INFLUENCE OF CHLOROTHIAZIDE ON WATER AND ELECTROLYTE EXCRETION IN PREECLAMPSIA

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It has long been a goal of research scientists to develop a diuretic drug which would be effective on oral administration and which would not produce serious electrolyte imbalance. Recently, chlorothiazide (Diuril), a new diuretic agent, has shown considerable promise in animal experiments. Chemically, chlorothiazide is 6-chloro-7-sulfamyl-1, 2, 4-benzothiadiazine-1, 1-dioxide. Its structure is represented in figure 1. This compound is structurally related to some carbonic anhydrase-inhibiting diuretics, in that it contains a sulfamyl group attached to a benzene ring.

Preclinical experiments indicate that this compound possesses a high degree of activity as an inhibitor of carbonic anhydrase in vitro. It is considered to be about 10 to 30 times as potent as sulfanilamide in this respect. In animals, chlorothiazide causes a marked increase in the urinary excretion of sodium, potassium, chloride, and water. Excreted sodium is matched approximately mol for mol by chloride ions. This effect is similar to that of mercurial diuretics, although chlorothiazide does not contain mercury. At high doses, bicarbonate excretion takes place, presumably because of inhibition of carbonic anhydrase. Because chlorothiazide is an effective diuretic in dogs at doses which do not produce bicarbonate excretion, these animal experiments suggest that its mechanism of action cannot be explained on the basis of carbonic anhydrase inhibition. Since the mechanism of this agent is still doubtful, we were particularly interested to investigate both the clinical effectiveness and the mechanism of action of chlorothiazide in some of the abnormalities of human pregnancy.

Materials and Methods

All patients diagnosed as having toxemia of pregnancy who were admitted to the obstetrics and gynecology service of King County Hospital during a period limited to the study of chlorothiazide were included in this study, with the exception of those patients who left the hospital against medical advice before the experimental period had elapsed. All patients were hospitalized during the period of investigation. The final diagnosis of toxemia was based on information obtained during the antepartum period, the period of hospitalization, and the follow-up period, at least three months postpartum. The series consisted of a total of 14 women, 9 Caucasian, 3 Negro, and 2 American Indian, who were investigated during the immediate postpartum period in the hospital. This group of patients lent itself to comparison with another group of similar patients with toxemia of pregnancy previously studied in the same manner, with the exception that no diuretic drug was administered. In this controlled study of hospitalized patients we were able to investigate extensively many factors bearing on the course of toxemia of pregnancy and to analyze the effect of chlorothiazide in modifying those factors.

Each patient was studied over a seven-day period. Bed rest was enforced for the first three days, after which the majority of patients were made ambulant. A food intake consisting of a 1,200-calorie, neutral-ash, low-salt diet, containing approximately 30 mEq. of sodium daily, was maintained unless the patient was unable to tolerate oral feedings, in which case intravenous feedings were
carried out. Food trays were weighed before and after each meal, and the actual daily intake of sodium, calories, acid, and basic ash was calculated. Sedation in varying degrees depending on the severity of the toxemia was prescribed as appropriate. All urine was collected as 24-hour specimens and kept under 25 ml. of mineral oil in order to prevent alterations in chemical values because of exposure to air. To prevent contamination by lochia, the urine from all postpartum patients was collected through indwelling Foley catheters.

The foregoing general measures constitute the general toxemia regimen of the department of obstetrics and gynecology of the University of Washington and have been kept constant for several years. The only modification from the usual program was the addition of 500 mg. of chlorothiazide given orally twice a day in the experimental group. Patients in the control group received no diuretic agents. During the first 24 hours of hospitalization no chlorothiazide was administered. On the second and third postpartum days, 500 mg. of chlorothiazide was given twice daily. During the fourth and fifth postpartum days, no chlorothiazide was given. On the sixth and seventh days the drug was again administered in the same dosage.

![Chemical structure of chlorothiazide](image)

Fig. 1.—Chemical structure of chlorothiazide.

