Spring 1972

The Effects Of Adrenalectomy On The Rat Electrocardiogram

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THE EFFECTS OF ADRENALECTOMY ON THE RAT ELECTROCARDIOGRAM

Submitted in Partial Fulfillment of the Requirements for Graduation with Honors in the Department of Biology at Carroll College, Helena, Montana

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April 10, 1972
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I thank Dr. Palase for their patience and time spent in technical advice, proof reading and

pointing out errors in typing and manuscript problems. I wish to thank the rat yarers for sodium and potassium 100 basis on in making the Adrenal Cortex A. Materials 33

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I wish to acknowledge the typing assistance given by my cousin, Margaret Illustrin. Special thanks are due to my mother for her time and patience during the preparation of this final copy.

Thanks to all who have helped, but whose names I have neglected to mention.
ACKNOWLEDGEMENT

I received much help in preparing this paper. I would be remiss if I failed to give credit to my major contributors. I would especially like to thank Gene Danisich, the Head Technician of the Laboratory at St. John's Hospital. He devoted much time and effort in taking the EKG's needed, and sampling the rat serum for sodium and potassium concentrations. I would also like to thank Dr. Manion, Dr. Jankowski and Dr. Palese for their advice and time which they contributed in technical advice, proof reading, and general encouragement.

I would like to acknowledge the typing assistance given by my cousin Michele Sustarsic. Special thanks must necessarily be given to my mother for her time and patience in preparing this final copy.

Thanks to all who have helped, but whom I have neglected to mention.
THE EFFECTS OF ADRENALECTOMY ON THE RAT ELECTROCARDIOGRAM
INTRODUCTION

This thesis is intended to serve several functions. One purpose is to acquaint the writer with the biological systems that have been studied over the past four years. It is also intended to study the correlation between biological systems. This is necessary since each system is involved in many of the hormonal systems studied upon by endocrinology, statistics, physiology, and literature.

The paper is divided into two halves. The first half is concerned with research. This section includes the methods upon which the author has first presented with a presentation of endocrinology and in particular, the two-fold nature of the first half.

The second half of the paper deals with an endocrinologist designed to actually study a correlation between body functions. In this case, the study centered on the correlation between the adrenal glands and the effects of electrolytes on the heart.
INTRODUCTION

This thesis is intended to serve several functions. One purpose is to acquaint the writer with the biological systems that have been studied over the past four years. It is also intended to study the correlation between biological systems. This is necessary since much complexity is involved. A study of this nature, then, would bring to light many of the tangential courses studied such as chemistry, statistics, philosophy, and literature.

The paper itself proceeds in two halves. The first half is concerned with research. This gained its impetus when the author was first presented with a monograph on aldosterone. Interest in the importance of electrolytes and in cardiology developed the two-fold nature of the first half.

The second half of the paper deals with an experiment designed to actually study a correlation between body functions. In this case, the study centered on the correlation between the adrenal glands and the effects of electrolytes on the heart.
PART I. THE ADRENAL CORTEX

In 1849, Dr. Thomas Addison noted a significant and vital relationship between a manifest disease and the adrenal glands. This syndrome bears his name, Addison's disease. This particular syndrome is characterized by high serum potassium, low serum sodium, slow and irregular cardiac rhythm and physical fatigue. In most cases, it is attributed to an aldosterone deficiency, hypoaldosteronism.

However, it was not until the 1930's that the manifest abnormalities were associated with anatomical regions or chemical imbalance in the adrenal gland. Subsequent research found that the adrenal glands carried on several functions. To it were attributed fluid volume control, electrolyte concentration, and protein and carbohydrate metabolism. In other words, the adrenal glands function in homeostasis. They help the organism to adjust to environmental changes.

The mammalian adrenal gland is actually a dual structure embryonically and physically. The inner core or Medulla is derived from neural crest tissue. It is ectodermal in origin. The outer layer or cortex is mesodermal in origin.
And both layers, for the most part, are autonomous and have few related functions.

