Effects of Reduced Glomerular Filtration Rate on Responsiveness to Chlorothiazide and Mercurial Diuretics

By F. C. Reubi, M.D., and P. T. Cottier, M.D.

It has generally been assumed that patients with impaired glomerular filtration would respond to any diuretic in a less satisfactory manner than normal individuals. Many authors believe, for instance, that the unresponsiveness to mercurials in certain cases of severe congestive heart failure is due to a marked decrease in the filtered load of sodium, chloride, and water. Evidence, however, is still limited that such a mechanism plays a major role in patients clinically resistant to diuretics. The importance of extrarenal factors, like adrenal cortical hormones, on the tubular reabsorption of sodium should not be underestimated. Patients with nephrotic syndrome and normal glomerular filtration rate may respond very poorly to mercurials, whereas in other subjects the same drug produces a good diuresis in spite of a low glomerular filtration rate. On the other hand, most experiments designed to demonstrate the role of a reduction in glomerular filtration rate on the responsiveness to diuretics have been performed in normal animals, in which the blood supply of the kidney was acutely restricted.

Little work has been done so far to compare the efficacy of diuretics in patients suffering from renal disease with different degrees of functional impairment. The present experiments were designed to investigate the effects of a chronic reduction of the glomerular filtration rate on the responsiveness to chlorothiazide and mercurials.

Material and Methods

Only patients without edema and without heart failure were selected in order to minimize variations due to tubular and extrarenal factors. Since most subjects with low filtration rate had also some degree of arterial hypertension, it was not possible to exclude cases with high blood pressure from this study. It seemed desirable, therefore, to include also hypertensive patients with normal or slightly reduced filtration rate.

Twenty-four individuals were studied. The group consisted of 12 patients with chronic pyelonephritis, 4 with subacute or chronic glomerulonephritis, 3 with essential hypertension, 1 with diabetic glomerulosclerosis, 1 with nephrolithiasis, and 3 subjects without renal disease. Thirteen subjects had a normal blood pressure, 11 had some degree of hypertension. The nonprotein nitrogen was either within normal range or increased.

The study was performed in the morning with the patient remaining in bed. After catheterization of the bladder, a priming infusion of inulin in saline was given intravenously. This was followed by the constant infusion of a solution containing 6 Gm. of inulin in 1,000 ml. of 0.9 per cent sodium chloride. This sustaining infusion was given at a rate of 8 ml. per minute per 1.73 M², so that the patient received 1,230 µEq. per minute per 1.73 M² of sodium during the whole procedure.

Urine and blood samples were first collected in 2 or 3 conventional clearance periods averaging 20 minutes each. In a first group of 12 experiments, chlorothiazide was then injected intravenously in the dose of 500 mg. per 1.73 M². Blood and urine collections were continued over 4 periods of 40 to 45 minutes. In a second group of 7 experiments, mercurials were given in the dose of 2 ml. per 1.73 M² (= 176 mg. per 1.73 M²) after the 2 control periods. Urine and blood samples were collected over 5 more periods of 40 to 45 minutes. Since the peak action was not attained before 1½ to 2 hours, only the results of the last 3 periods have been considered.

In another group of 5 experiments, mercurials were given as in group 2. But 80 to 90 minutes later the patient also received 500 mg. per 1.73 M² of chlorothiazide. Three more collection periods of 40 to 50 minutes followed the injection.

The blood pressure was measured frequently by the auscultatory technic. Blood and urine samples were analyzed for inulin, sodium, potassium, and chloride. Clearances were calculated by standard methods. Inulin was determined by the method of Schreiner, sodium and potassium with an internally standardized flame photometer, chloride by the method of Lang.

Kindly supplied by Merek, Sharp & Dohme, West Point, Pennsylvania.
REDUCED GLOMERULAR FILTRATION RATE

Results

Experiments with Chlorothiazide Alone (Table 1)

Effect on Blood Pressure

In no case was a significant hypotensive effect observed during the 3 hours following the injection.

