Five Years' Experience with the Evaluation of Diuretic Agents

By Charles Swartz, M.D., Robert Seller, M.D., Morton Fuchs, M.D., Albert N. Brest, M.D., and John H. Moyer, M.D.

Prior to the advent of potent oral diuretics, parenteral mercurial drugs were the mainstays of diuretic therapy. In the search for orally effective diuretic agents, several events stand out. In 1949, Schwartz reported the diuretic effect of sulfanilamide in patients with congestive heart failure. In 1953, acetazolamide, a sulfonamide derivative and a potent carbonic anhydrase inhibitor, became available for clinical use. Then, in 1957, Novello and Sprague synthesized chlorothiazide, a benzothiadiazine compound. The availability of the thiazide drugs represented a major breakthrough in the search for potent oral diuretics. Subsequently, in the continuing search for the ideal diuretic agent, the pharmaceutical industry has made available a large number of additional drugs. There are at least nine analogues of the basic benzothiadiazine molecule now available or soon to be released for clinical use. Also introduced during recent years were chlorothalidone (a phthalimididine diuretic), quinethazone (a quinazolinone), and spironolactone (an aldosterone agent). With such a plethora of agents it is obviously important for the practicing physician to know which drugs are superior.

During the past 5 years, we have investigated the clinical pharmacology of the newer diuretic agents by a standardized methodology. The analysis of the data obtained in the evaluation of 12 different diuretic agents plus 2 combinations of drugs comprise the body of this report. The sensitivity of the assay method involved and its clinical application are also considered.

Methods and Materials

The investigation of each diuretic agent was divided into three parts: inpatient bioassay, outpatient acute weight loss study, and chronic outpatient administration.

Inpatient Bioassay

In a group of "normal" hospitalized patients, the response of the urinary electrolyte (sodium, potassium, chloride) excretion that occurs during the acute administration of the drug was studied. The subjects had a wide variety of primary diagnoses but were excluded from the study if any clinical or laboratory evidences of renal disease, cardiac decompensation, or edema were found. The patients ranged in age from 20 to 70 years. They were placed on a standard 50-mEq. sodium diet for at least 5 days prior to drug administration. It has been our experience that this technic produces a relatively constant sodium and potassium excretion. Daily 24-hour urinary excretion of sodium, potassium, chloride, and creatinine were measured for at least three control days. When urinary sodium excretion reached 90 per cent of dietary intake, the diuretic was administered in different dosages to different subjects. The 24-hour urinary electrolyte excretion was measured and then compared with the control values. By employing varying dosages, a dose-response curve for natriuresis was obtained and the maximum effective dose of a particular diuretic was determined.

Outpatient Acute Weight-Loss Study

The studies were performed in an outpatient diuretic study group that included 30 cardiac patients who were in chronic mild to moderate congestive heart failure. All patients were on maintenance digitalis therapy and previously required one or more weekly injections of mercurial diuretics in order to maintain an edema-free state. Prior to the study of an individual drug, all diuretic therapy was discontinued for at least 2 weeks. In order to determine the weight-loss potency of a diuretic, the patients were examined and weighed, and a diuretic was administered for 48 hours. Weights were recorded before breakfast

Department of Medicine, Hypertension-Reflux Unit, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania.

Supported in part by grants from the Hahnemann Cardiovascular Research Center (NIH H-6368) and the Heart Association of Southeastern Pennsylvania.
EVALUATION OF DIURETIC AGENTS

and after voiding. Upon completion of 2 days of diuretic therapy, the patients were re-examined and re-weighed. Changes in weights were considered to approximate fluid depletion. After 5 days of placebo therapy, a different dosage of the diuretic being investigated was administered in similar fashion. Thus a dose-response curve by weight loss (fluid depletion) was obtained and a maximum effective dose was determined.

**Chronic Outpatient Administration Study**

The clinic patients who participated in the acute weight-loss study were also utilized in this investigation. The drug being studied was administered for a 6-week period at its maximum effective dose (i.e., the dose above which no greater natriuresis or acute weight loss could be elicited). This study was designed to provide information about clinical toxicity and serum electrolyte changes that occur during long-term drug administration.