The medulla contains tissue similar to nerve tissue. The chief secretory products, epinephrine and norepinephrine, are very similar to neural cell secretions. Epinephrines act chiefly on effector cells and are generally stimulatory by nature. The effect of stimulation, however, may be either excitatory or inhibitory. In general, the epinephrines are excitatory in the vascular system. They cause constriction on peripheral vessels, thus, diverting blood to more needed areas. But, they stimulate myocardial tissue, increasing the force, amplitude, and frequency of cardiac muscle contraction.

Of the two, epinephrine and norepinephrine, the latter has a greater myocardial effect: somewhere between three and five times greater than the effect of epinephrine (23). The greater pressor activity of norepinephrine is due, for the most part, to the fact that norepinephrine increases diastolic and systolic pressure, ultimately resulting in a slower heart rate. Epinephrine acts only to increase systolic pressure. The chief effect is tachycardia.
In the skeletal musculature, the chief effect of the epinephrines is to increase the rate of phospho-rylase resynthesis and the removal of lactic acid. The effect of this is to prolong the muscular contractions. Thus, the medulla functions chiefly in stimulation and it is not necessarily vital to the organism.

Of more importance, however, is the adrenal cortex. This area of the adrenal gland is rather small, yet it is absolutely necessary for maintaining the organism in the environment. The cortex is divided into three zones or regions. The innermost region is the zona reticularis, containing lipoid droplets and pigment granules. The next layer or zona fasciculata is rather broad and contains polyhedral cells in a radial array. The outermost layer or zona glomerulosa consists of columnar cells containing lipophilic materials in the cytoplasm (26) (Fig. 1).

The secretions of the cortex are essentially steroid in nature. Several sex hormones are secreted. Among these are progesterone, estrogen, and androgen. Adrenocorticoids are also secreted. These include cortisone, corticosterone, cortisol, desoxycorticosterone,
Fig. 1. The adrenal cortex of the rat. (A) Cross section of the adrenal gland of the rat. C, cortex; M, medulla. (B) Section from (A). G, glomerulosa; F, fasciculata; R, reticularis; M, medulla.
dehydrocorticosterones and aldosterone (Fig. 2). According to chemical structure and physiological activity, the adrenocorticoids are divided into two groups. The glucocorticoids are characterized by an 11-oxygen group (oxytocorticoids). Their principal effect is adaption to stress. This involves protein and carbohydrate metabolism. They also have a synergistic activity with growth hormones, causing fat accumulations in the liver, plus ketosis. Some mineralocorticoid functions are also noted. For instance, in studies conducted by Edelman, it was shown that corticosterone had an effect similar to, but weaker than aldosterone (8). The chief glucocorticoids are: corticosterone, cortisone, cortisol and the dehydrocorticosterones.

The other group of adrenocorticoids, the mineralocorticoids, function chiefly in electrolyte regulation of the organism. Comprising this group are the desoxycorticosteroids and aldosterone. However, it should be noted that aldosterone, the chief mineralocorticoid, is actually an 11-oxygenocorticosteroid. It differs from the glucocorticoid in that it contains an aldehyde group at carbon 18. Unlike desoxycorticosterone, aldosterone has relatively good glucocorticoid activity. But *in vivo* aldosterone is secreted in such small amounts that its glucocorticoid activity is greatly diminished (23).
As has been mentioned, the adrenal corticoids are
produced by the adrenal cortex. Attention is shared
upon the activity of the corticoids and mineralocorticoids in some
cases where there is a deficiency in the production of
these hormones. Corticosterone and aldosterone are the main products of the
adrenal cortex.

