The Effect of Mercurial Diuretics on the Excretion of Water

By J. N. Capps, M.D., W. S. Wiggins, M.D., D. R. Axelrod, M.D., and R. F. Pitts, M.D.

In experiments on 11 normal subjects and on three dogs it has been observed that mercurial diuretics do not prevent the stimulation of water absorption and formation of hypertonic urine which characteristically follows the infusion of Pitressin. Furthermore mercurial diuretics only rarely increase urine flow when administered in the course of maximal water diuresis. These two facts are interpreted as meaning that the diuretic agents have no primary effect on the reabsorption of water. Rather, increased urine flow results secondarily from increased elimination of ions.

In the treatment of edematous patients, dosage and frequency of administration of mercurial diuretics are customarily gaged by weight loss. Such loss of weight represents largely loss of water from the extracellular fluid compartment. Although it is generally conceded that mercurial diuretics block some fraction of the renal tubular absorption of sodium and chloride, no conclusive evidence exists of whether or not they affect the absorption of water directly. It is possible that loss of ions obligates in some way the excretion of equivalent quantities of water. On the other hand, renal tubular absorption of water per se might be inhibited to some extent by the diuretic agent. The present investigation was undertaken to provide experimental evidence on this point.

According to present concepts, large quantities of fluid, approaching 160 liters per day, are filtered through the glomeruli of normal man. Ordinarily all but one or two liters are absorbed as the filtrate progresses through the renal tubules. The absorption of the major fraction of this water, up to 140 liters per day, is presumed to occur passively in the proximal segment in consequence of the active absorption of salts, glucose and other valuable constituents from the tubular fluid. The absorption of these solutes, especially ions, is thought to establish the osmotic force which returns water to the blood stream. The absorption of the remainder of the water, up to 20 liters per day, is presumed to occur in more distal portions of the nephron, either in the distal segment of the renal tubule or in the collecting duct. The absorption of this moiety is independent of the absorption of solutes. At least solutes may be absorbed without the absorption of equivalent quantities of water and to some extent water may be transported actively, independently of solutes, and against an osmotic gradient. Two major factors condition completeness of absorption in this distal portion of the nephron and hence final urine volume: (a) the concentration of circulating posterior pituitary antidiuretic hormone; and (b) the load of osmotically active solutes demanding excretion.

It is possible that mercurial diuretics might depress the absorption of water, increase urine volume and reduce body weight in any one of three ways: (a) they might interfere directly with the mechanism for the active transport of water in the distal segment; (b) they might depress the proximal absorption of ions and hence interfere with the passive absorption of water; (c) they might increase the urinary load of solutes by depressing either the proximal

* Hereafter we shall refer to the distal portion of the nephron as the distal segment, recognizing that in reality the exact morphologic segment is undetermined.
METHODS

This report is based on 26 experiments performed on 11 adult male subjects and on three dogs. Nine of the 11 subjects were convalescent patients from the wards of the University Hospital. The other two were laboratory workers. None of these individuals exhibited any evidence of cardiovascular or renal disease. Two of the dogs were normal mongrel females; one had diabetes insipidus produced by stalk section. All experiments were performed without anesthesia or sedation.

The human subjects were water loaded by the administration of two liters of tap water, ingested usually over a two-hour period from 7 to 9 a.m. Thereafter, every 20 minutes for the duration of the experiment, urine was voided and a volume of water was ingested equivalent to the volume of urine excreted. We were forced to discontinue a number of experiments because of nausea and vomiting or failure to establish a high urine flow.

Attempts to hydrate animals by repeated administration of water by stomach tube were unsuccessful. Passage of the tube was followed almost invariably by a sharp drop in urine flow during some phase of the procedure. The intravenous infusion of distilled water at rates of 10 to 12 cc. per minute invariably resulted in progressive hemolysis. The procedure finally adopted was to administer by stomach tube 500 to 800 cc. of water at the start of the experiment and to infuse intravenously, at a rate equivalent to urine output, a 2.5 per cent solution of glucose in distilled water. During the three to five hours required for the performance of an experiment, little or no glucose appeared in the urine.

