Effects of Cortisone on Electrocardiographic Changes in Adrenal Insufficiency.* (19262)

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It is a commonly accepted finding in adrenal insufficiency, that functional defects in sodium and potassium metabolism result in a progressive depletion of body sodium reserves and an elevation of the plasma potassium level (1-3). Concomitantly with such alterations in electrolytes, there occur a number of disturbances in cardiac function; among those described have been bradycardia, various arrhythmias, heart block, and decreased cardiac output which eventuate in profound circulatory collapse and terminal cardiac failure(2,4-6). The abnormalities in cardiac function are reflected in electrocardiographic changes which are similar to those seen in other conditions where hyperkalemia is also a prominent finding(7-10). It has been reported(4,5,7) that the electrocardiographic abnormalities seen in adrenal insufficiency are reversed by the administration of sodium chloride or prevented by an adequate intake of sodium. Since cortisone has been found to be effective in correcting the renal functional defect on sodium excretion and in maintaining normal plasma levels of potassium and sodium in the adrenalectomized animal (3), it seemed reasonable that this steroid would have an effect in preventing the appearance of the abnormal electrocardiographic pattern seen in adrenal insufficiency.

With this in mind the experiments described below were done (1) to correlate the electrocardiographic changes in adrenal insufficiency with alterations in plasma levels of sodium and potassium and (2) to assess the effectiveness of cortisone in correcting these abnormalities.

Methods. All experiments were done on bilaterally adrenalectomized dogs. During the immediate postoperative period and in the interval between experiments the animals were maintained on desoxycorticosterone‡ and cortisone. Electrocardiograms and plasma values for sodium and potassium were obtained while the animals were on therapy; the hormone was then discontinued and the animals allowed to go into adrenal insufficiency. During this time serial electrocardiograms were taken and plasma sodium and potassium values determined. When the animals were in a state of severe insufficiency, the effects of intravenous injection of cortisone

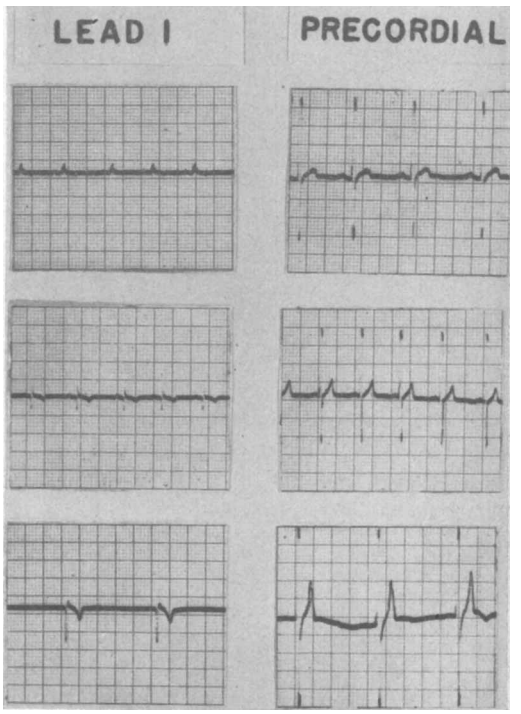

FIG. 1. Progressive EKG changes in adrenal insufficiency. The upper records were taken when plasma values for Na and K were normal. The lower records were taken when plasma sodium level was 129 mM/L and plasma potassium was 7.5 mM/L.

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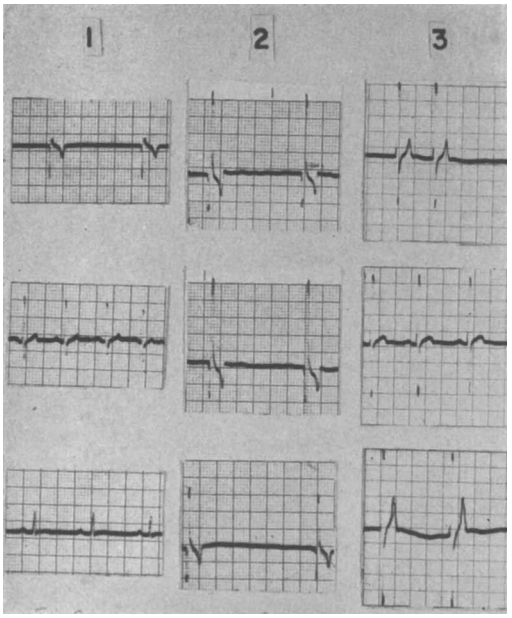

FIG. 2. Effects of (1) cortisone and NaCl on EKG record—lower record taken 3 days after hormone, (2) cortisone alone, (3) NaCl alone—lower record taken 20 hr after NaCl.

and/or sodium chloride on the abnormal electrocardiogram were determined.