Serum sodium, potassium, and chloride levels were determined daily. On the second, fourth, and sixth hospital days blood urea nitrogen level, total protein level, albumin-globulin ratio, and fibrinogen and serum carbon dioxide levels were measured. On each of the daily 24-hour urine samples, urine pH, total volume, albumin level, specific gravity, ammonia content, titratable acidity, and sodium, potassium, and chloride levels were determined. The weight of each patient in grams was determined daily at the same time by the same person on a specially constructed scale for bedside weighing. The weights were accurate to 10 Gm. Blood pressure and edema were evaluated daily by the same person.

Sodium and potassium levels were determined by a flame photometer method with use of the Baird spectrophotometer. The chloride level was determined by the method of Schales and Schales,5 blood urea nitrogen level by a slight modification of the method of Van Slyke and Cope,4 carbon dioxide content by a slight modification of the method of Van Slyke and Neill,6 titratable acidity by the method outlined by Hawk and co-workers,7 ammonia by a slight modification of the method of Van Slyke and Cullen,8 and pH with the Beckman, model G, pH meter.

All data were submitted to statistical analysis to determine the effect of chlorothiazide on the course of toxemia of pregnancy in the postpartum period. Since most reports attach great significance to the day-to-day changes occurring after the administration of a given drug, we considered it highly important to determine whether such changes would occur in a group of patients similarly treated except for the use of the drug. The fact that untreated patients may exhibit statistically significant changes from day to day makes it imperative that observations be made in a control group if the effect of a drug is to be properly evaluated. It is incorrect to ascribe to the action of a drug the finding of a significant difference until control studies have been performed. The failure to observe this principle has led to much confusion and misinformation in the past.

The Student's t test was used to compare means in the chlorothiazide and control groups on a day-for-day basis. The reproducibility of the individual determinations was considered in establishing the p values on levels thought to be significant. In general, those observations having a low coefficient of variation, such as on the serum electrolytes, were considered significant at a level of p=0.01. For observations having a high coefficient of variation, as on the urine electrolytes and weight gain, the level of significance was established at p=0.05.

**Results**

The results obtained in this study in the 14 postpartum patients with toxemia of pregnancy who were treated with chlorothiazide are summarized in table 1. The results obtained in the group of 23 patients with toxemia of pregnancy studied in the postpartum period who did not receive any diuretic drugs are summarized in table 2. The latter group will be referred to as the control group.

**Urine Sodium.—** As shown in table 1, the urine sodium excretion remained constant during the first three days, being 73.2 mEq. per 24 hours the first (no drug) day and 70.7 and 75.9 on the second and third postpartum days, which were the first two days that the drug was given. Thus, the patients treated with chlorothiazide did not experience the drop in sodium excretion that the control group did (fig. 2). Significant increases of sodium excretion were found on the second day of the first course of drug administration (control group 47.3 mEq. per 24 hours, chlorothiazide group 75.9 mEq. per 24 hours: p=0.05) and on both days of the second course (control group 23.6 mEq. per 24 hours, chlorothiazide group 59.7 mEq. per 24 hours: p=...
0.002; control group 28.0 mEq. per 24 hours, chlorothiazide group 66.2 mEq. per 24 hours; p = 0.005). On the fourth and fifth days, on which no drug was given, the chlorothiazide group excreted significantly less sodium than the control group (control group 59.1 mEq. per 24 hours, chlorothiazide group 44.9 mEq. per 24 hours; p = 0.001). Urine sodium excretion rose sharply from that of the control group during the first course of chlorothiazide therapy, as shown in figure 4 (first drug day: control group 77.4 mEq. per 24 hours, chlorothiazide group 129.1 mEq. per 24 hours: p = 0.007, second drug day: control group 51.0 mEq. per 24 hours, chlorothiazide group 107.4 mEq. per 24 hours; p = <0.001). The chloride excretion rose from 52.9 mEq. per 24 hours on the first (no drug) day to 129.1 mEq. per 24 hours on the first day of drug administration. As was also noted for the urine sodium excretion, the excretion rate of chloride fell below the control values on the rest days (days four and five) after the first course of chlorothiazide therapy. This decrease was statistically significant on the fifth day (fourth day: control group 50.5 mEq. per 24 hours, chlorothiazide group 33.3 mEq. per 24 hours; p = 0.02; fifth day: control group 47.7 mEq. per 24 hours, chlorothiazide group 25.1 mEq. per 24 hours; p = 0.005).