Figure 2. The relationship among the secretions of the Adrenal Cortex. (26)
As has been mentioned, the adrenocorticoids are secreted by the adrenal cortex. Allusion to shared activity of the glucocorticoids and mineralocorticoid in some cases suggests that there is a common precursor for the adrenocorticoids. This is the case. Biochemical research has developed a general pathway for the production of the various adrenocorticoids: acetate and cholesterol, \( \Delta^5 \)-pregnenolone, progesterone, 11-desoxycorticosterone, corticosterone, 11-hydroxycorticosterone, and 11-oxycortico-osterone or aldosterone. Cortisol is produced in the facicular region and is the chief product of the region. Conversion into cortisol of pregnenolone and progesterone, the precursors, is mediated by enzyme activity, 17-hydroxylase. This activity is absent in the glomerular region. The chief precursors here are: progesterone, 11-desoxycorticosterone and corticosterone. These are converted into aldosterone, the chief secretory product of the region. This difference has influenced many into giving the glomerular region a distinct endocrine function, apart from the rest of the cortex. (2, 12, 19, 23).

The mineralocorticoids function in the regulation of electrolyte excretion. This function is localized in the ascending loop of Henle and especially the distal
convoluted tubules (5, 12). The mineralocorticoid activity of glucocorticoids functions similar to mineralocorticoid activity, but the glucocorticoids specifically affect fluid excretion rather than electrolyte excretion (23).

Aldosterone is the most potent mineralocorticoid. Both aldosterone and desoxycorticosterone are found in very small quantities. The difference in potency has led many to believe that desoxycorticosterone is only a precursor that has leaked into the system (8). Aldosterone is the principal agent in sodium transport across the renal tubules.

Injection of aldosterone into adrenalectomized rats has produced some interesting observations. The most noticeable was a prominent lag time between injection and the antinatriuretic or sodium retention effect. It has been theorized that the lag time was necessary for the production of a protein intermediate for renal tubular transport (8, 12). These intermediates or sites of aldosterone action are believed to be proteins located in the nuclei of the effector epithelial cells of the kidney. This induction of protein intermediates is believed to be at the
level of DNA transcription. This would involve an increase in the rate of RNA synthesis and thus the resultant lag time for the antenatriuretic effect to aldosterone.

With respect to its actual effect on sodium transport, the aldosterone induced protein is theorized to stimulate sodium transport by operation on the enzymatic machinery of the renal tubular system or by stimulation of the synthesis of a high energy intermediate - ATP (5, 8, 12). Other researchers have suggested that the stimulation of the sodium transport system is actually by vasopressin. But subsequent studies have shown that vasopressin and aldosterone-induced proteins have different sites of action, and, therefore, both stimulators exist and may function synergistically (8, 12). Later, induction of sodium transport was attributed to aldosterone-induced proteins by their relationship to oxidative metabolism. They required molecular oxygen and the precursors of citrate. Vasopressin was not dependent on these substances. Thus, aldosterone induced proteins are believed to be involved in ATP production from the relationship with oxidative metabolism (8).
The question now turns to the stimulating mechanisms for aldosterone release. Six functional and interrelated mechanisms have been suggested: hyponatremia, osmolality, sodium deprivation, adrenocorticothropic hormone, renin-angiotensin, and hyperkalemia.

The strongest and most persistent stimulus to aldosterone secretion in man is sodium depletion (19). Hyponatremia is believed to directly affect the steps of aldosterone biogenesis prior to corticosterone productions. This effect is mediated by theorized sodium receptors. However, it should be noted that only indirect evidence suggests these receptors. Yet the fact remains that low sodium results in the antinatriuretic effect induced in the kidneys by aldosterone (9).

However, it is suggested that serum sodium is secondary to the role of fluid volume. The importance of extracellular fluid volume is so great that many support the view that is is extracellular fluid volume and not serum sodium per se which mediates aldosterone secretion (1).

In one study (1), 18 humans were presented with a variety of tissue fluid changes to determine the importance of fluid volume. When extracellular fluid volume
was expanded, aldosterone secretion decreased. Several subjects were presented with an increased fluid volume and a decrease in serum sodium (hyponatremia). Sodium was excreted, potassium retained, and aldosterone secretion dropped. Administration of hypertonic saline to sodium-depleted subjects was used to increase extracellular fluid volume, concurrently decrease intracellular fluid volume, and maintain total body water constant. Aldosterone secretion dropped, sodium was excreted, and potassium retained. Expansion by water alone increased intracellular and extracellular water pari passu. Intracellular and extracellular tonicity equally decreased.