Results. Fig. 1 shows electrocardiographic changes as the animals went into insufficiency. Following the withdrawal of hormonal therapy, the plasma sodium level fell and the potassium level rose. The upper record was taken while the animal was adequately maintained with cortisone; the lower 3 records were taken following the withdrawal of the steroid. From these it can be seen that the first alteration seen in the electrocardiographic pattern is an increase in the height and peaking of the T wave; this was frequently seen in the early stages of insufficiency and before any marked changes in sodium and potassium values were evident. With progression of severe insufficiency and marked alteration in plasma electrolyte concentration, there occurred widening of the T wave, bradycardia, disappearance of the P wave and various irregularities in cardiac rhythm.

Effects of sodium chloride. Fig. 2 (No. 3) shows the effects of intravenous administration of .9% NaCl on the precordial lead of the electrocardiogram during severe insufficiency. Within a short time following the administration of saline, the elevated potassium level is lowered and the abnormal tracing is restored toward normal. The beneficial effects of sodium chloride are, however, transient; if no more saline is administered, the animal slips again into exsiccation with a return of the abnormal serum electrolyte concentrations and electrocardiographic pattern within a few hours.

Effects of Cortisone. Although the administration of cortisone partially corrected the alterations in the electrocardiogram, this was true only if the steroid was given before the animals went into severe insufficiency and before marked alterations in plasma sodium and potassium levels had occurred. Cortisone had little or no immediate effect, however, on the electrocardiographic abnormalities if given at a time when the plasma sodium was already severely depressed and plasma potassium elevated. Fig. 2 (No. 2) shows the ineffectiveness of cortisone when given at such a time. However, if the plasma sodium level is restored by administration of sodium chloride and the animal is given cortisone at the same time, as shown in (No. 1) in Fig. 2, not only is the abnormal electrocardiogram restored toward normal within 2 hours but a more nearly normal pattern is maintained for 3 days without further therapy. Comparison of these results with those seen following NaCl shows that the effects of NaCl alone are transient; whereas, cortisone if given with saline will maintain the normal pattern for a longer period of time. Furthermore, it was found that adequate daily maintenance with cortisone, without benefit of added sodium, was effective in maintaining a normal electrocardiographic pattern and normal plasma sodium and potassium values.

Discussion and conclusions. The changes in the electrocardiogram in adrenal insufficiency were found to parallel the alterations in plasma sodium and potassium; these were prevented with adequate maintenance dosages of cortisone but not corrected completely by this steroid after marked abnormalities in the electrocardiogram had occurred. This is in keeping with the concept(2,6) that the defects in cardiac function, found in adrenal insufficiency are the result of losses of body sodium

and elevation of plasma potassium with a consequent imbalance of these ions. If this were the cause, it would be expected that abnormalities of the electrocardiogram would be reversed toward normal only by restoration or maintenance of adequate concentrations of sodium and potassium; such was found to be the case in our experiments.

It is currently taught that the difference in potential which exists across the cell membrane is dependent, in part, upon the difference in concentration of potassium between the intra- and extracellular compartments. Alterations in this concentration, as are seen in conditions of hyperkalemia, result in a variety of disturbances in neuro-muscular activity and, more particularly, myocardial function (9,11,12), which result in such clinically overt findings as described above.

In adrenal insufficiency it has been repeatedly observed(4,5,7), that sodium chloride administration in adequate amounts will lower plasma potassium concentration and restore the electrocardiographic abnormalities toward normal; from this it would appear that these disturbances are directly related to abnormalities in sodium and potassium metabolism and are reversible only if adequate concentrations of these ions are restored.

Since cortisone has been found to correct the renal functional defect on sodium excretion and to maintain normal plasma concentrations of sodium and potassium, it is conceivable that the disturbances in the electrocardiogram seen in adrenal insufficiency are effected by this steroid only in so far as it corrects the abnormalities in electrolyte metabolism.

That this is true under the conditions of these experiments is evident from the finding that cortisone is without effect when marked abnormalities in the plasma concentration of these ions has already occurred; but adequate maintenance with or administration of this steroid early in adrenal insufficiency, without added sodium, is effective in maintaining a normal electrocardiogram.

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Hepatic Fibrosis Produced by Chronic Ethionine Feeding.* (19263)

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Ethionine (α - amino- γ -ethylthiobutyric acid), an analogue of methionine, probably inhibits protein synthesis, since it has been shown to inhibit the incorporation of radioactive methionine into glycine(1). It produces within 24 to 48 hours a fatty infiltration of the liver in female but not in male rats(2,3).

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