure of mannitol diuresis to alter significantly the lymph-plasma ratios of Na⁺ and Cl⁻ provided evidence that the high electrolyte concentrations of the inner medulla were not reflected in hilar lymph. The finding that furosemide abolished the lymph-plasma concentration difference for Na⁺ and significantly reduced that for Cl⁻ was taken as evidence that the outer medulla was a significant source of renal hilar lymph.

ADDITIONAL KEY WORDS: mannitol, protein, chloride, potassium, calcium, furosemide, mersalyl, sodium transport, countercurrent mechanism.
the ensuing diuresis. Previous studies have failed to differentiate between such general and local effects of diuretics on the output of renal lymph. In the present study the problem of whether diuresis per se alters the flow of renal lymph was examined by comparing the effect of diuresis induced by solute administration (mannitol) with that of diuresis without a solute load (mersalyl and furosemide).

The composition of renal lymph, especially with regard to electrolyte concentrations, has been subject to conflicting reports. Although LeBrie and Mayerson (4, 6, 7) found lymph-plasma concentration ratios for Na⁺ and Cl⁻ in canine capsular lymph to be significantly greater than 1, this finding was not substantiated by Swann et al. (8), Keyl et al. (9), or Santos-Martinez and Selkurt (10) for capsular or hilar lymph. On the other hand, Papp and Szalay (11) found lymph-plasma ratios greater than for Na⁺ and Cl⁻ in hilar lymph, and in a continuation of their earlier work, Bell et al. (12) reported an average hilar lymph-plasma ratio for Na⁺ of 1.05.

Because of the concentration gradients within the renal medulla, high lymph-plasma ratios for Na⁺ and Cl⁻ would support the existence of a medullary source of renal lymph (13). Normal lymph-plasma ratios, on the other hand, raise the possibility that the medulla is not a significant source of renal lymph. From the functional standpoint, lack of a medullary lymphatic system would be surprising in view of the quantity of plasma proteins which leave the blood capillaries to enter the medullary interstitium (14-16). Although some studies show the failure of certain injection techniques to prove such a system (17, 18), others have shown lymphatic vessels ascending from the papilla through inner and outer medulla to the arcuate collecting vessels (19). Further evidence has been supplied by Rhodin (20), who, with the electron microscope, found a rich lymphatic capillary network in the medulla but a relatively sparse plexus within the renal cortex.

In the present work, control hilar lymph-plasma concentration ratios for Na⁺ and Cl⁻ were found to be consistently greater than 1.

A study was therefore carried out to determine whether these high ratios were related to the high concentrations of these electrolytes in the renal medulla. This was based on the assumption that if such a relationship existed, the lymph-plasma ratios for Na⁺ and Cl⁻ would approach 1 when the medullary electrolyte gradients were reduced or abolished.

Reduction of these gradients was carried out in two ways: (1) by inducing a severe mannitol diuresis known to eliminate the hyperosmotic environment of the inner medulla and papilla and (2) by the administration of furosemide, which inhibits the sodium pump in the ascending limb of Henle.

**Methods**

**General.**—Mongrel dogs of either sex were anesthetized with sodium pentobarbital (25 to 30 mg/kg body weight). Control lymph flow in single left hilar lymph vessels was measured in 58 dogs. In 34 experiments, a constant infusion of isotonic NaCl or 5% mannitol in isotonic NaCl was maintained at a rate of 0.5 to 1.5 ml/min. The remaining animals were not infused. Urine was collected separately from right and left kidneys. Periodic blood samples were collected from the inferior vena cava at the approximate level of the renal veins with a cannula inserted through a hind-limb vein. Blood was not collected directly from the renal vein because of the danger of renal venous constriction or intravascular clotting, either of which might have altered lymph production.

**Lymphatic Cannulation.**—The renal pedicle was exposed retroperitoneally. Interference with the renal artery and vein was kept to a minimum and care was taken to avoid injury to the renal nerves. In most experiments, only the lymphatic selected for cannulation was ligated, but occasionally a second lymphatic was tied and cannulated. The cannula (Portex tubing, o.d. = 0.025 inches, i.d. = 0.020 inches) was inserted toward the kidney with the aid of a dissecting microscope, and tied in place with fine thread. Once flow in the cannula was confirmed, all retractors were removed and the wound was closed. To prevent clot formation within the cannula, heparin was given intravenously to most animals in a dose of approximately 1,000 IU every 2 hours. In 80% of the experiments, lymph was collected under mineral oil in small glass tubes, and in the remainder into small capped polystyrene beakers. The length of consecutive collection periods depended on flow, but usually...
lasted for 10 to 30 minutes; total collection lasted for up to 10 hours.