### Table 1.—Data in Postpartum Patients with Toxemia of Pregnancy Treated with Chlorothiazide

<table>
<thead>
<tr>
<th>Day of Treatment</th>
<th>1</th>
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<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<tbody>
<tr>
<td>Sodium excretion, mEq./24 hr.</td>
<td>24.6</td>
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<tr>
<td>Potassium excretion, mEq./24 hr.</td>
<td>10.0</td>
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<td>Chloride excretion, mEq./24 hr.</td>
<td>24.6</td>
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<tr>
<td>Serum sodium level, mEq/liter</td>
<td>24.6</td>
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<tr>
<td>Serum potassium level, mEq/liter</td>
<td>24.6</td>
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* No. = number of patients; S.D. = standard deviation.

### Table 2.—Data in Postpartum Patients with Toxemia of Pregnancy Not Treated with Chlorothiazide

<table>
<thead>
<tr>
<th>Day*</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
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<tr>
<td>Sodium excretion, mEq./24 hr.</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
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<td>Potassium excretion, mEq./24 hr.</td>
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<tr>
<td>Chloride excretion, mEq./24 hr.</td>
<td>10.0</td>
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<td>10.0</td>
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<tr>
<td>Serum sodium level, mEq/liter</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
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<tr>
<td>Serum potassium level, mEq/liter</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
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* No. = number of patients; S.D. = standard deviation.
During the second course of chlorothiazide therapy the chloride excretion rate was markedly reduced and was significantly increased from that of the control group only on the second, or seventh postpartum, day (control 35.8 mEq per 24 hours, chlorothiazide group 59.2 mEq per 24 hours: p=0.02). The statistical level of significance for this determination was established at p=0.05.

**Urine pH.**—The urine pH showed no consistent pattern of change. The lowest mean value was 6.11 and the highest 6.40. No significant changes from day to day in mean pH were detected. In fact, on each day certain patients' urine pH went up slightly while that of other patients went down slightly. The level of significance for this determination was set at p=0.01.

**Titratable Acidity.**—Urinary titratable acidity varied from 27.7 mEq per 24 hours to 30.3 mEq per 24 hours during the seven days of observation.

With the level of significance set at p=0.01, no significant differences from day to day in mean titratable acidity were noted. As in the pH determination, some patients had slight increases in titratable acidity and others slight decreases on the same day. No consistent pattern of titratable acidity change with drug administration could be made out.

**Urine Ammonia.**—Mean urine ammonia level varied from 46.9 mEq per 24 hours to 83.2 mEq per 24 hours during the seven days of observation. With the level of significance set at p=0.01, no significant differences from day to day were noted. On the second day (first drug day) and the fifth day (second day of the rest period), increases in urine ammonia levels which might be labeled "almost significant" occurred (first drug day p=0.02; second rest day p=0.03). Since these increases in urine ammonia levels were observed both when the drug was given (second day) and when the drug was withheld (fifth day), it is difficult to attach much importance to this finding. On neither of these days was enough change seen to be considered statistically significant, and, therefore, we ascribe the changes on the first drug day and the second rest day to chance.

**Serum Carbon Dioxide.**—The serum carbon dioxide content did not change significantly from day to day during the administration of chlorothiazide.
Mean values were 23.1, 23.3, and 24.3 mEq per liter respectively. The statistical level of significance for this determination was set at p=0.01.