**Statistical Methods**

In order to compare drugs with different milligram potencies, only data obtained at the maximum effective dose of each drug were utilized. The maximum effective dose of an agent was defined as that dose above which no increase in natriuresis or acute weight loss could be obtained. The maximum effective doses of the drugs under consideration are listed in table 1. The bioassay data dealing with natriuresis, kaluresis, and acute weight loss were subjected to an analysis of variance. Since the number of patients in each sample was not the same, an average N was computed according to the method of Snedecor. The standard error of a group mean between individuals was computed by dividing the mean square by the N of that group of data. The means were then ranked and a Duncan multiple range test was applied with the use of the 95 per cent confidence limits.

The data obtained from the study of chronic administration of the drug to outpatients did not lend themselves to interdrug statistical analysis; therefore they will not be included in this report, but some impressions that were gained from this experience are described.

**Results**

The raw data are tabulated in tables 2, 3, and 4. The analysis of variance is recorded in tables 5, 6, and 7. In tables 8, 9, and 10, the means are ranked and subjected to multiple F tests at the 95-per cent confidence limits. For a detailed description of this method, the reader is referred to Duncan's original paper. In essence, the method summarizes multiple tests of significance between group means. If table 8 (the sodium bioassay data) is used as an example, 13 means must be analyzed for significant differences. Although the familiar t test could be applied to any two means in order to derive statistical significance, this would require 156 separate calculations. Instead, the pooled error (standard error) of a group mean was utilized. This was 14 mEq. for sodium, 8 mEq. for potassium, and 0.47 pound for acute weight loss.

As demonstrated in table 8, the means of 24-hour sodium excretion above control were ranked in ascending order and a line was then drawn connecting those means that could not be separated by chance alone. This resulted in three overlapping lines. Any two means not connected by the same black line were significantly different at the 95-per cent level. Again referring to table 8, it is seen that the mean sodium excretion (above control) for the combination of trichlormethiazide plus meralluride was 227.3 mEq. per 24 hours. This was not connected by a line to any other mean and was therefore significantly greater than any other regimens studied. At the opposite end of the scale, benzthiazide has a mean of 88.8 mEq. per 24 hours and was not significantly less than any means underlined by line c. However, the response of sodium excretion to benzthiazide was significantly less than the response to cyclothiazide and all the values

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Maximal Effective Dose of Diuretics Evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorothiazide</td>
<td>1,000 mg. b.i.d.</td>
</tr>
<tr>
<td>Chlorothalidone</td>
<td>200 mg. o.d.</td>
</tr>
<tr>
<td>Quinethazone</td>
<td>200 mg. o.d.</td>
</tr>
<tr>
<td>Benzthiazide</td>
<td>100 mg. b.i.d.</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>100 mg. b.i.d.</td>
</tr>
<tr>
<td>Hydroflumethiazide</td>
<td>100 mg. b.i.d.</td>
</tr>
<tr>
<td>Benzydroflumethiazide</td>
<td>10 mg. o.d.</td>
</tr>
<tr>
<td>Methyclothiazide</td>
<td>10 mg. o.d.</td>
</tr>
<tr>
<td>Cyclothiazide</td>
<td>4 mg. b.i.d.</td>
</tr>
<tr>
<td>Trichlormethiazide</td>
<td>4 mg. b.i.d.</td>
</tr>
<tr>
<td>Polythiazide</td>
<td>4 mg. b.i.d.</td>
</tr>
<tr>
<td>Meralluride</td>
<td>2 ml. i.m.</td>
</tr>
<tr>
<td>o.d.—once daily</td>
<td>b.i.d.—twice daily</td>
</tr>
<tr>
<td>i.m.—intramuscularly</td>
<td></td>
</tr>
</tbody>
</table>
to the right of cyclothiazide, since no single line connected any one of these to benzthia-
zide. Trichlormethiazide, with a mean of 109.3 mEq. per 24 hours was connected by line b to
all drugs up to the combination of hydrochlo-
rothiazide plus chlorthalidone and the combina-
tion of meralluride plus trichlormethiazide.
This indicated that trichlormethiazide pro-