**Diuresis.**—Mannitol was administered in one of two ways. In 17 experiments (nine dogs), after control urine and hilar lymph flow had been measured for ½ to 2½ hours, a rapid infusion of 100 ml of 20% mannitol was given intravenously. After the injection, consecutive samples of lymph and urine were collected and measured for 1 to 2 hours. In three further experiments, after isotonic NaCl had been infused at about 1 ml/min for 2 to 5 hours, the infusion was changed to 10% mannitol at about 2 ml/min and the effect on urine and lymph flow observed for 2 to 3 hours.

The effect of 1 to 6 ml of a mercurial diuretic (mersalyl) given intravenously was observed on hilar lymph and urine flow in five dogs, and on thoracic duct lymph and urine flow in two dogs.

Twelve intravenous injections of 2 to 8 ml of furosemide (Lasix, 20 mg/ml) were given to nine dogs in which a renal hilar lymphatic had been cannulated. In four other experiments, the effect on thoracic duct lymph and urine flow of 1 or 2 ml of furosemide injected intravenously was observed.

During diuresis the rate of intravenous saline infusion was adjusted to prevent dehydration.

**Analysis.**—The effects of evaporation from small lymph samples on the concentration of lymph constituents have been emphasized by Keyl et al. (9). In the present work, extreme care was taken to ensure that the concentrations of electrolytes in lymph were not affected by evaporation during and after sample collection.

In early experiments, Na⁺ and K⁺ were estimated by means of an Eel flame photometer, and Cl⁻ with an Eel chloride meter. In more recent experiments, Na⁺ and K⁺ were estimated with a Fisher automatic dilutor and an I.L. digital readout flame photometer, and Cl⁻ was estimated with a Fisher automatic dilutor and a Buchler Chloridometer. In these experiments, duplicate samples were analyzed for Cl⁻ immediately after the collection was completed, and duplicate samples were analyzed for Na⁺ and K⁺ on the day of experiment. Total protein and albumin concentrations were estimated by the biuret technique and optical densities were determined with either a Beckman Model B spectrophotometer or a Hitachi Perkin-Elmer UV-VIS spectrophotometer. Ca²⁺ concentrations were measured with an Oxford titrator.

**Results**

The average lymph flow from single hilar lymphatics in 58 dogs was 0.061 ml/hour/kg body weight (sd = 0.03). The correlation coefficient between hilar lymph flow and body weight was 0.50 (P < 0.01). It is probable that lymph flow was more closely related to kidney weight, but in most experiments control kidney weights could not be obtained because of subsequent experimental procedures such as diuresis, ureteric obstruction, and venous occlusion. During control measurements, left urine flow never exceeded 1.5 ml/min and in over three-fourths of the experiments, it was less than 0.5 ml/min; under these circumstances, no correlation was found between control hilar lymph flow and simultaneous left urine flow.

**Mannitol Diuresis.**—An illustration of the effect of mannitol on hilar lymph flow and left urine flow in one experiment is shown in Figure 1. The average results from all such experiments are given in Table 1. In all experiments, the increased lymph flow was apparent in the first sample after the injection, and frequently this sample represented peak flow. After the peak, lymph flow gradually returned toward, but did not always reach, control levels. A similar pattern was found for the response of urine flow to mannitol in that the diuresis was immediate and peaked in the first or second sample after the injection. Urine flow, however, did not return to its control value.

**Furosemide and Mersalyl.**—The effect of furosemide and mersalyl administration on lymph and urine flow is compared with that of mannitol in Table 1. In contrast to mannitol, the administration of furosemide resulted in a slight decrease in lymph flow in 10 experiments, no change in one, and a small increase in another. The average extent of the drop was 0.0035 ml/min or 22.5% (P < 0.005), whereas the average extent of the diuresis (4.8 ml/min) was higher than that with mannitol (3.4 ml/min). No correlation could be found between the fall in lymph flow and the extent of the diuresis or the quantity of furosemide injected. In general, the change in lymph flow was apparent in the first sample collected after injection, and flow was restored to control levels within an hour provided dehydration was avoided.
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Mersalyl, which induced a less marked but more prolonged diuresis than either mannitol or furosemide, had no consistent effect on hilar lymph flow (Table 1). Nor was a consistent change in thoracic duct flow seen after the administration of either furosemide or mersalyl.