When expansion was induced by normal saline, intracellular tonicity and fluid volume and extracellular tonicity remained unchanged. Expansion produced by hypertonic saline while thirsting caused intracellular volume to decrease, tonicity to increase, and extracellular volume to expand.

Contraction of extracellular fluid volume increased aldosterone secretion. Subjects presented with a decreased fluid volume accompanied by increased serum sodium (hypernatremia) caused decreased sodium excretion,
increased potassium excretion, and increased aldosterone secretion. Contraction by simple dehydration was also compared with predominantly extracellular dehydration produced with diuretics. Serum sodium was unaffected by the diuretics. Total body water was shown to be much less effective than extracellular water in increasing aldosterone secretion. In contraction by simple dehydration, intracellular water decreased. While intracellular and extracellular tonicity increased, contraction produced by diuretics showed no changes in intracellular fluid or tonicity or in extracellular tonicity.

Related with these experiments is the effect of sodium deprivation. In this situation, aldosterone secretion increased until sodium was restored to the diet. However, serum sodium concentration did not change significantly with deprivation or with restoration of sodium. This indicated that water was gained or lost pari passu with sodium.

Thus, the experiment demonstrated that aldosterone secretion was not mediated by the volume of intracellular fluid or by the sodium concentration of the extracellular fluid (1). In all cases, aldosterone secretions follow reciprocal changes in extracellular fluid
volume. The particular monitoring device for fluid volume has been theorized to be stretch receptors in the right atrium. Changes in fluid volume would be detected as changes in the right atrial volume (9).

Related with sodium and extracellular fluid is the concept of osmolality. Whatever directly activates movement and distribution of sodium ions in extracellular fluids, thereby indirectly regulates extracellular tonicity and fluid volume (12). The suggestion also exists that tonicity may also stimulate aldosterone production itself. But evidence is only indirect since any tonic effect would be masked by volume effects.

Another important aldosterone stimulating mechanism is the renin-angiotensin system. Its function is closely related to that of the juxtaglomerular apparatus; the latter consists of a particular group of cells - the juxtaglomerular cells - which surround the afferent arterioles of the renal cortical glomeruli and a group of special staining cells situated in the distal convoluted tubule - the macula densa (12). Both of these bodies contain renin - a proteolytic enzyme. Renin, when secreted, reacts with angiotensinogen to give angiotensin I which reacts with converting enzymes to yield angiotensin II (12).
Angiotensin II is the most powerful vasopressor agent known. Its action is directly on the peripheral arterioles and it is a very powerful stimulus of aldosterone. Its primary biogenic activity lies in the conversion of cholesterol into \( \Delta^5 \) pregnenolone.

Renin secretion is directly mediated by volume depletion. The juxtaglomerular cells serve as pressure transducers, thereby monitoring fluid volume in a similar manner to the right atrium as noted earlier. Renin secretion is also mediated by intrarenal control. The macula densa are reported to serve as chemoreceptors monitoring serum sodium levels. Thus, the renin-angiotensin system maintains volume by increasing aldosterone production and sodium retention in volume deficiency or by decreasing aldosterone and sodium retention in volume excess (12) (Fig. 3).

