Cardiac Necrosis Accompanying Potassium Deficiency and Administration of Corticosteroids

By Virginia L. Tucker, M.D., Hugh Hanna, M.D., Carolyn J. Kaiser, B.A., and Daniel C. Darrow, M.D.

Cardiac necrosis was first recognized in conjunction with potassium deficiency by Schrader et al.\(^1\) in 1937. No serum or tissue analysis was done in this study. Follis et al.\(^2\) in 1942 found low heart potassium in rats that developed cardiac necrosis while being fed diets deficient in potassium. The occurrence of cardiac lesions in rats secondary to administration of desoxyeorticosterone or low potassium diets was described by Miller and Darrow in 1942.\(^3\) Analysis of serum and skeletal muscle demonstrated the correlation of cardiac lesions with low muscle potassium and high muscle sodium. Subsequent work has indicated that these experimental procedures produce metabolic alkalosis as well as the changes in the muscle electrolytes.

Selye and associates\(^4-6\) observed cardiac necrosis in rats receiving injections of certain corticosteroids and large amounts of the sodium salt of certain anions by gavage. They suggested that the electrolytes sensitized the cardiac muscle to the toxic effects of the corticosteroid. This process was called "electrolyte steroid cardiac necrosis." The "activating" anions were specifically phosphate, sulfate or perchlorate. Lesions were increased by subjecting the animals to stress and prevented by previous exposure to less intense stress.\(^7\) Potassium and, to a less extent, magnesium protected the animals from the lesions by altering the response to "activating" sodium salts. Demonstration of low cardiac magnesium without alteration of heart potassium by Du Ruisseau and Mori\(^8\) from Selye's laboratory led them to believe that magnesium played a crucial role in the pathogenesis of cardiac lesions.

Nickerson et al.\(^9\) doubted the interpretation of the pathogenesis of the "electrolyte steroid cardiopathy" as described by Selye. From analysis of skeletal muscle and heart muscle, using the conditions outlined by Selye, they stated that the electrolyte steroid myocardial necrosis was due to "simple intracellular potassium deficiency and the roles of various procedures reported merely induced potassium depletion by various mechanisms." They felt the use of strong mineral corticoids and poorly absorbed anions which caused diarrhea when administered by gavage merely aggravated the depletion of body potassium.

Prioresechi\(^10\) recently reported data on rats that he felt refuted the role of potassium deficiency in the production of "electrolyte steroid cardiac necrosis." He was unable to produce lesions with desoxyeorticosterone or 2 alpha methyl 9 alpha fluorocortisol alone. Only when disodium phosphate was gavaged in addition to injection of 2 alpha methyl 9 alpha fluorocortisol were cardiac lesions found. Serum and heart muscle potassium were decreased in all animals receiving the fluorocortisol. In spite of low cardiac potassium, no cardiac necrosis was demonstrated when the corticoid was given alone or with magnesium or ammonium chloride. He thought the chloride anion protected against the lesions. Chloride salts of potassium, magnesium and ammonium are absorbed by the gastroin-
testinal tract and do not produce diarrhea enhancing potassium loss. It should be emphasized that in all groups the animals ate Lab Chow, a diet containing potassium, and drank tap water.

The present experiments were designed to measure the changes in body composition accompanying cardiac necrosis. Preliminary experiments with a diet practically devoid of sodium, potassium, and chloride invariably induced cardiac necrosis accompanied by metabolic alkalosis and depletion of muscle potassium when the rats drank a fluid containing sodium bicarbonate.

In order to provide either an acid or an alkaline load of sodium salts, rats were fed a diet practically devoid of sodium, potassium, and chloride and allowed to drink water freely containing 50 mM/liter of either NaH$_2$PO$_4$ or Na$_2$HPO$_4$. These loads of sodium phosphate were modified in other experiments by adding 20 mEq/liter of KCl or MgCl$_2$. In order to study the effects of corticosteroids, hydrocortisone or one of the mineral corticosteroids, desoxycorticosterone acetate or 2 alpha methyl 9 alpha fluorocortisol, was injected daily. On both the acid and alkaline phosphate without other salts, hydrocortisone and one of the mineral corticosteroids were given. Table 1 summarizes the design of our experiments.