Electrolytes.—Control values for one or more electrolytes were measured in samples of hilar lymph and plasma in 46 experiments. Lymph-plasma concentration ratios for Na⁺, Cl⁻ and K⁺ and Ca²⁺ are shown in Figure 2. The higher concentrations of Na⁺ and Cl⁻ and the lower concentration of Ca²⁺ in lymph than in plasma were highly significant ($P < 0.001$). The K⁺ lymph-plasma ratio, on the other hand, was not significantly different from 1.

During mannitol diuresis (Table 2), there was a small but significant decrease ($0.01 < P < 0.025$) in both plasma and hilar Na⁺ concentrations. A simultaneous decrease in Cl⁻ concentrations was significant for plasma ($P < 0.05$) but not for lymph. Neither the K⁺ concentrations in lymph or plasma nor the Na⁺ and Cl⁻ lymph-plasma concentration ratios differed significantly during mannitol diuresis from their control values.

Although furosemide, like mannitol, resulted in a lowering of Na⁺ and Cl⁻ concentrations in hilar lymph, this was not accompanied by a comparable fall in plasma concentrations (Fig. 3, Table 3). Since the average lymph Na⁺ reduction was 4.25 mEq/liter ($SD = 1.75; P < 0.001$) without any significant fall in plasma Na⁺, the lymph-plasma concentration ratio fell to approximately 1. Lymph Cl⁻ concentrations fell by a greater amount (9.75 mEq/liter) ($SD = 1.5; P < 0.001$), but in no experiment did the lymph-plasma ratio reach 1. This failure to reach unity cannot be fully explained by the small drop in plasma Cl⁻ (2.1 mEq/liter) ($SD = 1.2; P < 0.5$) since in the majority of experiments the lymph Cl⁻ concentration during diuresis did not fall to the plasma value which existed before the onset of the diuresis. It can also be seen from Table 3 that furosemide induced a significant fall in both the K⁺ concentration of lymph and in the lymph-plasma concentration ratios for K⁺:

In contrast to the effect of furosemide, mersalyl had no significant effect on the electrolyte concentrations of hilar lymph or plasma.

Protein.—Control protein concentrations in renal hilar lymph and plasma were measured in 18 experiments (Table 4) and found to be relatively independent of lymph flow.

The effect of mannitol on the protein concentration in renal lymph is also shown in Table 4. The test for paired differences...
showed a significant decrease (P<0.05) in the protein concentration of renal lymph during mannitol diuresis. However, since protein concentration decreased by an average of only 26% and lymph flow increased by an average of 150%, there was an overall increase in the rate at which protein left the kidney by the lymphatic system.

### Discussion

Flow from single renal lymphatics has been measured in a number of studies (3, 11, 21-23) but comparison between the results is complicated by differences in experimental design. Factors of special importance in this respect, and often unreported, include the size and the state of hydration of the animal, the rate of intravenous infusion, and the number

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**TABLE 1**

Comparison of the Effect of Mannitol, Furosemide and Mersalyl on Single Hilar Lymph Flow and Urine Flow

<table>
<thead>
<tr>
<th></th>
<th>Body wt (kg)</th>
<th>Hilar lymph flow (ml/min)</th>
<th>Change in lymph flow (ml/min)</th>
<th>Left urine flow (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>During diuresis</td>
<td>(%)</td>
</tr>
<tr>
<td><strong>Mannitol</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of experiments</td>
<td>9</td>
<td>9</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Average</td>
<td>14.5</td>
<td>0.0147</td>
<td>0.038</td>
<td>+0.023*</td>
</tr>
<tr>
<td>sd</td>
<td>2.8</td>
<td>0.0091</td>
<td>0.068</td>
<td>0.029</td>
</tr>
<tr>
<td><strong>Furosemide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of experiments</td>
<td>9</td>
<td>9</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Average</td>
<td>17.0</td>
<td>0.0162</td>
<td>0.0118</td>
<td>-0.0035*</td>
</tr>
<tr>
<td>sd</td>
<td>4.7</td>
<td>0.007</td>
<td>0.007</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Mersalyl</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of experiments</td>
<td>5</td>
<td>5</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Average</td>
<td>15.0</td>
<td>0.0132</td>
<td>0.0131</td>
<td>-0.0018</td>
</tr>
<tr>
<td>sd</td>
<td>2.2</td>
<td>0.010</td>
<td>0.009</td>
<td>0.0037</td>
</tr>
</tbody>
</table>

*P < 0.01.