**Serum Sodium.**—The mean serum sodium values for the chlorothiazide group and the control group are shown in Figure 5. It is seen that on the second day of drug administration essentially no change in serum sodium levels occurred. The mean value for the chlorothiazide group was 135.5 mEq per liter on the first drug day, changing to 135.3 mEq per liter on the second drug day (the third day of observation). The control group, however, experienced an increase on the corresponding day from 137.7 to 141.2 mEq per liter. The change in serum sodium levels exhibited by the control group constituted a significant difference, compared to the change exhibited by the chlorothiazide group (p=0.001). Thus, on the second day of drug administration the serum sodium levels in the drug group were not seen to have the same increase as in the control group. Similarly, on the second day of administration of chlorothiazide in the second course of therapy the chlorothiazide group did not show a corresponding elevation of serum sodium levels when compared with the control group (control 142.6 mEq per liter, chlorothiazide group 136.2 mEq per liter: p=0.001).

**Serum Potassium.**—The mean serum potassium level varied from a low of 4.38 to a high of 4.75 mEq per liter during the seven-day period of observation. No statistically significant variation in the serum potassium level was detected through the course of this study. The statistical level of significance for this determination was set at p=0.01.

**Serum Chloride.**—The serum chloride level varied from a low of 97.4 mEq per liter to a high of 101.1 mEq per liter. The statistical level of significance for this determination was set at p=0.01. No significant changes in the level of serum chloride were found.

**Patients’ Weight.**—Weight changes of the chlorothiazide patients were not impressive when compared with those of the control group (Fig. 6). The only day in which the drug group lost significantly more weight than the control group was on the second drug day (control 0.55 kg. [1% lb.], chlorothiazide group 1.25 kg. [3 lb.]: p=0.04). On the following day (the first rest day) the control group lost significantly more than the drug group (control 0.59 [1% lb.], chlorothiazide group 0.08 kg. [4 lb.]: p=0.025). While the average for all patients in the drug group was a net loss in weight each day, there actually were several cases in which patients gained weight while receiving chlorothiazide.

**Toxicity.**—In one patient who had bleeding during the third trimester, administration of the initial dose of chlorothiazide was followed by shock with increased pulse rate, decreased blood pressure, and pronounced diaphoresis. After blood transfusion, the patient improved; on subsequent delivery a partial abruption of the placenta was demonstrated. It is believed that her symptoms of shock could be considered secondary to the abruption of the placenta and not secondary to the administration of chlorothiazide. No definitely related instances of toxicity of any sort were noted during the course of the study.

**Comment**

Chlorothiazide, when administered in the postpartum period to patients with toxemia of pregnancy in doses of 500 mg twice a day, produced the following effects:

The urinary excretion of sodium, potassium, and chloride was markedly increased. Urine pH, titratable acidity, and ammonia levels were not changed significantly.
Serum chloride, potassium, and carbon dioxide levels were not significantly altered. The serum sodium level of these patients failed to show the control pattern of increase when chlorothiazide was given.

It is interesting that the chlorothiazide group excreted significantly less sodium in the urine than the control group during the fourth and fifth days of the study, on which no chlorothiazide was given. While one might have expected the urine sodium level to drop to the control level when chlorothiazide therapy was discontinued, it does seem surprising that the level of sodium excretion should actually drop below that of the control group. The mechanism of such a change is not clear, especially in view of the finding that the serum sodium level was not altered significantly during this period. One might postulate that, since the drug group lost more sodium early in the experimental period, it was lost in the process of converting the available sodium to a more excreted form.

One might postulate that when, sodium excretion was reduced, it was due to a change in the renal mechanism of reabsorption of sodium. The exact mechanism through which this increase reabsorption was accomplished remains to be determined. If chlorothiazide acts by blocking a normal renal mechanism for sodium reabsorption, the withdrawal of the drug could permit the "unblocking" of that mechanism with a subsequent decrease in urine sodium excretion. In the experimental group was compared with the control group, the urine potassium level was significantly increased during each day of drug administration.