**Methods**

Male albino rats weighing from 200 to 300 g were used in each experiment. The experimental groups were fed a low salt diet that is practically free of sodium, potassium and chloride. It has the following composition: 125 g Velka (commercial shortening), 250 g dextrin, 125 g casein (washed). Electrolyte solutions were given ad lib. in the drinking water. All corticoids were injected subcutaneously once daily.

The control animals consisted of twelve animals fed a balanced diet of Lab Chow and given tap water. Analysis of the heart was done in six of these animals. Serum and skeletal muscle were analyzed in all groups.

All animals in the experimental groups were

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**TABLE 1**

<table>
<thead>
<tr>
<th>Ratio</th>
<th>Added cation</th>
<th>Steroids, mg per day</th>
<th>HCort 2.5</th>
<th>DCA 2</th>
<th>DCA 0.5</th>
<th>MFOL 0.06</th>
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<tbody>
<tr>
<td>0/12</td>
<td>0</td>
<td>Lab Chow and water</td>
<td>0/6</td>
<td>0/6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0/18</td>
<td>K</td>
<td>Low salt and water</td>
<td>1/5</td>
<td>0/6</td>
<td>0/6</td>
<td>0/6</td>
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<tr>
<td>13/14</td>
<td>Na</td>
<td>Low salt and NaHPO$_4$, 50 mM per liter</td>
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<td>3/3</td>
<td>3/3</td>
<td>3/3</td>
</tr>
<tr>
<td>0/3</td>
<td>K</td>
<td>Mg, K</td>
<td>2/3</td>
<td>2/3</td>
<td>2/3</td>
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<tr>
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<td>Mg, K</td>
<td>3/3</td>
<td>3/3</td>
<td>3/3</td>
<td>3/3</td>
</tr>
<tr>
<td>2/3</td>
<td>Na</td>
<td>HGcort 4</td>
<td>3/3</td>
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</tbody>
</table>

HCort., DCA and MFOL indicate respectively hydrocortisone, desoxycorticosterone acetate and 2 alpha methyl 9 alpha fluorocortisol injected subcutaneously in the indicated mg dose. The drinking water has 20 mEq of the chloride indicated. The corticoid was injected subcutaneously in the indicated mg on each day. The ratio column shows two groups receiving hydrocortisone as well as other corticosteroids.
given distilled water or the monosodium or disodium phosphate, 50 meq/liter, in the drinking water. As indicated in the tables, 20 meq/liter of chloride salt of either potassium, magnesium, or sodium was added to the load of phosphate. Steroids were injected subcutaneously in the daily amounts shown in the table.

After 12 to 14 days all animals were anesthetized with ether and killed by exsanguination through the abdominal aorta. Sections of the heart and kidney were immediately fixed in neutral buffered formalin. The remaining portion of the heart was saved for tissue analysis. Sections of the heart and kidney were stained with hematoxylin-eosin. Skeletal muscle was excised from both lower extremities and the lumbar region of the back.

Water content was determined from the change of weight after drying at 100°C; fat content was estimated from the change of weight after 24 hours extraction with ether. The fat-free dry muscle was pulverized and 0.5 g aliquots of skeletal muscle and 0.1 g aliquots of heart muscle were ashed in platinum dishes at 575°C overnight. The ashed specimen of the heart was dissolved in 1 ml of 1.0 N HCl and diluted to a volume of 10 ml with distilled water. The ashed skeletal muscle samples were dissolved in 1 ml of 1.0 N HCl and diluted to a volume of 25 ml with distilled water. For chloride determination of skeletal muscle, 0.3 g of the pulverized, fat-free dry muscle was extracted with 4 ml of a phosphate buffer with a pH of 7.4 for 48 hours. Chloride was determined by the Cotlove chloridometer on a 1 ml aliquot of the water phase.