Effect on Glomerular Filtration Rate

After chlorothiazide there was a moderate decrease in 6 patients, the greatest drop observed being 17.7 per cent. In 1 patient the glomerular filtration rate increased 25.3 per cent. In the remaining patients there was no change at all. For the whole group the mean was a decrease of 7 per cent.

Effect on Urinary Flow and Water Reabsorption (Fig. 1)

Under control conditions the urinary flow was not related to the glomerular filtration rate. In all patients with a glomerular filtration rate above 15 to 20 ml. per minute, chlorothiazide elicited a prompt diuretic response. In most cases the highest rate of urinary flow was already reached during the first period after injection. In the following periods the diuresis was either sustained or decreased slowly. The highest urinary flow was observed in patient 2, with an inulin clearance of 123 ml. per minute. But in most patients with a glomerular filtration rate above 15 to 20 ml. per minute the urinary flow after chlorothiazide increased to 4 to 6 ml. per minute, these values bearing no relationship to the glomerular filtration rate itself. In patients with a very low glomerular filtration rate, however, the diuretic response was poor (patients 11 and 12).

When the tubular reabsorption of water is calculated from these data, it appears that with decreasing glomerular filtration rate the drug blocks an increasing fraction of the water reabsorption, so that at different levels of glomerular filtration rate the diuretic effect remains of the same order of magnitude. The tubular reabsorption obviously cannot be blocked by more than 40 per cent of the filtered water load. At this point a further drop in glomerular filtration rate results in a sharp decrease in the diuretic effect.

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Table 1

Effects of Chlorothiazide in Twelve Patients*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Period No.</th>
<th>Blood pressure mm Hg</th>
<th>Urine flow ml/min.</th>
<th>GFR† ml/min.</th>
<th>Tubular rejection of water %</th>
<th>Sodium Excreted µ Eq./min.</th>
<th>Filtered µ Eq./min.</th>
<th>Tubular rejection %</th>
<th>Chloride Excreted µ Eq./min.</th>
<th>Filtered µ Eq./min.</th>
<th>Tubular rejection %</th>
<th>Potassium Excreted µ Eq./min.</th>
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<td>123</td>
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<td>655</td>
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<td>92</td>
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<td>1003</td>
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<td>256</td>
<td>1,112</td>
<td>23.0</td>
<td>284</td>
<td>892</td>
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*Figures are average values of several periods.
†Glomerular filtration rate (inulin clearance).
‡After chlorothiazide, 500 mg. intravenously.
§Only the first 2 periods after chlorothiazide have been considered in this column.
Effect on Potassium Excretion

Whereas the diuretic and saline effect after chlorothiazide was usually sustained and lasted during the whole experiment, the kaliuretic effect was of short duration and obvious only during the first 2 periods after injection of the drug. We have, therefore, considered only these 2 periods in table 1 and figure 4. From our data the degree of kaliuresis after chlorothiazide appears almost proportional to the glomerular filtration rate. At low filtration rates there was no increase in kaliuresis above the control values.

Experiments with Meralluride Alone (Table 2)

There was no consistent change in blood pressure. In most cases a slight increase in glomerular filtration rate was observed. Although a kaliuretic effect was entirely lacking, the diuretic and saline response was very similar to that seen after chlorothiazide.

Effect on Urinary Flow and Water Reabsorption

Under control conditions the urinary flow was not related to the glomerular filtration rate (fig. 5). In all patients with a glomerular filtration rate greater than 10 ml. per minute, the diuretic response to meralluride was of the same order of magnitude, ranging from 4.96 to 8.88 ml. per minute. This means that meralluride, like chlorothiazide, blocks a fraction of the tubular reabsorption of water that increases more or less proportionately to the decrease in filtration rate. The highest value for the tubular rejection of water in this series was 48.6 per cent.