Aldosterone secretion is also mediated by the brain. A hypothalmus - pituitary - ACTH system is involved (9). The importance of adrenocorticotropic hormone is not great since aldosterone release is not as dependent upon pituitary release as is cortisol. Rather, ACTH
The renin-angiotensin system controls body fluid volume by regulation of aldosterone secretion. Renin release is initiated by changes in perfusion pressure secondary to changes in circulating blood volume. These initiating signals can be modulated by circulating catecholamines and by macula densa feedback mechanisms. Renin inhibitors have been experimentally isolated. The major area for the conversion of angiotensin I to angiotensin II is in the pulmonary circulation where the highest concentration of converting enzyme (CE) is found. The half-life of circulating angiotensin II is determined by tissue and enzyme inactivation. The quantitative action of aldosterone on renal tubular sodium transport will depend on the state of tubular sensitivity to the hormone. Sodium retained by the kidneys then expands circulating blood volume. (12)
serves mainly in a permissive capacity. Control of ACTH release is monitored in the posterior diencephalon and the rostral midbrain. Secretion of ACTH is limited to the posterior - commissure - peneal area. ACTH stimulates aldosterone production by affecting biogenic activity in the conversion of cholesterol to a Δ5 - pregnenolone. But, it should be noted that ACTH is a more effective stimulus to corticosterone and cortisol production (2, 9, 12, 18).

The final mechanism regulating aldosterone secretion is the serum potassium concentration. Aldosterone regulation by potassium concentration can be done independently of the renin-angiotensin system. Increases in serum potassium are reflected in increased serum aldosterone. A drop in potassium tends to reduce aldosterone output. It appears that the adrenal cortex monitors the potassium flux across the cell membranes of the renal tubular system. With hyperkalemia, there will be an increased potassium influx in the glomerular region and this will result in an increase in aldosterone production and release (12). The specific action of potassium on
aldosterone biogenesis is thought to be prior to the production of corticosterone. And potassium does not potentiate the steps between corticosterone and aldosterone (2). When serum potassium is decreased, the glomerular influx is less and causes a decrease in aldosterone production. Thus, it becomes apparent that aldosterone secretion is increased by hyperkalemia to prevent lethal kalemic intoxication and decreased by hypokalemia to conserve potassium.

Approximately 85% of the serum aldosterone is inactivated in the liver. The major metabolite formed, tetrahydroaldosterone, conjugates with glucuronic acid and this water soluble compound is easily excreted in the urine.

With the adrenal glands, certain abnormalities are observed. Given the interdependence of sodium and potassium in cellular transport, these abnormalities are consequently reflected in reciprocal changes in these electrolytes.

Among the more prominent adrenal abnormalities, aldosteronism is most notable. Characteristics of this syndrome are high serum sodium and low serum potassium. Primary aldosteronism is caused by an aldosterone-producing
adenoma. Secondary aldosteronism may be caused by hypertension, 17-hydroxylase deficiency, nephrosis, cirrhosis, juxtaglomerular hyperplasia, and sodium-losing renal disease (12).

Another interesting adrenal disorder is hypoaldosteronism or aldosterone deficiency. In this situation, aldosterone secretion is deficient as in Addison's disease or absent as after adrenalectomy. Characteristics of this syndrome are low sodium or sodium wasting, high potassium, and resultant reduced blood pressure and irregular cardiac rhythm. High serum potassium may be detected by the abnormally high, peaked T waves of the electrocardiogram (19).
PART II. ELECTROLYTES AND CARDIAC TISSUE

In the course of study of living organisms, the most fascinating aspect is the interrelation of the various systems comprising the organism. Particular emphasis has been placed on the adrenal glands of the endocrine system. The importance of these glands in maintaining electrolyte balance, body fluid volume, and various other functions has been discussed. But, particular interest lies in the effect of electrolytes in maintaining homeostasis of the organism. The importance of this function is realized when considering the musculature, especially the heart.

Heart muscle is placed in the active state through changes in the electrolyte equilibrium. Sodium, potassium, calcium, and magnesium all demonstrate particular effects on cardiac excitation. Induced electrolyte changes result in specific electrical phenomena. These phenomena are associated with muscular contraction. Abnormalities in the electrolyte balance would be reflected in abnormal changes in contraction, resulting in various arrhythmias.