Serum analyses were obtained by the following methods: bicarbonate, manometric Van Slyke and Neill; chloride, Cotlove chloridometer; sodium and potassium, Coleman flame photometer; phosphorous, Fiske and Subbarow; magnesium, Titan Yellow. Suitable modifications of these methods were used for tissue analyses. The intracellular sodium was derived by the calculations of Yannet and Darrow.11

Results

The mean and standard deviations of serum, muscle and heart electrolytes are shown in tables 2 through 4. The rats on Lab Chow are considered normal while those receiving the low salt diet and distilled water illustrate the changes produced by the diet. In all other experiments, the rats were supplied with drinking fluid containing either monosodium or disodium phosphate. As is indicated in the tables, the effects of further modification of the drinking fluid by addition of the chloride salts of potassium, magnesium, and sodium were determined both with and without injections of hydrocortisone or a mineral corticoid. The effect of each change in experimental procedure is indicated by comparison with the group subjected to the same conditions excepting the one modification being investigated.

The data will be presented first so as to reveal the evidence of metabolic alkalosis and potassium deficiency. The characteristic changes of this condition are high bicarbonate associated with low chloride and potassium in serum and low potassium and high intracellular sodium in skeletal muscle.

The diet alone produced moderate reduction of serum and muscle potassium and slight increase of intracellular sodium. Although the average heart potassium decreases by 5.8 meq/100 g of fat-free solids, the scattering of values is too great to establish a certain decrease of heart potassium. Injection of hydrocortisone restores serum potassium concentration and muscle and heart composition. Injection of desoxycorticosterone does not produce definite metabolic alkalosis of the serum but muscle potassium becomes quite low and intracellular sodium moderately high.

The addition of either monosodium or disodium phosphate to the drinking water induces definite metabolic alkalosis associated with low muscle potassium and high intracellular sodium. The changes in heart potassium are essentially the same as those of the rats receiving low salt diet and no sodium salt of phosphate in the drinking fluid. The rats receiving hydrocortisone show essentially normal muscle composition. The rats receiving desoxycorticosterone show greater metabolic alkalosis — particularly those getting Na₂HPO₄ — and greater reduction of muscle potassium and increase of intracellular sodium.

When magnesium chloride is added to the sodium phosphate in the drinking water of the rats receiving hydrocortisone or desoxycorticosterone.
<table>
<thead>
<tr>
<th>Steroid Added</th>
<th>Cation</th>
<th>No.</th>
<th>Meq</th>
<th>K</th>
<th>Meq</th>
<th>Cl</th>
<th>Meq</th>
<th>P</th>
<th>Meq</th>
<th>HCO₃⁻</th>
<th>Meq</th>
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<tr>
<td>Low Salt, Water, No Steroid</td>
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<td>12</td>
<td>111</td>
<td>2.3</td>
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<td>2.3</td>
<td>2.6</td>
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<tr>
<td>Low Salt, Water, DCA 0.5 mg</td>
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<td>139</td>
<td>3.5</td>
<td>1.9</td>
<td>100</td>
<td>2.8</td>
<td>2.9</td>
<td>3.0</td>
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<tr>
<th>Steroid Added</th>
<th>Cation</th>
<th>No.</th>
<th>Meq</th>
<th>K</th>
<th>Meq</th>
<th>Cl</th>
<th>Meq</th>
<th>P</th>
<th>Meq</th>
<th>HCO₃⁻</th>
<th>Meq</th>
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</thead>
<tbody>
<tr>
<td>Low Salt, NaH₂PO₄ 50 mM/L</td>
<td>0</td>
<td>11</td>
<td>141</td>
<td>3.0</td>
<td>1.6</td>
<td>96</td>
<td>2.6</td>
<td>2.6</td>
<td></td>
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<tr>
<td>Low Salt, NaH₂PO₄ 50 mM/L</td>
<td>0</td>
<td>12</td>
<td>140</td>
<td>2.9</td>
<td>1.4</td>
<td>94</td>
<td>2.6</td>
<td>2.4</td>
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<table>
<thead>
<tr>
<th>Steroid Added</th>
<th>Cation</th>
<th>No.</th>
<th>Meq</th>
<th>K</th>
<th>Meq</th>
<th>Cl</th>
<th>Meq</th>
<th>P</th>
<th>Meq</th>
<th>HCO₃⁻</th>
<th>Meq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Salt, Water, DCA 0.5 mg</td>
<td>0</td>
<td>6</td>
<td>140</td>
<td>3.7</td>
<td>1.6</td>
<td>97</td>
<td>2.4</td>
<td>2.9</td>
<td>3.0</td>
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<thead>
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<th>Steroid Added</th>
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<th>Meq</th>
<th>K</th>
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<td>Low Salt, Water, DCA 0.5 mg</td>
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<td>2.6</td>
<td>2.4</td>
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</table>