Effect on Sodium and Chloride Excretion and Reabsorption

The control excretion of these electrolytes was not related to the glomerular filtration rate (figs. 6 and 7). After meralluride, the saline effect was comparable in all cases with a glomerular filtration rate greater than 15 to 20 ml. per minute. In the 2 patients with a glomerular filtration rate of about 12 ml. per minute, the saline effect was still present but of lower magnitude. It seems, therefore, that the tubular rejection of sodium and chloride increases after meralluride more or less proportionally to the decrease in filtered load. The highest values observed in these experiments were 39.5 per cent for sodium and 41.5 per cent for chloride.

Effect on Potassium Excretion

The control excretion was unrelated to the glomerular filtration rate. After meralluride there was, as a rule, a significant decrease, averaging for the whole group 26 per cent.

Experiments with Meralluride and Chlorothiazide (Table 3)

Effect on Glomerular Filtration Rate

In most cases there was some decrease, averaging 10 per cent for the whole group.

Effect on Urinary Flow and Water Reabsorption

In the 2 patients with normal glomerular filtration rate, the diuretic effect of chlorothiazide was markedly enhanced by the previous administration of meralluride. The comparison of the rates of urinary flow observed in these subjects with data on patients receiving chlorothiazide alone or meralluride alone, suggests a summation of the individual effects. But in 2 patients with a moderate reduction of the glomerular filtration (58 and 30.6 ml. per minute) the diuretic response to both drugs given together was not greater than after meralluride alone. In patient 5, with a very low filtration rate, there was practically no diuretic effect, the decrease in water reabsorption being compensated by the decrease in water filtration. The rejected frac-
### Table 2

**Effects of Meralluride in Seven Patients**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Period No.</th>
<th>Blood pressure mm. Hg</th>
<th>Urine flow ml./min.</th>
<th>GFR† ml./min.</th>
<th>Tubular rejetion of water</th>
<th>Sodium Excreted µ Eq./min.</th>
<th>Filtered µ Eq./min.</th>
<th>Tubular rejection %</th>
<th>Chloride Excreted µ Eq./min.</th>
<th>Filtered µ Eq./min.</th>
<th>Tubular rejection %</th>
<th>Potassium Excreted µ Eq./min.</th>
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</tbody>
</table>

*Average values of 2 or 3 periods. The first 2 periods following the injection were left out, as the maximal effect was not attained at this time.
†Glomerular filtration rate (inulin clearance).
‡After meralluride, 2 ml. intravenously.