The inulin clearance was used as a measure of glomerular filtration rate in man. The creatinine clearance was used in the dog. In both, the parahippurate clearance at low plasma levels was used as a measure of minimum effective renal plasma flow. The osmotic concentrations of plasma and urine were determined by freezing point depression and are expressed in terms of "effective osmolarity," that is, values have not been corrected for activity. Methods employed are described in other communications.

RESULTS

An experiment on a dog with diabetes insipidus which illustrates the basic elements of the thesis we wish to present is summarized in table 1. In this experiment the animal was

* We are indebted to Dr. Allen D. Keller of the Medical Department, Field Research Laboratory, Fort Knox, Kentucky, who kindly prepared three diabetic insipidus animals for us. Unfortunately two were lost in early laboratory accidents.
water loaded and after the urine flow appeared to have stabilized near 10 cc. per minute, three control urines were collected. Eighty mg. of mercury as Mercurin* were then administered intravenously and five additional clearance observations were made. During the remainder of the experiment, Pitressin was infused at a rate of 250 milliliters per hour. After three more collection periods to determine the effects

The peak urine flow attained during the control periods of this experiment amounted to 10.75 cc. per minute. Although this animal had diabetes insipidus of at least moderate severity,* some variability of urine flow under constant hydration was observed, not only in this, but in other experiments as well. However, with the exception of the second period after the administration of 80 mg. of mercury

TABLE 1.—An experiment on a dog with diabetes insipidus which illustrates the fact that mercurial diuretics do not specifically block the absorption of water, but rather that they block ion absorption and secondarily impose an osmotic limitation on the absorption of water.

<table>
<thead>
<tr>
<th>Time</th>
<th>Urine Flow</th>
<th>Glom. Filt. Rate</th>
<th>Renal Plasma Flow</th>
<th>Plasma</th>
<th>Urine Conc.</th>
<th>Rate of Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min.</td>
<td>cc./min.</td>
<td>mEq./L.</td>
<td>m.osmols/L.</td>
<td>mEq./min.</td>
<td>m.osmol/min.</td>
<td></td>
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<tr>
<td>0-20</td>
<td>10.75</td>
<td>84.4</td>
<td>236</td>
<td>141</td>
<td>111</td>
<td>2.87</td>
</tr>
<tr>
<td>20-40</td>
<td>9.60</td>
<td>85.6</td>
<td>256</td>
<td>138</td>
<td>110</td>
<td>2.66</td>
</tr>
<tr>
<td>40-60</td>
<td>7.90</td>
<td>81.9</td>
<td>256</td>
<td>139</td>
<td>108</td>
<td>2.62</td>
</tr>
</tbody>
</table>

80 mg. Hg as Mercurin, intravenously

<table>
<thead>
<tr>
<th>Time</th>
<th>Urine Flow</th>
<th>Glom. Filt. Rate</th>
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<th>Plasma</th>
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<td>Min.</td>
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<td>mEq./L.</td>
<td>m.osmols/L.</td>
<td>mEq./min.</td>
<td>m.osmol/min.</td>
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<tr>
<td>60-80</td>
<td>8.50</td>
<td>84.7</td>
<td>194</td>
<td>137</td>
<td>106</td>
<td>2.58</td>
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<tr>
<td>80-100</td>
<td>11.65</td>
<td>84.9</td>
<td>194</td>
<td>136</td>
<td>105</td>
<td>2.87</td>
</tr>
<tr>
<td>100-120</td>
<td>9.51</td>
<td>72.8</td>
<td>184</td>
<td>134</td>
<td>103</td>
<td>2.83</td>
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<tr>
<td>120-140</td>
<td>7.29</td>
<td>69.4</td>
<td>183</td>
<td>133</td>
<td>103</td>
<td>2.87</td>
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<tr>
<td>140-160</td>
<td>7.90</td>
<td>72.7</td>
<td>208</td>
<td>132</td>
<td>101</td>
<td>2.70</td>
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</tbody>
</table>