---

**Table 2**

*Acute Bioassay of Sodium Excretion (mEq. per 24 Hours above Control)*

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>No. of Pts.</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>10</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>8</th>
<th>9</th>
<th>12</th>
<th>11</th>
<th>10</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzthiazide</td>
<td>115</td>
<td>40</td>
<td>57</td>
<td>124</td>
<td>96</td>
<td>81</td>
<td>81</td>
<td>108</td>
<td>148</td>
<td>145</td>
<td>57</td>
<td>81</td>
<td>259</td>
<td></td>
</tr>
<tr>
<td>Quinethazone</td>
<td>83</td>
<td>177</td>
<td>139</td>
<td>97</td>
<td>69</td>
<td>102</td>
<td>101</td>
<td>195</td>
<td>188</td>
<td>153</td>
<td>146</td>
<td>165</td>
<td>201</td>
<td></td>
</tr>
<tr>
<td>Benoxethiazide</td>
<td>72</td>
<td>85</td>
<td>113</td>
<td>117</td>
<td>127</td>
<td>103</td>
<td>55</td>
<td>194</td>
<td>126</td>
<td>51</td>
<td>170</td>
<td>206</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorothiazide</td>
<td>110</td>
<td>83</td>
<td>195</td>
<td>97</td>
<td>85</td>
<td>92</td>
<td>112</td>
<td>189</td>
<td>180</td>
<td>193</td>
<td>185</td>
<td>127</td>
<td>254</td>
<td></td>
</tr>
<tr>
<td>Metalluride</td>
<td>78</td>
<td>39</td>
<td>217</td>
<td>132</td>
<td>131</td>
<td>148</td>
<td>113</td>
<td>154</td>
<td>71</td>
<td>208</td>
<td>152</td>
<td>158</td>
<td>235</td>
<td></td>
</tr>
<tr>
<td>Hydrochlorothiazide and</td>
<td>75</td>
<td>117</td>
<td>59</td>
<td>85</td>
<td>104</td>
<td>79</td>
<td>120</td>
<td>62</td>
<td>117</td>
<td>189</td>
<td>134</td>
<td>292</td>
<td>228</td>
<td></td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>173</td>
<td>39</td>
<td>100</td>
<td>152</td>
<td>116</td>
<td>129</td>
<td>117</td>
<td>168</td>
<td>145</td>
<td>116</td>
<td>153</td>
<td>208</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polythiazide</td>
<td>72</td>
<td>62</td>
<td>96</td>
<td>120</td>
<td>132</td>
<td>157</td>
<td>140</td>
<td>174</td>
<td>163</td>
<td>198</td>
<td>153</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclothiazide</td>
<td>51</td>
<td>102</td>
<td>127</td>
<td>164</td>
<td>125</td>
<td>99</td>
<td>226</td>
<td>139</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorothiazide</td>
<td>60</td>
<td>90</td>
<td>170</td>
<td>170</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>88.8</td>
<td>98.3</td>
<td>99.2</td>
<td>104.0</td>
<td>111.6</td>
<td>125.0</td>
<td>127.5</td>
<td>151.7</td>
<td>151.8</td>
<td>152.0</td>
<td>169.7</td>
<td>227.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Table 3**