**Note:** The table represents the concentrations per L of serum: mean and S.D. for various conditions and treatments.
The rats receiving 2 alpha methyl 9 alpha fluorocortisol undergo essentially the same changes in serum and muscle as those receiving desoxycorticosterone. The addition of both magnesium and potassium chloride to the diet of rats receiving 0.5 mg desoxycorticosterone practically restores serum and muscle composition of rats on disodium phosphate.}

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The same findings are shown when the fluorocortisol was used.

The tissue and serum changes developing in rats receiving methyl fluorocortisol are diminished when 4 mg of hydrocortisone is injected concomitantly.

Serum phosphorus is lower in all experimental groups than in the rats on the normal diet. All experimental groups have low muscle phosphorus; the decrease may be slightly greater in the group receiving disodium phosphate and hydrocortisone.

Muscle magnesium shows no certain changes. Heart magnesium is slightly greater in rats receiving MgCl₂ or KCl than in rats receiving phosphate alone.

Serum sodium is slightly low in the groups on the low salt diet and distilled water but is normal in the other experimental groups excepting those receiving 2 mg of desoxycorticosterone. These rats have slightly high serum sodium concentrations.

In table 4, increase of cardiac water and sodium is shown in the rats with changes in serum and muscle electrolytes. Heart magnesium shows considerable variations so that a significant difference between the control and experimental groups is not demonstrated. However, the heart magnesium is greater in rats receiving MgCl₂ or KCl or both salts.

Table 5 shows the relationship between the individual analyses and incidence of cardiac lesions. In rats with serum bicarbonate values greater than 32 mEq/liter, approximately 80% develop myocardial lesions. If the serum potassium falls below 3 mEq/liter and if the muscle potassium decreases below 34 mEq/100 g of fat-free solids, approximately 75% of the rats develop cardiac lesions. Almost 85% of rats with intracellular sodium above...
10 mEq/100 g of fat-free solids have cardiac lesions. When the heart potassium falls below 32 mEq/100 g of fat-free solids, there is about a 65% incidence of lesions.

Table 6 shows the correlation coefficients between certain serum values, skeletal muscle potassium and intracellular sodium and heart muscle values. Although correlation coefficients are statistically significant with the numbers involved in these experiments, when r is less than 0.5, the improved prediction over the average is not sufficiently great to warrant consideration of correlation coefficients below 0.5. Consequently, the correlations above 0.5 are the only ones considered.

A high negative correlation is noted between the serum chloride and the bicarbonate. As a result the rest of the data are analyzed on the basis of serum bicarbonate. One may conclude that the serum chloride shows the corresponding negative correlations with tissue composition. A significant positive correlation exists between the serum bicarbonate and intracellular sodium of skeletal muscle. The correlation of the bicarbonate with muscle and serum potassium is negative. There is a marginal positive correlation between serum potassium and heart potassium but a high positive correlation between the potassium of serum and that of skeletal muscle. A high negative correlation exists between the intracellular sodium and potassium of skeletal muscle. Other than the minimal correlation between the serum potassium and cardiac muscle potassium, none of the serum or muscle values could be related to the analysis of the heart muscle. There is a positive correlation between the heart water and heart sodium concentration. No correlation was manifest between the potassium and sodium or magnesium of the heart. One may conclude that for these experiments, high serum bicarbonate and low chloride are associated with low serum potassium and low muscle potassium and high intracellular sodium. These changes tend to occur together and are associated with high incidence of cardiac lesions.