250 milliliters Pitressin per hour added to infusion

<table>
<thead>
<tr>
<th>Time</th>
<th>Urine Flow</th>
<th>Glom. Filt. Rate</th>
<th>Renal Plasma Flow</th>
<th>Plasma</th>
<th>Urine Conc.</th>
<th>Rate of Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min.</td>
<td>cc./min.</td>
<td>mEq./L.</td>
<td>m.osmols/L.</td>
<td>mEq./min.</td>
<td>m.osmol/min.</td>
<td></td>
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<tr>
<td>160-180</td>
<td>7.40</td>
<td>72.0</td>
<td>224</td>
<td>130</td>
<td>96</td>
<td>2.54</td>
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<tr>
<td>180-200</td>
<td>3.00</td>
<td>74.2</td>
<td>214</td>
<td>129</td>
<td>94</td>
<td>2.62</td>
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<tr>
<td>200-220</td>
<td>1.24</td>
<td>72.3</td>
<td>209</td>
<td>126</td>
<td>93</td>
<td>2.58</td>
</tr>
</tbody>
</table>

1 cc. BAL, intramuscularly

<table>
<thead>
<tr>
<th>Time</th>
<th>Urine Flow</th>
<th>Glom. Filt. Rate</th>
<th>Renal Plasma Flow</th>
<th>Plasma</th>
<th>Urine Conc.</th>
<th>Rate of Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min.</td>
<td>cc./min.</td>
<td>mEq./L.</td>
<td>m.osmols/L.</td>
<td>mEq./min.</td>
<td>m.osmol/min.</td>
<td></td>
</tr>
<tr>
<td>220-240</td>
<td>0.60</td>
<td>62.8</td>
<td>165</td>
<td>128</td>
<td>90</td>
<td>1.90</td>
</tr>
<tr>
<td>240-260</td>
<td>0.63</td>
<td>71.9</td>
<td>167</td>
<td>130</td>
<td>92</td>
<td>1.55</td>
</tr>
<tr>
<td>260-280</td>
<td>0.60</td>
<td>67.0</td>
<td>167</td>
<td>130</td>
<td>93</td>
<td>1.50</td>
</tr>
</tbody>
</table>

of Pitressin, 1 cc. of BAL was given intramuscularly to inhibit the action of the diuretic. A final series of three clearance periods permitted an assessment of the action of Pitressin in the absence of mercurial diuresis.

* Mercurin was supplied through the courtesy of the Campbell Products, Inc., New York. Most of our experiments were performed with this product to avoid the complicating factor of the action of the theophylline contained in the commonly used mercurial diuretics.

as Mercurin, urine flow remained below the average of the values established during the control periods. Since this animal in other experiments exhibited control urine flows as high as 13.5 cc. per minute, we feel that an increase to 11.6 cc. per minute has little significance with respect to the action of mercury. With the infusion of Pitressin, urine flow dropped progressively to reach a value of 1.24

* The 24 hour fluid output varied between 4 and 6 liters.
cc. per minute. Following BAL it dropped still further to 0.6 cc. per minute.

The urine formed during the control periods was dilute. Although osmolarity increased following the administration of Mercurin due largely to increased excretion of sodium and chloride* ions, the urine remained hypotonic to the plasma. Following Pitressin, osmotic pressure† of the urine rose promptly, exceeding that of the plasma during the ninth and tenth periods. In fact, during the tenth period the total effective osmotic concentration of the urine was more than double that of the plasma. The fact that the urine flow diminished only to 1.24 cc. per minute is no doubt a consequence of the large load of osmotically active material presented for excretion. The lower urine volume and somewhat higher osmotic pressure after BAL is probably a consequence of the reduced osmotic load of sodium and chloride attained once the action of the mercury had been abolished.

We interpret this experiment to mean that a dose of 80 mg. of mercury, roughly 4 mg. per kilogram body weight, or four times the normal therapeutic dose in man, does not block the active distal tubular absorption of water, for it does not prevent the establishment of a high osmotic gradient between urine and plasma when Pitressin is infused.

Identical results were obtained in another experiment in which a dose of 8 mg. of mercury per kilogram of body weight were administered. In line with this view is the statement of Gilman and Kidd that “mercurial diuretics, even when increasing diuresis rate by 300 per cent, do not lower the osmotic ceiling for NaCl.”