*Acute Bioassay of Potassium Excretion (mEq. per 24 Hours above Control)*

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>No. of Pts.</th>
<th>10</th>
<th>9</th>
<th>8</th>
<th>10</th>
<th>10</th>
<th>11</th>
<th>8</th>
<th>9</th>
<th>6</th>
<th>12</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzthiazide</td>
<td>28</td>
<td>-13</td>
<td>1</td>
<td>18</td>
<td>52</td>
<td>10</td>
<td>21</td>
<td>9</td>
<td>37</td>
<td>51</td>
<td>73</td>
<td>62</td>
</tr>
<tr>
<td>Metalluride</td>
<td>53</td>
<td>-9</td>
<td>84</td>
<td>23</td>
<td>19</td>
<td>56</td>
<td>56</td>
<td>22</td>
<td>6</td>
<td>56</td>
<td>69</td>
<td>70</td>
</tr>
<tr>
<td>Benoxethiazide</td>
<td>-11</td>
<td>63</td>
<td>30</td>
<td>37</td>
<td>17</td>
<td>65</td>
<td>16</td>
<td>18</td>
<td>53</td>
<td>6</td>
<td>27</td>
<td>60</td>
</tr>
<tr>
<td>Quinethazone</td>
<td>-10</td>
<td>8</td>
<td>21</td>
<td>27</td>
<td>17</td>
<td>9</td>
<td>25</td>
<td>77</td>
<td>20</td>
<td>66</td>
<td>46</td>
<td>77</td>
</tr>
<tr>
<td>Trichlorothiazide</td>
<td>8</td>
<td>-18</td>
<td>6</td>
<td>9</td>
<td>19</td>
<td>27</td>
<td>36</td>
<td>105</td>
<td>29</td>
<td>54</td>
<td>0</td>
<td>81</td>
</tr>
<tr>
<td>Methylchloothiazide</td>
<td>7</td>
<td>4</td>
<td>36</td>
<td>14</td>
<td>14</td>
<td>10</td>
<td>45</td>
<td>0</td>
<td>79</td>
<td>17</td>
<td>76</td>
<td>31</td>
</tr>
<tr>
<td>Hydrochlorothiazide and</td>
<td>12</td>
<td>18</td>
<td>49</td>
<td>29</td>
<td>53</td>
<td>69</td>
<td>13</td>
<td>43</td>
<td>47</td>
<td>59</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>5</td>
<td>12</td>
<td>-12</td>
<td>9</td>
<td>26</td>
<td>31</td>
<td>54</td>
<td>28</td>
<td>46</td>
<td>78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polythiazide</td>
<td>5</td>
<td>13</td>
<td>62</td>
<td>14</td>
<td>58</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclothiazide</td>
<td>-22</td>
<td>29</td>
<td>62</td>
<td>53</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorothiazide</td>
<td>34</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>7.5</td>
<td>8.7</td>
<td>21.6</td>
<td>22.0</td>
<td>30.8</td>
<td>35.3</td>
<td>37.4</td>
<td>37.8</td>
<td>41.4</td>
<td>41.7</td>
<td>47.4</td>
<td>50.3</td>
</tr>
</tbody>
</table>
duced significantly less natriuresis than either combination of drugs. On the other hand, trichlormethiazide was also connected by line c to benzthiazide; and this indicates that it cannot be considered to be significantly more potent than any of the drugs evaluated. As another example, polythiazide with a mean sodium excretion of 152 mEq. per 24 hours was connected by line a down to methyleloretazine and by line b to trichlormethiazide. It was also connected by line a to the combination of hydrochlorothiazide plus chlorothalidone. It can therefore be seen that polythiazide is a more potent natriuretic agent than chlorothiazide, benzhydroflumethiazide, quinethazone, or zenthiazide and a less potent natriuretic than the combination of meralluride plus trichlormethiazide. This technic of summarizing tests of significance is repeated for potassium in table 9 and acute weight loss in table 10.

The maximum effective dose of each of the various diuretics was administered daily to outpatients for 6-week intervals. Although the data obtained in these studies do not lend themselves to statistical comparisons, certain clinical observations can be made. All the oral drugs tested were capable of maintaining this group of patients clinically "dry" and free from signs and symptoms of congestive edema.

Table 4

<table>
<thead>
<tr>
<th>Methyleloretazine</th>
<th>Trichlormethiazide</th>
<th>Quinethazone</th>
<th>Benzthiazide</th>
<th>Hydroflumethiazide</th>
<th>Polythiazide</th>
<th>Cytothiazide</th>
<th>Hydrochlorothiazide</th>
<th>Meralluride</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Pts.</td>
<td>25</td>
<td>18</td>
<td>20</td>
<td>12</td>
<td>26</td>
<td>15</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>1.91</td>
<td>2.19</td>
<td>2.49</td>
<td>2.69</td>
<td>2.78</td>
<td>3.03</td>
<td>3.17</td>
<td>3.29</td>
</tr>
</tbody>
</table>

Circulation, Volume XXVIII, December 1963
Table 5

Analysis of Variance—Bioassay Data on Sodium

<table>
<thead>
<tr>
<th>Source of variation</th>
<th>Degrees of freedom</th>
<th>Sum of squares</th>
<th>Mean square</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>117</td>
<td>332,634</td>
<td></td>
</tr>
<tr>
<td>Groups</td>
<td>12</td>
<td>137,774</td>
<td>11,481</td>
</tr>
<tr>
<td>Individuals in groups</td>
<td>105</td>
<td>194,860</td>
<td>1,856</td>
</tr>
</tbody>
</table>

\[ F = 5.85 \]

\[ P < 0.01 \]

Standard error of group mean \( = \sqrt{1856 / 9.0} = 14.4 \) mEq.