![Graph](https://example.com/graph.png)

**FIGURE 2**

Lymph-plasma concentration ratios of Na⁺, Cl⁻ (Cl'), K⁺, and Ca⁺⁺ in control hilar lymph samples.

* Circulation Research, Vol. XXVI, April 1970
of collateral lymphatics ligated Mayerson (3) obtained an average flow of 0.0128 ml/min in renal hilar lymphatics. He postulated that since the kidney is drained by about 8 to 10 lymphatics, an upper limit for the output of lymph by one kidney under the conditions of his experiments might be 0.128 ml/min. By the same method, unilateral renal lymph flow can be estimated from the values reported here at 0.5 to 0.6 ml/hour/kg body weight, an upper limit for the output of lymph by one kidney under the conditions of his experiments might be 0.128 ml/min. By the same method, unilateral renal lymph flow can be estimated from the values reported here at 0.5 to 0.6 ml/hour/kg body weight.}

The effect of mannitol diuresis in the present study can also be compared with that obtained in previous work (2) since the method of administration was similar. Previously, an average value for unilateral renal lymph flow during mannitol diuresis of 0.36 ml/hour/kg body weight was obtained, which represented an increase of 150% (range 10 to 290%) over the control value derived in different animals. In the present study, the average value for unilateral renal lymph flow was 0.18 ml/hour/kg body weight, which represented an increase of 300% (range 25 to 300%) over the control value derived in different animals. In the present study, the average value for unilateral renal lymph flow was 0.18 ml/hour/kg body weight, which represented an increase of 300% (range 25 to 300%) over the control value derived in different animals.

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**TABLE 3**

Effect of Furosemide on the Na⁺, Cl⁻ and K⁺ Concentrations (mEq/liter) of Renal Hilary Lymph and Plasma

<table>
<thead>
<tr>
<th></th>
<th>No. of expts</th>
<th>Sodium</th>
<th>SD</th>
<th>Chloride</th>
<th>Average</th>
<th>SD</th>
<th>Potassium</th>
<th>Average</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before furosemide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph</td>
<td>8</td>
<td>152.5</td>
<td>1.7</td>
<td>123.2</td>
<td>3.8</td>
<td>3.74</td>
<td>0.46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td>7</td>
<td>148.6</td>
<td>1.3</td>
<td>110.6</td>
<td>2.6</td>
<td>3.68</td>
<td>0.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph-plasma ratio</td>
<td>7</td>
<td>1.027</td>
<td>0.009</td>
<td>1.111</td>
<td>0.024</td>
<td>1.009</td>
<td>0.037</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>During furosemide diuresis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph</td>
<td>8</td>
<td>148.1</td>
<td>1.6</td>
<td>113.5</td>
<td>3.1</td>
<td>3.01</td>
<td>0.41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td>7</td>
<td>149.0</td>
<td>1.8</td>
<td>108.4</td>
<td>3.6</td>
<td>3.40</td>
<td>0.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph-plasma ratio</td>
<td>7</td>
<td>0.996</td>
<td>0.010</td>
<td>1.045</td>
<td>0.022</td>
<td>0.885</td>
<td>0.039</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Paired differences</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph</td>
<td>8</td>
<td>-4.25*</td>
<td>1.75</td>
<td>-9.75*</td>
<td>1.5</td>
<td>-0.72*</td>
<td>0.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td>7</td>
<td>+0.4</td>
<td>0.9</td>
<td>-2.1†</td>
<td>1.2</td>
<td>-0.28†</td>
<td>0.23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph-plasma ratio</td>
<td>7</td>
<td>-0.032*</td>
<td>0.014</td>
<td>-0.066*</td>
<td>0.018</td>
<td>-0.124*</td>
<td>0.031</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.001.
†P < 0.05.