### Table 3

**Diuretic and Saluretic Effect of Meralluride Combined with Chlorothiazide in Five Patients**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Period No.</th>
<th>Blood pressure mm. Hg</th>
<th>Urine flow ml./min.</th>
<th>GFR† ml./min.</th>
<th>Tubular rejetion of water</th>
<th>Sodium Excreted µ Eq./min.</th>
<th>Filtered µ Eq./min.</th>
<th>Tubular rejection %</th>
<th>Chloride Excreted µ Eq./min.</th>
<th>Filtered µ Eq./min.</th>
<th>Tubular rejection %</th>
<th>Potassium Excreted µ Eq./min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. T. A. Control</td>
<td>1-2</td>
<td>140/70</td>
<td>3.89</td>
<td>137</td>
<td>2.8</td>
<td>471</td>
<td>19,200</td>
<td>2.5</td>
<td>422</td>
<td>14,300</td>
<td>3.0</td>
<td>49</td>
</tr>
<tr>
<td>After M + C†</td>
<td>5-7</td>
<td>130/85</td>
<td>10.76</td>
<td>119</td>
<td>9.0</td>
<td>1830</td>
<td>16,800</td>
<td>10.9</td>
<td>1465</td>
<td>13,400</td>
<td>10.9</td>
<td>54</td>
</tr>
<tr>
<td>2. I. M. Control</td>
<td>1-2</td>
<td>120/65</td>
<td>1.94</td>
<td>129</td>
<td>1.5</td>
<td>100</td>
<td>18,500</td>
<td>0.5</td>
<td>150</td>
<td>13,700</td>
<td>1.2</td>
<td>88</td>
</tr>
<tr>
<td>After M + C</td>
<td>5-7</td>
<td>118/63</td>
<td>14.63</td>
<td>106</td>
<td>13.7</td>
<td>2360</td>
<td>15,250</td>
<td>15.5</td>
<td>2200</td>
<td>11,250</td>
<td>19.7</td>
<td>56</td>
</tr>
<tr>
<td>3. E. J. Control</td>
<td>1-2</td>
<td>115/65</td>
<td>1.17</td>
<td>58</td>
<td>2.0</td>
<td>123</td>
<td>8,100</td>
<td>1.5</td>
<td>168</td>
<td>6,450</td>
<td>2.6</td>
<td>30</td>
</tr>
<tr>
<td>After M + C</td>
<td>5-7</td>
<td>110/63</td>
<td>4.93</td>
<td>52.5</td>
<td>9.4</td>
<td>700</td>
<td>7,600</td>
<td>9.2</td>
<td>640</td>
<td>5,890</td>
<td>10.9</td>
<td>35</td>
</tr>
<tr>
<td>After M + C</td>
<td>5-7</td>
<td>140/90</td>
<td>7.91</td>
<td>33.6</td>
<td>23.3</td>
<td>1002</td>
<td>4,517</td>
<td>22.1</td>
<td>939</td>
<td>3,755</td>
<td>25.5</td>
<td>29</td>
</tr>
<tr>
<td>5. M. F. Control</td>
<td>1-2</td>
<td>235/138</td>
<td>1.79</td>
<td>5.9</td>
<td>30.3</td>
<td>211</td>
<td>834</td>
<td>25.3</td>
<td>156</td>
<td>600</td>
<td>26.0</td>
<td>21</td>
</tr>
<tr>
<td>After M + C</td>
<td>5-7</td>
<td>235/130</td>
<td>1.94</td>
<td>4.4</td>
<td>44.0</td>
<td>231</td>
<td>597</td>
<td>38.8</td>
<td>196</td>
<td>457</td>
<td>42.8</td>
<td>26</td>
</tr>
</tbody>
</table>

*Average values of 2 or 3 periods. Periods between the 2 injections have been left out.
†Glomerular filtration rate (inulin clearance).
‡After meralluride, 2 ml. intravenously, and chlorothiazide, 500 mg. intravenously 80 to 90 minutes later.
REDUCED GLOMERULAR FILTRATION RATE

Figure 3
Chloride excretion before and after chlorothiazide in 13 patients (same experiments as in figs. 1 and 2).

Figure 4
Potassium excretion before and after chlorothiazide in 12 patients. The kaliuretic action is proportional to the glomerular filtration rate.

Discussion
In discussing the effects of a reduction of the glomerular filtration rate on the responsiveness to diuretic agents, we must consider not only the decrease in the filtered amount of sodium, chloride, and water but also the extent to which their tubular reabsorption can be blocked by these drugs. Furthermore, we must take in account that in patients with reduced glomerular filtration rate, but without edema, there is already a marked permanent decrease in tubular reabsorption under basal conditions and during loading with saline as well. This decrease is roughly proportional to the reduction of the inulin clearance, so that comparable amounts of salt and water are still excreted at any level of glomerular filtration (fig. 9, dotted line O), as long as renal functions are not too severely impaired.

The mechanism of action of diuretic agents is not easily understood. At least three different possibilities may be considered. First, it could be assumed that chlorothiazide and meralluride block the tubular reabsorption up to an invariable percentage of the filtered load. This would imply a decrease in the diuretic and saline responses proportional to the reduction of the glomerular filtration rate (fig. 9, straight line A). There is some evidence that such a mechanism does operate under certain experimental conditions. Davidson et al. found in the dog that mechanical compression of one renal artery would reduce the sodium excretion more than the filtration rate (fig. 9, line B'). However, when Salyrgan

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was given in similar experiments, mechanical reduction of the filtration rate was followed by a proportional decrease in the sodium excretion (fig. 9, line A'). In representative experiments, the calculated tubular rejection of sodium (assuming a plasma sodium of 140 mEq. per liter) was, on the constricted side, 14.4 per cent before and 15.8 per cent after clamping, on the other side 14.1 per cent and 16.2 per cent, respectively, which is practically identical. Somewhat different results have been reported by Pitts and Duggan. By compressing the aorta of dogs receiving large doses of a mercurial diuretic, these authors produced a reduction of the sodium excretion greater than that of the glomerular filtration rate, the tubular rejection decreasing from 20 to 10 per cent of the filtered load (fig. 9, line B).