The incidence of cardiac necrosis is compared with the presence or absence of electrolyte solution and steroid received in table 1. Although there are obvious differences in the intensity of the lesions, the data will be discussed in terms of unmistakable lesions or no lesions. This practice undoubtedly underestimates the incidence of lesions because only a small part of the heart was sectioned. Serial sections of the specimens were not examined. No cardiac lesions are present in the control rats or rats on electrolyte-free diets. The addition of hydrocortisone or desoxycorticosterone in the rats receiving low salt diet and distilled water did not alter the incidence of lesions except for one small lesion in the hydrocortisone group. Hydrocortisone appears
to reduce the incidence of lesions in both phosphate groups. Neither potassium nor magnesium is completely effective in prevention of the lesions in the Na3HPO4 groups. However, both are equally effective in the NaH2PO4 group. Rats receiving Na3HPO4 show well-developed lesions when 20 mEq/liter of sodium chloride is added to the drinking water. No lesions are present when sodium chloride is added to the NaH2PO4 animals.

Since all rats receiving 2 mg of desoxycorticosterone showed cardiac lesions, the incidence of lesions is modified only in those rats receiving 0.5 mg of this steroid per day. Even this lower dose of desoxycorticosterone is associated with lesions. Only when both potassium and magnesium are given with NaH2PO4 is any protection demonstrated. Potassium alone offers as good protection as the combined salts in the NaHPO4 group, but no protection in the Na3HPO4 group. The effect of magnesium alone has not been tested with 0.5 mg of desoxycorticosterone.

The heart necrosis and changes in tissue composition are essentially comparable when 0.05 mg of 2 alpha methyl 9 alpha fluorocortisol or 0.5 mg of desoxycorticosterone are injected. This is indicated by similar elevations of serum bicarbonate and intracellular muscle sodium and reduction of muscle potassium. Lesions are produced equally well in rats receiving either NaH2PO4 or Na3HPO4. Potassium partially protected the group on NaH2PO4. Magnesium provided little or no protection for either group. Since hydrocortisone appeared to protect some animals it was given in combination with 2 alpha methyl 9 alpha fluorocortisol. It did diminish the number of lesions in both phosphate groups.

Seldin et al.13 attributed the protection from tissue changes induced by cortisone to the potassium freed by increased catabolism. The probable magnitude of catabolic potassium may be estimated as follows:

The weight changes of five rats receiving the low salt diet and distilled water and 0.05 mg of desoxycorticosterone is compared to a similar group receiving 2.5 mg hydrocortisone. The average change of the first group was +35±14 g/kg and the change of the second group, -73±16. Attributing all the weight loss of the hydrocortisone group to catabolism of muscle indicates the freeing of about 0.7 mm of K/kg in 14 days. At the usual intake of water in the rats receiving KCl, about 40 mm of K/kg would be taken. It does not seem likely that this small amount of catabolic potassium would be as effective as the large amount ingested.
Discussion

The data clearly demonstrate that cardiac lesions are associated with the serum changes of metabolic alkalosis, decrease of potassium and increase of intracellular sodium of skeletal muscle and moderate decrease of heart potassium. These changes are comparable in rats receiving no steroid when either monosodium or disodium phosphate is added to the drinking water of rats on a diet practically devoid of sodium, potassium, and chloride. The changes are, however, somewhat greater in rats drinking water containing the basic phosphate. Addition of potassium chloride to either sodium salt of phosphate prevented serum and muscle changes when no steroid was given. Potassium chloride is essentially as effective when hydrocortisone is injected but almost no protection is provided when desoxycorticosterone or 2 alpha methyl 9 alpha fluoro-cortisol is given. Magnesium chloride certainly did not prevent the alterations of tissue composition in these experiments. Since the experimental conditions always tended to produce metabolic alkalosis, the data give no information on the occurrence of heart lesions accompanying deficits of potassium with acidosis such as occur in diarrhea and other conditions.