Table 6

Analysis of Variance—Bioassay Data on Potassium

<table>
<thead>
<tr>
<th>Source of variation</th>
<th>Degrees of freedom</th>
<th>Sum of squares</th>
<th>Mean square</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>107</td>
<td>76,580</td>
<td></td>
</tr>
<tr>
<td>Groups</td>
<td>11</td>
<td>19,989</td>
<td>1,817</td>
</tr>
<tr>
<td>Individuals in groups</td>
<td>96</td>
<td>56,501</td>
<td>589</td>
</tr>
</tbody>
</table>

\[ F = 3.08 \]

\[ P < 0.01 \]

Standard error of group mean \( = \sqrt{589 / 8.9} = 8.1 \) mEq.

heart failure. No significant differences were noted in the frequency of side effects among the various drugs. Though electrolyte changes were inconstant, there was some tendency toward hypokalemic alkalosis. In addition, there was a trend toward elevation of the serum uric acid.

Discussion

Comparison of drug efficacy should be conducted preferably in a clinical setting that will duplicate the ordinary use of such agents. With regard to diuretics, this implies that comparisons should be made in edematous patients. Although this would seem to be an ideal method, it involves certain practical difficulties. In particular, the severity of the disease processes underlying the edema varies so greatly from patient to patient that this factor alone imposes sufficient spread, or variance, of data to obscure the effects caused by the differences among drugs.

If the drugs under study have a physiologic action on normal persons, as do diuretics, then the easiest way to minimize the variability of data is to perform the assay in persons in whom the factor of different degrees of illness has been removed, i.e., "normal" subjects. In this sense, the spread of data will be the minimum biologic variation present in any sample. A commonly employed study group of "normal" or homogeneous populations are healthy young medical students or laboratory technicians. Although this group provides definitive data with which to separate drug effects, they in no way represent the usual population for whom diuretics are intended. Therefore we have accepted a compromise between the unacceptable wide variance of data in patients with disease and the less meaningful narrow variance of data obtained in "normal" persons. In our studies we utilized a hospitalized population with wide age spread and varying states of health in whom evidence of renal disease or derangement in water or electrolyte metabolism was absent.

There has been some discussion in the recent literature concerning the type of diet to be employed during diuretic bioassay. A 50-mEq. sodium (3-gram salt) diet was employed in the present studies because it provides the minimum sodium content consistent with palatability. Higher salt intakes make it difficult to achieve stable control excretions of sodium and potassium. Although this low salt diet may stimulate minimal endogenous hyperaldosteronism in subjects formerly accustomed to higher sodium intake, it is consistent with the clinical situations in which diuretics are

*Circulation, Volume XXVIII, December 1963*
employed, i.e., dietary salt restriction and disease states frequently characterized by hyperaldosteronism. This technic has provided bioassay data with a standard error of the mean of 15 mEq. for sodium and 8 mEq. for potassium (for samples of size nine). This situation still represents considerable variability and therefore this method of bioassay can separate drugs into only a few large categories.

To confirm diuretic efficacy under conditions of clinical usage, acute weight loss was evaluated in a clinic population of 15 to 30 patients in mild to moderate congestive heart failure. The average sample size is 17, and the standard error of this sample was one-half pound. Unfortunately this technic also allows the drug to be categorized into only a few groups.

It is not surprising that there is no correlation between weight loss and natriuretic potency. This discrepancy occurs because acute weight reduction reflects acute water loss, and water loss does not necessarily parallel sodium loss. Thus the mercurial diuretics cause the greatest acute weight loss but are only moderate in natriuretic potency. Mercurial drugs tend to increase free water clearance and produce large amounts of dilute urine. Thus the mercurials are the diuretics of choice in the treatment of edema complicated by the presence of hyponatremia. On the contrary, the thiazides decrease free water clearance and produce a more concentrated urine than do the mercurials. It is this attribute of the thiazides that has commended their use in diabetes insipidus. Since the mercurials cause a greater water (weight) loss per milliequivalent of sodium excretion, assays based on weight loss alone show mercurials to be most potent whereas those studies based on sodium excretion alone show the thiazides and phthalimidine diuretics to be most potent.

