The importance of potassium and various chlorides in the pathogenesis of several experimental cardiac necroses was first suggested by the observation that all the potassium salts (phosphates, sulfates, chloride, etc.) and all the chlorides (of magnesium, potassium, ammonium, etc.) tested were effective in preventing the myocardial lesions, while no other salts had such an effect.\(^1\)

In a previous paper\(^2\) we demonstrated that during the development of the "Electrolyte-Steroid-Cardiopathy with Necrosis" (ESCN) the decrease of myocardial potassium observed in the prenecrotic stage of the syndrome was not the only factor responsible for the production of the cardiac lesions.

The experiments described in this paper were performed in an attempt to clarify the role of potassium and the various chlorides in the pathogenesis and prevention of this experimental cardiac necrosis.

**Methods**

Thirteen groups of female Sprague-Dawley rats with a mean initial body weight of 197 g (185 to 205 g) were treated as described in tables 1 and 2.

In the first experiment (table 1), the electrolytes were given in a single dose of 3 mmole (except NH\(_4\)Cl, which was administered at the dose of 4.5 mmole) in 3 ml of water by stomach tube to animals which had been kept without food for 17 hours. The rats were killed 90 minutes after the gavage.

In the second experiment (table 2) a microcrystal suspension of 1.5 mg of 9a-fluorocortisol (F-COL)* in 0.2 ml of water was administered subcutaneously once daily. The electrolytes were given separately in 2 ml of water by stomach tube, twice daily (9 AM and 4 PM) in the following doses: Na\(_2\)HPO\(_4\) 1.5 mmole, KCl 2 mmole, MgCl\(_2\) 2 mmole, NH\(_4\)Cl 4 mmole, MgSO\(_4\) 2 mmole. The animals, maintained on Purina Laboratory Chow and tap water, were killed on the eighth day of treatment one hour after the last electrolyte gavage.

In both experiments just before the sacrifice, blood was taken under ether anesthesia from the abdominal aorta. The ventricles were first examined for gross lesions, then dried at 110°C until constant weight, and dissolved in concentrated nitric acid. After proper dilution, the potassium was measured with a Beckman DU flame spectrophotometer. The means of the determinations and the standard errors are listed in the tables: the values are expressed in mEq/100 g dry weight for the heart ventricles and in mEq/liter for the serum.

**Results**

As shown in table 1, KCl, MgCl\(_2\), K\(_2\)HPO\(_4\), NH\(_4\)Cl, and CaCl\(_2\) increased the potassium concentration in the myocardium, whereas MgSO\(_4\) was inactive in this respect. The rise of the heart potassium was always concomitant with hyperkalemia with the exception of group 3, which was treated with MgCl\(_2\).

Table 2 shows that the decrease of the cardiac potassium in the F-COL + Na\(_2\)HPO\(_4\) treated rats (group 2) was completely or partially corrected by the administration of KCl, MgCl\(_2\) or NH\(_4\)Cl (groups 3, 4, and 5). On the other hand, the hypokalemia elicited in group 2 was rectified by KCl (group 3), but not by MgCl\(_2\) or NH\(_4\)Cl (groups 4 and 5).

Magnesium sulfate caused a decrease of myocardial potassium in the normal animals (table 1), but it had no action in the rats treated with F-COL + Na\(_2\)HPO\(_4\) (table 2). The doses of F-COL and Na\(_2\)HPO\(_4\) were such that the animals of group 2 (table 2) would have developed cardiac necroses between the ninth and the twelfth day of treatment. For this reason no lesions were ob-
TABLE 1
Concentration of K in Serum and in Heart Ventricles after Gavage of Various Electrolytes*

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Serum</th>
<th>Heart</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(25)</td>
<td>(20)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>5.11 ± 0.08</td>
<td>33.05 ± 0.22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(10)</td>
<td>(20)</td>
</tr>
<tr>
<td>2</td>
<td>KCl</td>
<td>10.02 ± 0.14</td>
<td>37.11 ± 0.37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(10)</td>
<td>(18)</td>
</tr>
<tr>
<td>3</td>
<td>MgCl₂</td>
<td>4.64 ± 0.11</td>
<td>35.60 ± 0.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(7)</td>
<td>(18)</td>
</tr>
<tr>
<td>4</td>
<td>K₂HPO₄</td>
<td>11.31 ± 0.70</td>
<td>37.60 ± 0.73</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(7)</td>
<td>(9)</td>
</tr>
<tr>
<td>5</td>
<td>MgSO₄</td>
<td>4.72 ± 0.10</td>
<td>31.48 ± 0.29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(9)</td>
<td>(9)</td>
</tr>
<tr>
<td>6</td>
<td>NH₄Cl</td>
<td>7.03 ± 0.36</td>
<td>34.42 ± 0.37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(7)</td>
<td>(7)</td>
</tr>
<tr>
<td>7</td>
<td>CaCl₂</td>
<td>8.34 ± 0.31</td>
<td>36.88 ± 0.27</td>
</tr>
</tbody>
</table>

The values in italics are statistically significant in comparison with the controls (P < 0.025).
*/Parentheses enclose the number of animals used for each determination.