Cook and associates attributed the changes in muscle and serum to high urinary potassium resulting from metabolic alkalosis. Furthermore, deficit of potassium impairs the ability of the kidneys to form a concentrated and alkaline urine. Consequently, metabolic alkalosis produces potassium deficiency and potassium deficiency tends to produce metabolic alkalosis. Accordingly, the changes in tissue composition are critically dependent on the excretory loads provided by the experiments, and the alterations of renal response dependent on corticosteroids.

Koch et al. provide a theory explaining some of the changes in renal function in potassium deficiency. Briefly, filtered potassium is considered to be largely reabsorbed in the proximal tubules. In the distal tubules potassium is excreted by a process involving exchange of either hydrogen ions or potassium as sodium is transported from distal tubular to interstitial fluids. This is essentially the hypothesis of Berliner and co-workers. When potassium is deficient the tubular cells have a low potassium and high hydrogen ion concentration. Consequently, hydrogen ions rather than potassium tend to be exchanged for sodium transported by distal tubular cells. This process is augmented by large amounts of sodium reaching the distal tubules. Under these circumstances the increased excretion of hydrogen ions may induce metabolic alkalosis. On the other hand, when potassium of the body is abundantly available, exchange of potassium for reabsorbed sodium readily takes place. Consequently, the kidneys form an alkaline urine; metabolic alkalosis does not tend to develop and metabolic alkalosis is corrected by excretion of an alkaline urine.

The changes in muscle composition result largely from renal excretion of potassium. The process is augmented by high sodium intakes and certain corticosteroids. In this process about two-thirds of the deficit of potassium is replaced by sodium. Cooke and associates showed that hydrogen ions are liberated during recovery. This finding has been confirmed by Orloff and associates. Presumably intracellular hydrogen ions increase during development of metabolic alkalosis and protons are accepted by intracellular bases. Since muscle water does not decrease, increase of intracellular osmols other than sodium and potassium occurs. This would not be the case with simple exchange of potassium for hydrogen ions at the pH of cellular fluids. Eckel and colleagues found increase in dibasic amino acids which can act as cations and account for increase of cellular osmols. Irvine et al. have determined gradients of potassium and hydrogen ion concentration in potassium deficient rat muscle. Using a nontoxic weak acid, 5,5-dimethyl-2:4-oxazolidinedione (D.M.O.), which is readily diffusible in all fluid compartments of the body, they demonstrate a low intracellular pH in the face of
extracellular alkalosis and intracellular potassium deficiency. Accordingly, both hydrogen ions and basic amino acids increase in skeletal muscle in metabolic alkalosis as well as the changes found in the present study.

Desoxycorticosterone and other mineral corticoids tend to increase the renal exchange of potassium for reabsorbed sodium. Thus, “stress” and corticosteroids sensitize the animals to cardiac necrosis by altering the rate of excretion of potassium. The phosphate provides an anion that is excreted in the urine. Since sodium salts of phosphate increase the load of sodium reaching the distal tubules, the tendency to excrete potassium rises. It is striking that the dihydrogen sodium phosphate produced metabolic alkalosis. The seeming paradox of production of metabolic alkalosis by an acid salt is not surprising when one recalls that the observations of Cooke and colleagues showed a greater apparent retention of hydrogen ions in cells than the deficit of extracellular fluids.

The above explanation is essentially the one proposed by Nicerson and colleagues. In their experiments the load of phosphate was given in a single dose by gavage and produced watery stools that are known to involve losses of potassium. In our experiments phosphate was given throughout the day. None of the rats developed diarrhea and the stools looked normal. Prioreschi considered that Nicerson’s explanation of the production of cardiac necrosis was untenable. However, he failed to recognize the effect of phosphate in the renal excretion of potassium when given with a strong mineral corticoid, 2 alpha methyl 9 alpha fluorocortisol.