It now seems well established that almost all of the potassium found in the urine results from an exchange with sodium in the distal convoluted tubule. Apparently that potassium which is filtered through the glomerulus is almost entirely reabsorbed in the proximal tubule. It follows, therefore, that any process which increases the sodium concentration in the distal tubule will enhance the excretion of potassium. In the distal tubule, both potassium and hydrogen ions within the tubule cell are exchanged for tubular sodium. Therefore, a process reducing the available hydrogen ion within the tubule cell would enhance potassium excretion, as occurs with carbonic anhydrase inhibitors. One can see that potassium excretion is affected by several varying processes; therefore, it is difficult to draw conclusions as to possible mechanisms of drug action from changes in the level of urine potassium.

The acidification of urine is dependent on the enzyme carbonic anhydrase. Its mechanism of action may be depicted as follows: In the renal

<table>
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<tr>
<th>BLOOD</th>
<th>TUBULE CELLS</th>
<th>TUBULAR LUMEN</th>
<th>TUBULE CELLS</th>
<th>BLOOD</th>
</tr>
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<tbody>
<tr>
<td>CO₂ + H₂O</td>
<td>Na₂HPO₄</td>
<td>Na⁺</td>
<td>HPO₄⁻</td>
<td>Na⁺</td>
</tr>
<tr>
<td>Carbonic Anhydrase Inhibitor</td>
<td>(Absence of H⁺)</td>
<td>Na₂HPO₄</td>
<td>Na⁺</td>
<td>HPO₄⁻</td>
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<td></td>
<td>Diuresis natriuresis decreased...</td>
<td>Acidification of urine</td>
<td>Acidification of urine</td>
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<td></td>
<td>titratable acidity</td>
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Fig. 7.—How inhibition of carbonic anhydrase decreases urine acidification.

because of the administration of chlorothiazide, an increased reabsorption of sodium occurred when the drug was withdrawn. The exact mechanism through which this increased reabsorption was accomplished remains to be determined. If chlorothiazide acts by blocking a normal renal mechanism for sodium reabsorption, the withdrawal of the drug could permit the "unblocking" of that mechanism with a subsequent decrease in urine sodium excretion. When the experimental group was compared with the control group, the urine potassium level was significantly increased during each day of drug administration.

The chloride ions were transported into the tubule cells carbon dioxide from internal metabolism is combined with water to form carbonic acid which dissociates into hydrogen ions and bicarbonate ions. The hydrogen ions then pass across the cell membrane into the lumen of the tubule where they replace basic ions (for example, sodium) in the urine. This mechanism results in a conservation of the fixed basic ions of the body and in their replacement by hydrogen ions in the urine (fig. 7).

The urine pH may be considered as a measure of carbonic anhydrase activity in the kidney. As urinary acidification occurs, the pH of the urine should decrease. Therefore, a carbonic anhydrase inhibitor should cause an increase in the urine pH, because it reduces urinary acidification by blocking the formation of carbonic acid from carbon dioxide.
in the tubule cell. In animal experiments no instance of the pH rising above 7.0 was observed when single doses of chlorothiazide were given. It has been reported that large doses of chlorothiazide in man cause an increase in urinary pH but as dosage is reduced the urine becomes more acid, because the chloruretic effect persists in the face of a decreased bicarbonate excreting power.

In some of our patients, the urine was alkaline. However, no statistically significant change in urine pH was demonstrated. This is an indication that, in the clinically effective doses used in this study, no measurable carbonic anhydrase inhibitory activity is detectable.

If chlorothiazide is an effective inhibitor of carbonic anhydrase activity, one would expect the titratable acidity to fall during the administration of the drug and to rise after its withdrawal, as is observed with classic carbonic anhydrase inhibitors. No such change was detected, indicating that carbonic anhydrase inhibition did not occur in our patients.