Results of acute experiments in normal animals suggest therefore that lowering of the glomerular filtration rate during mercurial saluresis decreases the excretion of sodium correspondingly or even to a greater extent. Should this hold true in patients with chronically reduced filtration rate, the regression curves A and B would intercept the straight line 0 at relative high levels of filtration. Below this level, there should be a complete loss of diuretic response. It appears clear from our figures (figs. 1 to 3 and 5 to 8) that this is not so; even at very low filtration rates, some diuretic and saluretic effects still occur.

A second possibility is also conceivable, at least theoretically: the drug would block a fixed percentage of the tubular reabsorption in addition to the variable rejected fraction responsible for the control excretion. This would mean a great diuretic response at high filtration levels, because in these cases the control values of tubular rejection are very small, but only a slight increase at low filtration levels, where the rejected fraction is already large (fig. 9, tracing C). However, there is no definite evidence that this possibility applies to acute experiments or to patients receiving meralluride or chlorothiazide alone. Our data show that the additional fraction of tubular reabsorption blocked by meralluride or chlorothiazide is not constant, but increases with the reduction of glomerular filtration rate. Only those few experiments performed with a combination of both diuretics suggest some kind of proportional relationship of this type. The existence of a curvilinear correlation cannot be excluded, however, with so little data on hand.

Finally, a third mechanism may be involved: the diuretic agent might increase by a constant multiplying factor the fraction of the filtered load already rejected under control conditions. For instance, chlorothiazide would produce a 3-fold increase at any level of tubular rejection. In a case with a glomerular filtration rate of 100 ml. per minute and a tubular rejection of 1 per cent, the rejected amount would increase to 3 per cent. In a case with a glomerular filtration rate of 25 ml. per minute, and tubular rejection of 4 per cent, the latter would increase to 12 per cent. It follows that the excretion of sodium, chloride, and water after chlorothiazide would be similar in both cases (fig. 9, tracing D). A further drop in glomerular filtration rate to 3 ml. per minute should, however, limit the effectiveness of this mechanism, as a 3-fold increase in the control rejection of 33 per cent should bring it up to 100 per cent.
low this critical level of glomerular filtration, 
the excretion of sodium, chloride, and water 
should fall very sharply. As it is very un-
likely that tubular reabsorption can be 
blocked completely by any diuretic agent, we 
might assume a more reasonable limit, for 
instance 40 per cent (fig. 9, line E). Our data 
on chlorothiazide and meralluride alone cer-
tainly seem to fit this last hypothesis best. 
While such a mechanism cannot be easily 
understood, we must recognize that in our 
observations the decrease in responsiveness 
to diuretic agents is much less than one would 
expect from the reduction in filtration rate, 
should the blocked fraction of tubular reab-
sorption remain constant. As a matter of fact, 
our experimental data are more consistent 
with the assumption of a 2-to-3-fold increase 
in the fraction rejected prior to the admin-
istration of chlorothiazide or meralluride. But 
the total rejection cannot exceed a certain 
limit and its maximum seems to lie at about 
30 to 40 per cent of the filtered load. The 
highest figures observed after chlorothiazide 
are 40.1 per cent for water, 31.1 per cent for 
sodium, and 37.6 per cent for chloride. After 
meralluride these figures are 48.6, 39.5, and 
41.5 per cent, respectively. Even when both 
drugs are combined, water reabsorption can 
be blocked only to 44 per cent, sodium to 38.8 
per cent, and chloride to 42.8 per cent. It 
would seem desirable to have more data on 
patients with a very low filtration rate, in 
order to determine these limits and draw the 
lower part of the experimental curve with a 
reasonable degree of accuracy. Unfortunately, 
patients with a glomerular filtration rate of 
about 5 ml. per minute are markedly azotemic 
and may tolerate the experimental procedure 
rather poorly. Anyway, our figures are very 
close to the value found by Pitts in the 
normal dog for the maximal fraction that can 
be blocked by the combined action of mer-
curials and chlorothiazide.