Holliday and colleagues demonstrated renal lesions characteristic of potassium deficiency in rats made potassium deficient by prolonged administration of electrolyte-free diets and phosphate loads. No observations were made concerning cardiac lesions. In our experiments it is unlikely that the phosphate exerted a specific influence in inducing lesions in the heart. Neither serum nor tissue phosphate was elevated. Preliminary experiments using NaHCO₃ in rats fed electrolyte-free diets invariably produced severe cardiac necrosis. All of these animals developed metabolic alkalosis and muscle changes characteristic of potassium deficiency. Since alkalosis seemed to be an important feature, phosphate salts were used in order to permit both an acid and alkaline excretory load. These preliminary observations produced lesions despite absence of a load of phosphate. The role of phosphate may be simply to provide an anion that is not absorbed completely in the proximal tubules. Consequently, sodium reaching distal tubules remains high. Sodium chloride did aggravate the lesions with Na₂HPO₄ but not with NaH₂PO₄.

As one would expect from this explanation, magnesium chloride provided little or no protection while potassium chloride did. In some of Selye’s experiments, the diet contained abundant potassium. It was for this reason that we investigated the effects of both potassium chloride and magnesium chloride in the drinking water. In our experiments, magnesium provided no striking protection from cardiac lesions or change in tissue composition. We are unable to confirm Selye’s contention that magnesium chloride provides protection against cardiac necrosis.

Low cardiac magnesium in rats developing cardiac lesions reported by Du Ruisseau and Mori was not confirmed by us. Although variation of cardiac magnesium does occur, the alterations were most consistent with the presence or absence of this salt in the drinking water. We were unable to correlate the magnesium values with heart lesions.

The association of cardiac necrosis with various abnormalities of serum and tissue composition (table 5) cannot be interpreted in the strict sense that a given abnormality of serum or tissue electrolyte inevitably leads to heart lesions. For example, the rats on the low salt diet and distilled water do not develop cardiac necrosis but heart potassium reaches the range found in rats with lesions. On the other hand, the muscle potassium of rats on the low salt diet and distilled water
does not decrease to the levels frequently accompanied by cardiac necrosis. The findings indicate that the level of potassium and intracellular sodium of skeletal muscle and the degree of metabolic alkalosis are the best measures of the severity of the changes in body composition associated with cardiac necrosis. The data illustrate some of the mechanisms producing the changes in body composition and some procedures preventing these changes. The data do not reveal how these changes induce cardiac necrosis though deficiency of potassium and metabolic alkalosis apparently play important roles.

Although kidney sections were taken and reviewed, the results are not reported since only very early lesions were seen and were not uniformly present. In accordance with the observations of Oliver et al., renal lesions are seldom detected before 10 to 14 days of potassium depletion. Had the rats been kept under test conditions for a longer period of time, renal lesions might have been more readily demonstrable.

Summary

Rats were given distilled water or subjected to a load of 50 mM of either NaH$_2$PO$_4$ or Na$_2$HPO$_4$ in drinking water while on a diet low in sodium, potassium, and chloride for 12 to 14 days. The drinking water was modified by addition of either 20 mM of potassium chloride, 20 mM of sodium chloride or 20 mEq of magnesium chloride/liter or a combination of the salts. The effects of hydrocortisone, desoxytocorticosterone and 2 alpha methyl 9 alpha fluoreocortisol were also tested. Serum, muscle, and heart were analyzed for electrolytes.

Both Na$_2$HPO$_4$ and Na$_2$HPO$_4$ induced metabolic alkalosis, decrease in muscle potassium, increase of intracellular sodium and slight decrease in heart potassium. Necrosis of heart muscle was associated with metabolic alkalosis, loss of muscle potassium and high intracellular sodium. The lesions and tissue changes are aggravated by the mineralocorticoids but not hydrocortisone. Adding potassium chloride but not magnesium chloride decreased or prevented the lesions and changes in tissue composition.

References

15. Cooke, R. E., Segar, W. E., Reed, C., Ettwiler, D. D., Vita, M., Brublow, S., and Darrow,


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doi: 10.1161/01.RES.13.5.420

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