**TABLE 4**

Effect of Mannitol on the Protein Concentrations (g/100 ml) in Renal Hilary Lymph and Plasma

<table>
<thead>
<tr>
<th></th>
<th>Lymph</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Albumin</td>
<td>Globulin</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>3.42</td>
<td>2.33</td>
</tr>
<tr>
<td>No. of expts</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td><strong>During mannitol diuresis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>2.0</td>
<td>0.7</td>
</tr>
<tr>
<td>No. of expts</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td><strong>Paired differences before and during mannitol diuresis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>-0.64</td>
<td>(P &lt; 0.05)</td>
</tr>
<tr>
<td>No. of expts</td>
<td>0.43</td>
<td>0.40</td>
</tr>
</tbody>
</table>

may be compared with that of 450 reported by LeBrie (5) for capsular lymph flow. The higher values of LeBrie may be due in part to a different response by capsular lymph, but could also be explained by differences in the quantity of mannitol administered. In the present work, 20 g of mannitol in 100 ml fluid was given regardless of body weight, whereas LeBrie administered 20 to 50 g in 200 to 400 ml of water, depending on body weight.

It is apparent that when mannitol is administered, a number of factors combine to cause the increased flow of lymph, although the comparative importance of each of these is not clear. It has been suggested that the increase in interstitial fluid during osmotic diuresis is a consequence of venous congestion from compression of the interstitial veins by...
distended tubules (24). Because of the different sites of action, such an effect might be expected to be more marked with mannitol than with furosemide and would thus be in keeping with the experimental findings. However, when venous pressure is raised, not only does the flow of protein increase but the concentration of protein in renal lymph (7) also does. (C. C. C. O'Morchoe, unpublished observation.) In contrast, the protein concentration of renal lymph in this study decreased (Table 4) during mannitol diuresis. LeBrie (5) has also reported a fall in the protein concentration of renal lymph and in the lymph-plasma protein ratios during osmotic diuresis. In spite of these concentration differences, an increased flow of protein from the kidney does occur during mannitol diuresis, since the increase in lymph flow is proportionately greater than the decrease in protein concentration. This increased flow of protein could result either from a faster washout of the interstitial protein pool (14, 15) or from an increased rate of protein extravasation; either might result from a change in renal hemodynamics.

LeBrie (5) measured para-aminohippuric acid (PAH) clearance and extraction to obtain an index of renal blood flow and its intrarenal distribution during mannitol diuresis, and found a correlation between the increase in capsular lymph flow and an apparent increase in medullary blood flow. There is no evidence, however, that the former is dependent upon the latter; both may be independent consequences of mannitol infusion.

That diuresis per se is not the main factor responsible for the increased output of lymph is suggested by the failure of both mersalyl and furosemide to increase the flow of renal lymph (Table 2). Such evidence indicates that the effect of mannitol on renal lymph is probably less a direct consequence of the diuresis itself than a renal manifestation of the general increase in lymph production associated with mannitol infusion. This general effect is due to expansion of the extracellular volume by the infusion fluid and by movement of intracellular water, to dilution of plasma protein, and to the escape of mannitol from blood capillaries to tissue space from where it and its osmotically bound water is cleared at least in part by lymphatics. None of these factors apply during furosemide or mercurial diuresis where there is a reduction in tubular reabsorption and no additional solute to attract water to the tissue spaces and lymphatic capillaries.

Support for this general interpretation of the evidence may be obtained from LeBrie's findings (5). He reported that, whereas hypertonic solutions of mannitol and saline increased renal lymph flow by about 400%, urea did not have a significant effect even though it caused the greatest diuresis. It is significant that the infusion rate of urea was half that of mannitol and saline and that urea was excreted more rapidly than either of the other two. In most of the urea experiments, 100% of the infused volume had been excreted within 10 to 30 minutes and 200% within 90 minutes. In mannitol experiments, on the other hand, 100% of the infused volume was not excreted until 50 to 90 minutes after the onset of the infusion. Both the slow rate of infusion and the fast excretory response in the urea experiments would have tended to limit extracellular expansion and thus minimize the general effects on lymph flow mentioned above.

The reduction in hilar lymph flow which was found to accompany furosemide diuresis (Table 2) has yet to be explained. That it was not due to a general alteration in tissue fluid dynamics is suggested by the failure of furosemide to have a significant effect on thoracic duct flow. One possibility is that the contribution to hilar lymph by tubular reabsorbate, distal to the tip of Henle's loop, is reduced during the decrease in distal reabsorption associated with furosemide. The conclusion that distal reabsorbate normally contributes to hilar lymph is based on the low lymph-plasma concentration ratio that has been found for glucose (8, 25) in renal lymph. This involves the assumption that any lymph formed from proximal reabsorbate and capil-
lary filtrate is likely to have a glucose lymph-plasma ratio close to 1. An alternative explanation is suggested by Birtch et al. (26), who found a redistribution of renal blood flow during furosemide diuresis. Although the precise relationship between blood flow and lymph production is not clear, a reduced output of lymph could result from a decrease in the medullary circulation of blood.