In figure 9 we have drawn the experimental 
curve F as a coarse visual approximation from 
data in tables 1 and 2. This curve lies rather 
close to the tracing DE, differing from the 
latter only in two respects: the line F shows 
a smooth inflexion instead of the sharp an-
gluation seen in tracing DE and its upper part 
is neither linear nor quite horizontal. We be-
lieve that these differences can be best ex-
plained by assuming a certain dispersion in 
the glomerulo-tubular activity. A comparison 
with glucose titration curves obtained by 
Smith in hypertensive patients and by our-

selves in patients with renal diabetes 
indicates that such a mechanism may also play a 
role in the present experiments. This would 
implicate that the single tubules are not reject-
ing exactly the same fraction of the filtered
load, or that they are receiving from the corresponding glomeruli slightly different loads.

The observation that mercurials may enhance the diuretic and saluretic effects of chlorothiazide has already been made by others.9,12 It may be concluded that the two drugs block two different reabsorptive mechanisms or the same mechanism in two different ways.9 It is of interest, however, that at very low filtration rates the maximal fraction of the tubular reabsorption that can be blocked by chlorothiazide or meralluride alone is not increased when both drugs are given together (patient 5). In 2 patients with a moderate reduction of the glomerular filtration rate the effect of the combination was within the usual range of response to the individual drugs. Only in the 2 patients with normal glomerular filtration rate were the saluretic and diuretic actions of chlorothiazide markedly enhanced by the previous administration of meralluride, suggesting summation of the individual effects. Obviously, the potentiation of chlorothiazide by mercurials is of practical significance in cases with a high glomerular filtration rate only.

We have made no attempt to correlate further the response to the combination of both drugs with the level of the glomerular filtration. While a few points on figure 9 are suggestive of direct proportionality, we consider that a curvilinear relationship cannot be ruled out. Such a tracing might result from the summation of the individual curves observed with chlorothiazide or meralluride alone, which would increase the splay correspondingly.

The striking influence of a chronic reduction of the glomerular filtration upon the kaliuretic effect of chlorothiazide is not too surprising. The simplest explanation of our findings is to assume that the increased tubular rejection of sodium observed at low filtration rates leaves only a small amount of this electrolyte available for exchange with potassium. The observation that the kaliuretic response decreases almost proportionately to the glomerular filtration rate is not in agreement with the data reported in animals.6 But the discrepancy between the results in animals and our data may arise from the different behavior of the rejected fraction of sodium in the two types of experiments: this fraction was increased in our patients, but decreased or was unchanged in the dogs.6

The inhibitory effect of mercurials on chlorothiazide kaliuresis might be due to a similar mechanism. The previous administration of meralluride enhances the natriuretic properties of chlorothiazide and increases the tubular rejection of sodium. This might reduce the amount of sodium available for exchange with potassium and therefore decrease the excretion of the latter. An alternative and perhaps more likely explanation is to attribute to mercurial compounds a specific inhibitory effect on the potassium secretion itself.13 It should be kept in mind, however, that under clinical conditions, mercurial agents do not always block the excretion of potassium. Patients with cirrhosis of the liver and nephrotic syndrome may respond to meralluride with an increased potassium output, instead of saluresis.5