The measurement of urine ammonia level provides another indication of carbonic anhydrase activity. Glutamine is acted on in the renal tubule cell to give glutamic acid, plus ammonia, through the action of the enzyme glutaminase. The ammonia combines with hydrogen ions from the carbonic acid reaction to produce ammonium ions, which diffuse into the urine and replace basic cations (fig. 8). Of course, the urine ammonia determination may not be considered as specific a test for carbonic anhydrase function as those for pH and titratable acidity because, in addition to depending on available hydrogen ions, the urine ammonia level also depends on a functioning glutaminase and on urine pH. As the patient’s nitrogen intake is held relatively constant, inhibition of carbonic anhydrase by chlorothiazide should be reflected by decreased urine ammonia levels during periods of drug administration. No such decrease was observed. The observation that there was no significant change in urine ammonia levels may be interpreted best as an indication that no dysfunction of either the glutaminase or carbonic anhydrase systems occurred as a result of chlorothiazide therapy. This agrees with and lends support to the finding that there is no significant change in titratable acidity and pH and is strong evidence that no inhibition of carbonic anhydrase activity occurred in our patients.

The carbon dioxide content did not change significantly during the administration of chlorothiazide. The classic carbonic anhydrase inhibitor type of diuretic produces a state of metabolic acidosis after a day or two of administration. This may be explained on the basis of the electrolyte excretion pattern. Thus, sodium, potassium, and bicarbonate are excreted in large amounts, while almost no hydrogen ion is excreted. This means that there is a net loss of basic cations (sodium and potassium) with the production of hyponatremic, hypokalemic, metabolic acidosis. The serum carbon dioxide level is, therefore, markedly reduced.

The fact that no significant reduction in serum carbon dioxide content was observed indicates that
acidosis was not evident in our patients with the doses used in our study. This observation provides evidence that carbonic anhydrase inhibition does not explain the mechanism of action of chlorothiazide. Neither is this action similar to that of mercurial diuretics. These agents characteristically cause hypochloremic metabolic alkalosis with a compensatory increase in serum carbon dioxide level. In its effects on serum carbon dioxide, chlorothiazide differs from both of these groups of diuretics.

Some cardiac patients have been reported to exhibit signs and symptoms of low serum sodium levels after administration of chlorothiazide. This was observed in one of our patients with chronic renal disease, diagnosed as diabetic glomerulosclerosis after renal biopsy. No other patient exhibited an unusually low serum sodium level.

Comparison of Chlorothiazide with Carbonic Anhydrase Inhibitors.—When compared with carbonic anhydrase inhibitors, chlorothiazide exhibits striking differences, as shown in figure 9. Carbonic anhydrase inhibitors characteristically produce an increase in urine pH and a decrease in urine titratable acidity and ammonia level. These changes were not observed during the administration of chlorothiazide. Chlorothiazide is similar to carbonic anhydrase inhibitors in that both agents produce increased urinary excretion of sodium and potassium. While carbonic anhydrase inhibitors cause little change in chloride excretion, chlorothiazide results in a markedly increased excretion of chloride. Carbonic anhydrase inhibitors tend to lower serum sodium and potassium levels. This did not occur in the chlorothiazide group. However, a rise in serum sodium level which occurred in our untreated, control patients did not occur in the chlorothiazide group. Finally, carbonic anhydrase inhibitors cause metabolic acidosis, as determined by low serum carbon dioxide content; in our hands chlorothiazide caused no acid-base imbalance, and the serum carbon dioxide content was not significantly changed. At the doses used the carbonic anhydrase inhibitory properties of chlorothiazide demonstrable in vitro were not observed in vivo.

Animal experiments reported by Ford and others have indicated that the diuresis mechanism of chlorothiazide is different from that of the classic carbonic anhydrase inhibitor acetazolamide. Apparently, the carbonic anhydrase-inhibiting properties which are demonstrable in vitro are not responsible for the diuretic effect, for, unlike acetazolamide, chlorothiazide causes (in animals) the excretion of similar amounts of sodium and chloride. It does not result in acidosis and does not lose its effectiveness if given on successive days. In general, our results in women with toxemia of pregnancy confirm those found by Ford and Spurr in their animal experiments.

It is important to consider that the statements made about lack of carbonic anhydrase inhibition apply to the dosage schedule used in our study. Perhaps at a higher dosage level or with prolongation of administration carbonic anhydrase inhibition might manifest itself, causing a much different excretion of electrolytes.