Two of four experiments on man, which are subject to similar interpretation, are summarized in figure 1. These individuals were hydrated in the standard fashion outlined in the section on methods. Mercurin in a dose of 80 mg. of mercury per kilogram was administered intravenously some 60 to 210 minutes prior to the start of the experiment. After two control periods a prime dose of 30 milliunits of Pitressin was given intravenously and the hormone was infused thereafter at a rate of 100 milliunits per hour. Urine flow, which varied between 13 and 20 cc. per minute during the control periods, dropped sharply following the administration of Pitressin to values between 1 and 3 cc. per minute. It is true that this Pitressin-induced antidiuresis was less striking after a mercurial diuretic than in a normal untreated subject. We interpret to be a consequence of the large quantities of osmotically active electrolyte which appeared in the urine after mercury and which must have obligated the excretion of the water. Thus the urine which had been hypotonic to the plasma during the control periods became markedly hypertonic to the plasma after the administration of Pitressin, a fact which indicates that the characteristic action of the hormone in stimulating water absorption was not abolished by the mercurial diuretic. Furthermore, the lower the urinary osmotic load of solutes, largely sodium and chloride, the lower the urine flow following Pitressin, that is, the less the osmotic effect of these solutes in abstracting water from the body.

These experiments on man confirm the observations on the dog that the administration of a mercurial diuretic does not block the active tubular reabsorption of water, for it does not prevent the establishment of a high osmotic gradient between urine and plasma when Pitressin is infused. The fact that the

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* The rates of sodium excretion which we have observed during mercurial diuresis under conditions of marked hydration have been rather low in comparison with those described in previous experimental work. At least two factors must have played some role in reducing salt loss in these studies. It is evident from table 1 that the plasma concentrations of sodium and chloride dropped progressively throughout the course of the experiment. In addition, the rate of glomerular filtration declined after the fifth clearance period. Both factors operate to reduce the filtered load of ions, a circumstance which has previously been shown to reduce the efficacy of mercurial diuretics.

† Osmotic concentrations in table 1 and figures 1 through 5 are expressed in terms of “effective osmolarity” in milliosmols per liter, calculated as $1000 \times \frac{\Delta E}{1.86}$ uncorrected for activity. Osmotic load is expressed in milliosmols per minute, calculated as the product of urine flow and urine osmotic concentration, divided by 1000.
urine flow after Mercurin cannot be reduced to as low a level as in the normal subject is no doubt correlated with the greater load of water, and although they suggest that the increased flow of urine may be a consequence of the increased osmotic load presented to the distal tubule, they do not rule out the possibility that the excess water excreted might actually be derived from the proximal segment of the renal tubule. If mercurial diuretics were to block some fraction of the proximal tubular absorption of sodium and chloride ions, an extra amount of water would be delivered into the distal segment. This extra water might well account for the increase in urine flow.

An experiment designed to test this hypothesis is presented in figure 2. This experiment was performed on a normal dog, hydrated according to the standard procedure. Following two control periods during which the urine flow averaged 11.1 cc. per minute, 80 mg. of mercury as Mercurin were given intravenously. During the succeeding three hours, urine flow varied only between limits of 8.9 and 12.6 cc. per minute. Such changes as were observed were in no way correlated with the fairly marked changes which occurred in the rate of excretion of sodium. This experiment was a fortunate one, for glomerular filtration rate remained very constant throughout.

Eight experiments in all, including four on normal dogs and four on the diabetes insipidus dog, yielded results in close agreement with those presented in figure 2. Although urine flow

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**Fig. 1.** Experiments on two normal subjects during mercurial diuresis illustrating their capacity to form urine hypertonic to plasma when infused with Pitressin.

**Fig. 2.** An experiment on a normal dog in which a large dose of Mercurin, administered during so-called maximal sustained water diuresis, did not significantly increase urine flow.
and glomerular filtration rate varied considerably more in the experiments on the diabetes insipidus dog than in the ones on normal dogs, in no instance did urine flow after Mercurin appreciably exceed the maximum value established during the control periods. Furthermore, there was no evident correlation between the rate of excretion of water and the rate of excretion of sodium. However, there may well be some correlation, imperfect though it may be, between the rate of glomerular filtration and the rate of urine flow. In general, urine flow tended to be lower in those periods in which filtration rate was most reduced. However, in two experiments on one dog, increases

in urine flow from 9 to 13 and from 11 to 14 cc. per minute were observed following the administration of Mercurin. In both instances the rate of glomerular filtration was appreciably increased above the control level during the periods of increased urine flow. Urine flow appeared to correlate somewhat better with filtration rate than with sodium excretion.