Cardiac activity can be monitored by the electrocardiograph, thus, arrhythmial changes would be reflected. Herein lies the interrelation among systems. If one system
is abnormal, this is reflected in some manner in the other system. A specific abnormality of the adrenal cortex could manifest itself in cardiac activity. This change could be reflected on the electrocardiogram. However, an understanding of the involvement of electrolytes in the contractile process is necessary before discussing specific electrolyte manifestations in cardiac activity.

The action potentials of cardiac tissue are manifest on the electrocardiogram and demonstrate the change in distribution of the electrolytes. The activities of the specific ions are due mainly to a potential difference between the inside and the outside of the cardiac cell of -90 millivolts. This phenomenon is attributed to the difference in permeabilities of sodium and potassium having the greater permeability.

In a recent review of cardiac contractility, Langer analyzed the electrolyte developments during the action state (15). His discussion focused first on the behavior of sodium. Sodium is characterized as having a transmembrane gradient with lower intercellular concentrations. Further, it is noted that this gradient is maintained by active sodium extrusion. An enzyme
system, ATPase, is actively stimulated by sodium at the inner membranal surface by increasing sodium concentrations. But, this activator is inhibited by calcium at the inner membrane. An exchange diffusion also exists and contributes to some extent in maintaining the sodium gradient.

During activation, depolarization depends on an increase in sodium permeability. This results in an increase in intracellular sodium, and this influx accounts for the sharp ascent stage of the action potential (AP). This particular stage is responsible for the QRS wave of the electrocardiogram (16). The return to normal of the sodium permeability accounts for the spike on the AP (Fig. 4).

Corresponding to this decrease in sodium permeability, is a decrease in sodium conductance. But, this process is slow and partially accounts for the plateau phase of the AP. Accompanying the intracellular sodium increase is an equivalent potassium efflux. This results in an increased potassium permeability and an increased potassium current. But, this phase is slow, thus adding to the plateau phase of the AP. Efflux potassium is collected in the transversely oriented tubules, (T system)
Fig. 4: Relation of membrane permeability for sodium (Na⁺) and potassium (K⁺) to the trans-membrane fluxes of these ions, the ventricular intracellular potential and the electrocardiogram. The permeabilities and fluxes are estimated from corresponding findings in nerve cells (2).
formed from sarcolemmal invaginations, as well as in the extracellular space around the cell. Increased extracellular potassium was noted to stimulate the ATPase pump only at the outer membrane, adding a further dimension to the sodium pump. Calcium also participates in the AP. It is thought that it contributes to depolarization aside from its crucial contribution in contractility. During the active state, a net sodium increment and a net potassium loss within the cytoplasm are noted. This is attributed to a sodium pump lag since time is required for pump activation. Finally, with relaxation, calcium is returned to the sarcotubular membrane, sodium permeability returns to normal, and potassium permeability reaches its greatest level. These changes are represented by phase 3 of the AP. This corresponds to the ST segment and T wave in the electrocardiogram. (15, 16, 24)

Langer also discussed potassium changes. As has been noted, potassium permeability declines with depolarization. And with repolarization permeability of the membrane to potassium increases. Repolarization is contingent upon the inactivation of the sodium conductance and the activation of the potassium conductance. The net
result is the plateau phase of the AP. This maintains the cell in a partially depolarized state. Along with this, there occurs an influx of positively charged ions, particularly calcium, and this accounts in some measure for the total cation influx.