In addition to the difficulties involved in choosing proper subjects for evaluation, the problems imposed by the biologic variation in response to a given drug, and the difficulties inherent in using different measures to determine potency (i.e., weight loss versus sodium excretion), there is still another limitation to be considered. The methods of study employed are applicable only to the comparative evaluation of diuretic agents that have a relatively rapid onset of action, i.e., marked increase in natriuresis within 24 hours of administration and decrease in body weight within 48 hours. Thus these technics do not lend themselves to the evaluation of such drugs as the aldosterone antagonists. These compounds do not elicit significant natriuresis in acute bioassay studies nor do they produce significant weight loss when administered for only two days to patients with uncomplicated congestive heart failure.

It is our opinion that no single agent has

Table 8

<table>
<thead>
<tr>
<th>Drug</th>
<th>Benzothiadiazide</th>
<th>Quinethazone</th>
<th>Thiazide methyldiethylsulphonate</th>
<th>Thiazide methyldiethylsulphonate</th>
<th>Meralloride</th>
<th>Methylphenothiazide</th>
<th>Hydrochlorothiazide</th>
<th>Cyclochadine</th>
<th>Chlorothalidone</th>
<th>Polythiazide</th>
<th>Hydrochlorothiazide and Chlorothalidone</th>
<th>Meralloride and Thiazide methyldiethylsulphonate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>88.8</td>
<td>98.3</td>
<td>99.2</td>
<td>104.0</td>
<td>109.3</td>
<td>111.6</td>
<td>125.0</td>
<td>127.5</td>
<td>151.7</td>
<td>151.8</td>
<td>152.0</td>
<td>169.7</td>
</tr>
</tbody>
</table>

(a)

Note: Any two means not underscored by the same line are significantly different.

Any two means underscored by the same line are not significantly different.
proved itself to be the ideal diuretic and that insufficient evidence exists to judge one agent superior to all others. In our studies all the oral diuretics evaluated proved to be potent agents capable of achieving and maintaining an edema-free state in patients with mild to moderate congestive heart failure. The fact that so many agents are commercially available reflects the continuing search for the ideal compound, which hopefully will provide maximal natriuresis and diuresis, minimal kaluresis, and few or no side reactions. The practicing physician may take comfort in the knowledge that he can choose from a large group of potent agents with proved clinical efficacy.

**Summary**

Twelve diuretics and 2 combinations of diuretics were evaluated by a standard methodology. Electrolyte excretion patterns were evaluated in "normal" hospitalized patients, and acute weight loss was evaluated in outpatients in congestive failure. The large standard errors of the means for natriuresis, kaluresis, and acute weight loss reflect the inherent biologic variation of such assays and permit separation of drugs into only a few overlapping categories of potency. The combination of a mercurial and a thiazide caused significantly greater sodium excretion than any other drug used alone. No single diuretic was significantly more potent than all others.
EVALUATION OF DIURETIC AGENTS

Acknowledgment

We are indebted to Dr. S. Free, Chief statistician, Research and Development Section, Smith, Kline and French Laboratories for his assistance in preparing the statistical analysis. We would also express our appreciation for the technical assistance rendered by Miss Ellen Lippmann and Miss Regina Burns.

References


William Withering

Withering testified himself to his excellent upbringing. As respects his education, it was not remarkable. He received a good grounding apparently in the classical languages from a neighboring clergyman, the Reverend Henry Wood of Ercall, and passed through the usual course of study in mathematics, geography and history, necessary for entrance into the University. He seems to have been a good student but showed little in the way of either precocity or brilliance of intellect. His father desired him to study medicine and his own inclinations were toward his father's profession. In 1762, at the age of twenty-one, he entered the University of Edinburg, then becoming celebrated for the excellence of its medical school.—LOUIS H. RODD, M.D. William Withering: The Introduction of Digitalis into Medical Practice. New York, Paul B. Hoeber, Inc., 1936, p. 4.
Five Years' Experience with the Evaluation of Diuretic Agents
CHARLES SWARTZ, ROBERT SELLER, MORTON FUCHS, ALBERT N. BREST
and JOHN H. MOYER

Circulation. 1963;28:1042-1049
doi: 10.1161/01.CIR.28.6.1042

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/28/6/1042

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/