TABLE 2
Concentration of K in Serum in Heart Ventricles during Development of ESCN and One Hour after Gavage of Various Electrolytes*

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Serum</th>
<th>Heart</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(10)</td>
<td>(18)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>5.10 ± 0.20</td>
<td>33.36 ± 0.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(16)</td>
<td>(21)</td>
</tr>
<tr>
<td>2</td>
<td>F-COL + Na₂HPO₄</td>
<td>2.90 ± 0.18</td>
<td>30.37 ± 0.29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(10)</td>
<td>(10)</td>
</tr>
<tr>
<td>3</td>
<td>F-COL + Na₂HPO₄ + KCl</td>
<td>4.74 ± 0.10</td>
<td>33.51 ± 0.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(7)</td>
<td>(8)</td>
</tr>
<tr>
<td>4</td>
<td>F-COL + Na₂HPO₄ + MgCl₂</td>
<td>3.09 ± 0.11</td>
<td>31.34 ± 0.39</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(6)</td>
<td>(10)</td>
</tr>
<tr>
<td>5</td>
<td>F-COL + Na₂HPO₄ + NH₄Cl</td>
<td>3.17 ± 0.21</td>
<td>32.55 ± 0.36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(10)</td>
<td>(10)</td>
</tr>
<tr>
<td>6</td>
<td>F-COL + Na₂HPO₄ + MgSO₄</td>
<td>2.91 ± 0.11</td>
<td>30.63 ± 0.40</td>
</tr>
</tbody>
</table>

The values in italics are statistically significant in comparison with the controls (P < 0.025).
In the last column the values of groups 2 and 6 are statistically significant in comparison with the controls (group 1) and the values of groups 3, 4 and 5 are significant in comparison with those of groups 2 and 6.
*/Parentheses enclose the number of animals used for each determination.

Discussion
We already knew that KCl, MgCl₂ and all the other potassium salts and chlorides tested are effective in preventing the ESCN, whereas other electrolytes are not. In the experiments described in this paper it is shown that the administration of KCl, MgCl₂, K₂HPO₄, NH₄Cl or CaCl₂ produces an increase of the potassium content of the heart of normal animals (table 1) and that KCl, MgCl₂ and NH₄Cl completely or partially inhibit the cardiac potassium depletion produced by F-COL plus Na₂HPO₄ (table 2). On the other hand, MgSO₄ which is inactive against the ESCN, does not increase the myocardial potassium (tables 1 and 2).
These findings strongly suggest that the protective action of chlorides and potassium salts depends upon the inhibition of the cardiac potassium decrease which is produced by the action of F-COL plus Na₂HPO₄.

A low potassium concentration in the heart seems to be a condition necessary, but not sufficient, for the development of the ESCN. It is proven necessary because the correction of this abnormality inhibits the development of the syndrome; it is proven not sufficient because the same depletion is observed in animals treated with F-COL alone and which do not develop cardiac lesions.²

It must be underlined that the potassium depletion in the myocardium is no longer corrected 17 hours after the gavage of the protective salts.² In our experiments, prevention of the ESCN is obtained by administration of chlorides at 9 AM and at 4 PM; therefore, it is evident that an intermittent correction of K-depletion is sufficient to protect the heart against the cardiotoxic treatment.

It is interesting that other types of quite unrelated experimental necrotizing cardiopathies (for instance, those produced by papain, neomycin, polymyxin, and dihydrotachysterol plus sodium phosphate) and some experimental myopathies can also be prevented by the administration of various chlorides and potassium salts.³ 4 5 Further work will be necessary to examine the possibility of a single pathogenic mechanism common to all these syndromes.

Summary
It is known that the cardiac necroses produced by 9α-fluorocortisol (F-COL) plus Na₂HPO₄ are prevented by the administration of chlorides or potassium salts. In this paper it is shown that various chlorides not only significantly correct the depletion of myocardial potassium elicited by F-COL + Na₂HPO₄ but increase the potassium concentration in the heart of normal animals.

In view of these facts and of earlier experiments that have shown that F-COL alone diminishes cardiac potassium without producing necrosis, it is concluded that the depletion of potassium is necessary, but not sufficient, for the development of infarctoid cardiopathy and that the protective electrolytes (chlorides and potassium salts) act through the correction of this abnormality of the potassium level in the heart.

References
Chlorides, Potassium and Experimental Cardiac Necroses

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