Discussion then focused on calcium. Calcium is localized between the intracellular and extracellular compartments. The T system serves as a storage area and it is noted that the T tubules are continuous with the interstitial space. Calcium is important in muscular contraction. And maintenance of muscular contraction is due to the presence of free calcium ion in the intracellular medium. During the phase 2 mentioned, calcium influx is maximizing. The increased flux is associated with an increased rate of contraction. Here external calcium would have the effect of extending the duration of the plateau, since an apparent minimum amount of calcium is required for contraction. It should also be noted that calcium efflux lags calcium influx, leaving a net intracellular calcium increment. (This fact is particularly manifest during extended contractions. Sequestration of calcium by the sarcoplasmic reticulum results in relaxation. This is done actively by a calcium pump, also requiring ATP.)
It now becomes important to fully examine the interrelationship of sodium, potassium, and calcium. At activation, sodium influx increases. There is a net cellular loss of potassium. The greater the sodium increment, the greater the potassium loss. Following the initial phase, there is a slow phase of sodium conductance inactivation, and a slow increase, or even initial decrease in potassium conductance. During this period, a sharp uptake of calcium occurs. The intracellular increment of calcium from interstitial fluids sustains contraction. If perchance, extracellular calcium is low, the duration of the plateau would be further increased suggesting a minimum calcium level. This would have a retarding effect on the increase in potassium conductance. Sodium and calcium have a particular relationship at this stage. Calcium is assumed to operate in a closed cycle from membrane sites to contractile sites and back. It is further reported that sodium and calcium compete for sites on the sarcotubular membrane. During phase 2, there is a sodium shift to the inner part of the membrane due to a pump lag (15). This interiorly displaced sodium would be replaced by an influx of calcium from the storage site and the increment in calcium would increase the tension development. Thus,
it becomes apparent that electrolytes play an important role in cardiac contraction. This, of course, leads to a series of questions involving the effect of electrolyte imbalance on the action potential. But, perhaps, a better consideration would be from the viewpoint of the electrocardiogram.

Sodium abnormalities have their principal effect on the QRS complex and the ST interval of the electrocardiogram. Increased extracellular sodium decreases the duration of the QRS interval. This is associated with a steeper ascent of phase 0 of the AP. The duration of the ST interval is increased (24,25). This may be explained by an increased sodium gradient across the cell membrane causing a more rapid sodium influx. This would be related to a longer rate of diffusion of potassium from the cell.

In addition to these changes, decreases in the amplitude of the electrocardiogram have been reported (16). Decreased extracellular sodium has an opposite effect. QRS increases in width and the ST segment becomes shorter. Apparently, in this case, the transmembrane sodium gradient is decreased, causing a slower sodium influx, thus allowing the rate of potassium diffusion to restore the resting potential more rapidly (16). However, in most cases
reported, hyponatremia did not alter the electrophysiological properties of the cardiac fibers to present any noticeable electrocardiographic changes. In the hypernatremic condition, inverted T waves were reported. These, however, may be due to imbalances in other electrolytes, specifically potassium, rather than sodium.

Calcium, as has been mentioned, is associated with plateau duration. Increased serum calcium decreases the duration of the plateau. No effect is observed on the rapidly descending portion of the AP (15, 16, 24). The resulting electrocardiographic effects, then, are a short or absent ST segment, slight QRS expansion, and an absence of effect on the T wave. Overall, an expansion of the QT interval is observed. Hypocalcemia produces an extended plateau of the AP. On the electrocardiogram, a long ST segment is observed. The QRS complex decreases slightly. There is no effect on T wave duration. In one report, severe hypocalcemia was thought to alter T wave polarity (16, 24). Calcium, however, appears to act more in conjunction with potassium. Interventricular and atrioventricular conduction disturbances and the facilitation of ventricular fibrillation caused by an increased extracellular concentration of potassium
can be reversed or prevented by increasing the external concentration of calcium (24, 25). In hypokalemia, hypercalcemia will also reverse the effect of potassium. This relation is manifest in the electrocardiogram. For instance, in the case of hyperkalemia and hypocalcemia, a prolonged QT interval and a narrow, peaked T wave are produced. The QT interval is longer than in pure hyperkalemia and the T wave is more peaked and narrower than in pure hypocalcemia. The overall role of calcium in relation to potassium is one of enhancement.

Potassium produces its principal effect on the T wave. AP changes associated with high serum potassium or hyperkalemia are a decreased duration of the action potential, an increased velocity of phase 3, and a lowered resting membrane potential. The decreased duration and the increased velocity of phase 3 are accounted for by an increased potassium permeability (6, 16, 24). These effects would lower sodium influx, thus decreasing phase 0 of the AP.