Lymph-plasma concentration ratios for Cl⁻ were found to be consistently higher than those for Na⁺ in all experiments. If lymph reflects the composition of interstitial fluid, then this ionic difference can be adequately explained by the Gibbs-Donnan equilibrium. Similarly, this phenomenon could account for the failure of the lymph-plasma ratio for Cl⁻, in contrast to that for Na⁺, to reach 1 during furosemide diuresis. The low lymph-plasma ratio for Ca²⁺ in control lymph, on the other hand, is more probably a consequence of protein binding than of the Gibbs-Donnan effect.

The lymph-plasma ratios for Na⁺ and Cl⁻ that were higher than unity in control lymph suggest a possible relationship with the high concentrations of these electrolytes in the renal medulla. Bell et al. (12) considered this relationship by looking for a correlation between the lymph-plasma ratios and the concentrating mechanism of the kidney. Since they found no alteration in lymph-plasma osmolality, or Na⁺ ratios with different urine-plasma osmolality ratios, they concluded that renal lymph composition normally bears no relationship to the countercurrent multiplier system of the renal medulla.” This conclusion, however, cannot be accepted without reservations since urine concentration need not reflect the status of the osmotic gradient within the renal medulla.

A different approach was adopted in the present work on the basis that the inner medullary electrolyte gradient is reduced during an osmotic diuresis. The finding that a severe mannitol diuresis did not significantly affect the lymph-plasma ratios of Na⁺ and Cl⁻ suggested that the high control ratios were not primarily due to the high concentrations of these electrolytes in the papilla or inner medulla. This finding is not unexpected since, according to Rawson (19), lymphatics from the inner region ascend through the outer medulla before joining the collecting arcuate vessels. Lymph following this pathway may be expected to equilibrate with the interstitium of the outer medulla, especially as the movement of lymph is generally slow and the walls of lymphatic capillaries are thin. Under control conditions, this interstitium develops a higher concentration of Na⁺ and Cl⁻ than does the cortex as a consequence of the selective reabsorption of these ions by the thick ascending limb of Henle. Atherton et al. (27) have shown that, in contrast to the inner medulla, the outer medullary concentration of Na⁺ increased slightly during mannitol diuresis. This finding is consistent with the view that during mannitol diuresis Na⁺ continues to be reabsorbed without an osmotically equivalent volume of water by the ascending limb of Henle. Thus lymph from this region, which, according to Rhodin (20), has a relatively large number of lymphatics, will show lymph-plasma ratios for Na⁺ and Cl⁻ greater than 1, not only under control conditions but also during mannitol administration.

The evidence suggests that a contrasting situation exists during furosemide diuresis. Clapp and Robinson (28), among others, have concluded that the major effect of furosemide on the dog kidney is mediated through an inhibition of Na⁺ reabsorption in the ascending limb of Henle. Where Na⁺ reabsorption is isosmotic, a change in the reabsorptive rate would not be expected to alter the Na⁺ concentration of interstitial fluid or lymph. On the other hand, where reabsorbed Na⁺ is not accompanied by an equivalent volume of water, as in the ascending limb of Henle, a reduced reabsorptive rate would lead to a decrease in the Na⁺ concentration of interstitial fluid. Thus Cannon et al. (29) found that during furosemide diuresis the concentrations of Na⁺, Cl⁻ and K⁺ in the outer medulla were reduced by approximately 28%, 38% and 22%, respectively, from control values, whereas the concentra-
tions of these ions in the cortex were slightly increased during the diuresis. These findings support the hypothesis that the reduction in control lymph-plasma ratios for Na⁺ and Cl⁻, observed during furosemide diuresis in the present study, was a consequence of inhibition of Na⁺ reabsorption in the ascending limb of Henle. If this hypothesis is accepted, it may be concluded that renal hilar lymph reflects in part the interstitial fluid of the outer medulla and that therefore the outer medulla is a significant source of renal lymph.

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