The practical significance of our findings is
subject to certain limitations due to the short duration of the experiment and to the fact that only patients with diseased kidney but without edema have been examined. We think, however, that our results may have some clinical implications. The peak response to 2 ml. of meralluride is somewhat greater than that observed after 500 mg. of chlorothiazide, but there is a considerable overlapping of both ranges of responses. After chlorothiazide the effect is immediate; after meralluride the peak action is delayed but may last longer. It would appear, therefore, that in patients with a chronic reduction of the glomerular filtration rate, both drugs give comparable diuretic and saluretic results. These results depend upon renal and extrarenal factors. Over a wide range, i.e., from 15 to 20 ml per minute up to normal values, the level of glomerular filtration is of little significance, when chlorothiazide or meralluride are used alone. Only at very low filtration rates is the saluretic effect markedly impaired. These facts seem to indicate that in the course of most chronic renal diseases without edema there is a functional adaptation of the reabsorptive mechanisms to the reduced glomerular activity, not only under basal conditions, but also after administration of a diuretic. This is in good agreement with the observation that the diseased kidney may retain its ability to concentrate and to dilute urine.\textsuperscript{14}

The applicability of our findings to the problem of the refractoriness to diuretics in congestive heart failure remains open to question. The assumption, that in these patients the lack of response is due to a very low filtration rate, rests mainly upon acute experiments in normal dogs and would need more adequate support. On the other hand, our results show that a permanent reduction of the filtration rate per se has little influence on the diuretic response, provided the fraction of the filtered sodium rejected under basal conditions is large. In patients with cardiac or nephrotic edema this fraction is very small and even a 4-fold increase will not lead to a marked saluresis. The refractoriness to diuretics, therefore, can best be correlated with a reduction of the rejected fraction. This in turn depends largely on extrarenal factors rather than on the level of filtration.

The well-known kaliuretic effect of chlorothiazide, which may be very disturbing during the course of sustained therapy, becomes less important when the glomerular filtration is substantially reduced. Since meralluride appears to be capable of blocking this effect and also markedly enhances the saluretic properties of chlorothiazide in patients with high filtration rate, the combination of both drugs seems to be advisable in such patients.

Finally, it must be noted that a single injection of chlorothiazide does not lower the arterial blood pressure, even in hypertensive patients. This is in agreement with observations made by others.\textsuperscript{15} Our patients were studied, however, under conditions of loading with saline, which may well explain the lack of any hypotensive effect related to saluresis.

**Summary**

Clearance experiments have been performed in 24 subjects with different levels of glomerular filtration, suffering from renal disease without edema, in order to compare the diuretic, saluretic, and kaliuretic responses to a single intravenous injection of meralluride, chlorothiazide, or both together. The inulin clearances of these patients ranged from 5.9 to 133 ml. per minute. The effects of the

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drugs were studied under constant loading with saline over 3 hours after injection.

Our results indicate that over a wide range (15 to 20 ml. per minute up to normal values) a permanent reduction of the glomerular filtration rate has little influence on the diuretic and saluretic effects of meralluride or chlorothiazide. Below 15 to 20 ml. per minute a further reduction results in a sharp decrease in the diuretic and saluretic actions. This can be best explained by assuming that the diuretic agents block an increasing fraction of the tubular reabsorption of water, sodium, and chloride related to the decrease in glomerular filtration rate. This fraction, however, seems to be limited to 30 to 40 per cent of the filtered load. Some dispersion in the glomerulo-tubular activity may account for the splay of the experimental curves.

The kaliuretic effect of chlorothiazide is proportional to the glomerular filtration rate. This effect can be blocked by meralluride.

At high levels of glomerular filtration the diuretic and saluretic actions of meralluride and chlorothiazide are additive. At lower levels of filtration, such a summation effect is not demonstrable. Apparently, both drugs given together cannot block the reabsorption of more than 30 to 40 per cent of the filtered load.

A single injection of chlorothiazide does not lower the arterial blood pressure of hypertensive subjects, loaded with saline, but produces a slight decrease in the glomerular filtration rate, averaging 7 per cent.

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Effects of Reduced Glomerular Filtration Rate on Responsiveness to Chlorothiazide and Mercurial Diuretics

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