Additional evidence for a different mechanism of action between chlorothiazide and carbonic anhydrase inhibitors is provided by the studies of Finnerty and associates on patients with toxemia of pregnancy. Their results, based on weight losses without electrolyte studies in clinic outpatients, showed a potentiation of acetazolamide diuresis when chlorothiazide was administered. The foregoing evidence, both from the literature and from our own studies, seems to indicate conclusively that chlorothiazide acts through some mechanism other than inhibition of the enzyme carbonic anhydrase.

Comparison of Chlorothiazide with Mercurial Diuretics.—The electrolyte excretion pattern of sodium and chloride is qualitatively similar with both chlorothiazide and mercurials (fig. 9). Chlorothiazide causes a marked excretion of potassium, which is not observed with mercurials. In the serum, mercurials tend to cause hypochloremia with associated metabolic alkalosis and elevated serum carbon dioxide level. These serum changes were not observed with chlorothiazide.

While the electrolyte excretion pattern of chlorothiazide in the moderate doses used for this study somewhat resembles that of mercurial diuretics, Laragh has cited several reasons to indicate that a different mechanism is involved. The activity of chlorothiazide is neither inhibited nor reversed by
dimercaprol. Conditions refractory to mercurials have responded to chlorothiazide, while those refractory to each drug given separately may respond to both drugs given simultaneously. The addition of a second drug for patients already receiving one agent often gives an increased diuresis. Steroid-induced edema is inhibited or reversed by chlorothiazide, while the mercurials are usually ineffective in such cases. Chlorothiazide is effective in hypo-chloremic alkalosis, while mercurials are not. The addition of ammonium chloride results in a potentiation of mercurial action, while chlorothiazide action is unaffected.

These facts, together with the differences in serum and urine electrolyte balances demonstrated in our study, provide good evidence that chlorothiazide has a different mechanism of action from mercurial diuretics.

**Possible Mechanism of Chlorothiazide.**—One explanation of the mechanism of chlorothiazide which accounts for the observations made in our study is that the drug in some way inhibits sodium reabsorption in the proximal renal tubule. This would result in the delivery of an increased amount of sodium into the distal renal tubule. The increased sodium level would provide more opportunity for potassium exchange in the distal tubule, leading to an increased excretion of potassium. Because not all of the extra sodium is replaced by potassium, the amount of sodium delivered into the urine would be increased also. Since it is believed that chloride ions follow sodium ions rather passively, with the blocking of sodium reabsorption in the proximal tubule, a larger amount of chloride would flow into the distal tubule. There is no known active mechanism affecting chloride ions in the distal tubule, and the increased amount of chloride is thought to pass into the urine in association with the increased sodium and potassium levels. Thus, increased excretion of sodium, potassium, and chloride could occur on the basis of a blocking of reabsorption of the single ion, sodium.

**Conclusions**

Chlorothiazide is a potent agent in promoting the excretion of sodium, potassium, and chloride from the body. When it was administered in a dosage of 500 mg. twice daily for two-day periods with a two-day rest period between each course of therapy, no serum electrolyte abnormalities were noted to occur. Despite the pronounced elevation of electrolyte excretion caused by chlorothiazide, patients with toxemia of pregnancy studied during the postpartum period did not lose weight at a significantly faster rate than patients not given the drug. Chlorothiazide is equally effective on readministration after a two-day rest period. No instances of toxicity or undesirable side-effects were noted.

This study was supported, in part, by a grant from the Pacific Northwest Obstetrical and Gynecological Society.

The chlorothiazide used in this study was supplied as Diuril through Dr. John R. Beam of Merck Sharp & Dohme, Division of Merck & Co., Inc., Philadelphia.

We wish to express our appreciation to Miss Gloria E. Bratkovl, Research Associate, Miss Janice Ekholst and Miss Donna Simkins for technical assistance, and Miss Ruth Portman for assistance in statistical analysis.

**References**

10. Personal communication to the authors.