In figures 3 and 4 are presented results obtained in similar experiments on two convalescent patients. In the experiment on Ma., figure 3, control urine flow averaged 19.5 cc. per minute. Following 80 mg. of mercury as Mercurhydrin, urine flow rose to 23.1 cc. per minute but rapidly returned to the control levels. The increase in urine flow was obviously unrelated in this experiment to the increase in the rate of excretion of sodium induced by the mercurial diuretic. Filtration rate remained fairly constant near control values. In contrast, in the experiment on Va., figure 4, control urine flow averaged 15.5 cc. per minute (somewhat below the expected maximal rate), increased promptly to 23.5 cc. per minute after 100 mg. of mercury as Mercurhydrin, dropped briefly and then rose gradually to a peak of 27.9 cc. per minute at the time that the peak rate of sodium excretion was attained. In this experiment a very real increase in urine flow occurred which correlated well in the

later stages with the increase in rate of sodium excretion. However, it is possible that the marked and sustained increase in glomerular filtration rate may have been responsible in some way for the increase in urine flow. In all, six experiments of this type have been performed on human subjects. Three have followed the pattern outlined in figure 3, in which no significant increase in urine flow was observed following the administration of a mercurial diuretic. The other three followed the pattern outlined in figure 4. A significant increase in urine flow over and above the control level was observed in these instances. In all, some correlation could be established be-
between urine flow and glomerular filtration rate. However, from the data available it is impossible to quantitate in any exact fashion the effect of a given increase in glomerular filtration rate on urine flow. In fact, it is even impossible to prove conclusively that a cause and effect relationship exists between these two variables.

**Discussion**

The data presented above establish the fact that a full therapeutic dose of a mercurial diuretic in man, or as much as eight times this dose per kilogram body weight in the dog, does not prevent the stimulation of the active absorption of water and the formation of hypertonic urine which normally follows the infusion of Pitressin. Although urine flow is not reduced to as low levels by Pitressin after a mercurial diuretic as before, the limiting factor appears to be the increased load of osmotically active materials demanding excretion rather than some primary effect of mercury on the water absorptive mechanism. In the presence of a large load of urinary sodium and chloride the kidney is unable to concentrate to as great a degree or to restrict flow to such low values as it can if the load is small. These results are consonant with the view that mercurial diuretics do not interfere with the active absorption of water in the distal tubule, that is, that moiety subject to control by Pitressin.

It has been somewhat less conclusively established that a mercurial diuretic does not block the passive absorption of water in the proximal tubule. In the majority of the dog experiments and in half of the experiments on man our findings support this view. However, in two dog experiments and in three experiments on man, urine flow increased more or less in proportion to sodium and chloride excretion after the mercurial diuretic. This finding might be interpreted as favoring the concept that mercury inhibits the proximal absorption of sodium and chloride and hence indirectly inhibits the passive absorption of water. However, in each instance glomerular filtration rate increased. We favor the concept that the increase in urine flow is related in some fashion to the increase in filtration rate in these later experiments, rather than to blockage of the proximal absorption of fluid. However, we recognize the fact that this view has not been firmly established.

If mercurial diuretics do not primarily affect water absorption in either the proximal or distal tubule, the increase in urine flow and the loss of weight which accompanies successful therapy must be assigned in one way or another to osmotic forces. Blockage of ion absorption (the majority of our data favor the view of distal blockage) delivers increased quantities of osmotically active solutes into the urine, hindering thereby the active absorption of water in the distal segment. In addition, primary loss of ions might be expected to reduce the osmotic pressure of the body fluids, inhibit the secretion of Pitressin and permit an increased flow of urine.

**Conclusions**

Mercurial diuretics do not interfere with the active distal tubular absorption of water, that is, that moiety subject to control by Pitressin. It is suggested that the increased load of ions demanding excretion imposes an osmotic limitation on the active absorption of water in this segment, or in other words, osmotically abstracts water from the body. In addition the primary loss of ions might be expected to dilute the body fluids, inhibit the secretion of Pitressin and reduce the activity of the Pitressin-sensitive mechanism of water absorption. From the data available it is impossible to state definitively whether or not mercurial diuretics affect the passive proximal tubular absorption of water.

**References**


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