Changes in the electrocardiogram begin with T wave changes. These are followed by a widening of QRS and a slowing of the heart rate. Acute hyperkalemia is
characterized by a decrease in the P wave amplitude and in the duration of the P-R interval. Death shortly ensues.

T wave changes are the primary effect of hyperkalemia. Due to the increased velocity of phase 3, the ST segment is shortened. This also accounts for narrowing and peaking of the T waves from the normal round and broad pattern (25). Wide QRS complexes occur at higher potassium concentrations. At this stage - 6.8 mEq/L., ventricular depolarization is so slow that the determination of the end of QRS is difficult. Repolarization begins before depolarization is completed (14).

At still higher potassium concentration - 8.0 mEq/L., the P wave amplitude broadens and finally disappears. The pacemaker may also displace from the sinoatrial to the atrioventricular node. Partial or complete AV block may occur at these values (16, 22, 25).

Hypokalemia is noted by a decrease in the T wave. In this case, an elevated potassium gradient exists. This increases the resting membrane potential. Duration of the AP is also prolonged due to phase 3. The slope of phase 2 is steeper and the slope of phase 3 proceeds with less velocity. At very low concentrations, the AP changes from
concave to convex (24) (Fig. 5). The resting membrane potential and the amplitude of the ventricular action potential increase. Hyperpolarization could possibly decrease the conduction velocity by increasing the interval between the resting membrane potential and the threshold potential (14, 24). Electrocardiographic changes that are associated with hypokalemia are: a depressed ST segment; a diphasic T wave; QRS of prolonged duration. This last characteristic is theorized to be due to a slowing in the conductance in the ventricular myocardium and/or in the peripheral conducting system (24). In advanced stages, there is a greater frequency of ectopic beats due to the fact that the membrane potential is closer to the firing threshold and spontaneous firings are more probable (22, 25). At this stage, second degree AV block and AV disassociation are characteristic.

The purpose of this paper, thus far, has been to acquaint the reader with electrolyte functions in two systems. A review of the adrenal glands has shown that they control sodium and potassium levels in the body. A study of electrolyte abnormalities has shown their inverse relationship. One particular case, that of hyponatremia,
Fig. 2. Diagram of the ventricular AP superimposed on the electrocardiogram for extracellular concentrations of potassium ($K_E$) of 4.0 (A), 3.0 (B), 2.0 (C), and 1.0 (D) mEq/L. The numbers on the left designate the trans-membrane potential in millivolts, as in Fig. 4. The KMP, the amplitude of the AP, and the overshoot in the control tracing (1) are the same as for the ventricular AP in the Fig. 1.4. Note the progressively increasing velocity of Phase 2, decreasing velocity of Phase 3, and increasing duration of the AP. Furthermore, note the progressive increase in the KMP (more negative), and the increasing amplitude of the AP. The electrocardiographic changes are described in the text.
coupled with hyperkalemia, bears particular note.

In the heart, the effect of the electrolytes was observed on the cellular level. The manifest changes transpiring during the action potential were discussed from the viewpoint of the electrocardiogram. Of the ions discussed, potassium had the most observable effect: T wave changes are rather prominent. Calcium, for the most part, may be disregarded since its manifest effects occur only in acute conditions. Thus, a correlation is suggested. Does adrenal control of potassium affect the electrocardiogram, especially the T wave? It was mentioned that Addison's disease, or adrenalectomy, were characterized by hyperkalemia and hyponatremia. And hyperkalemia caused narrowing and peaking of the T wave. Does a correlation exist? Or, will the body compensate and stifle any manifest changes?

Blood was centrifuged and the serum analyzed by flame photometry using lithium as the standard.

The second phase of the experiment was concerned with the administration of drugs. Dependent on treatment...
PART III. MATERIALS AND METHODS

A. Materials

Recording of the rat electrocardiogram initially presented problems. Several works were consulted (3, 11, 20, 21). However, in this experiment, a Sanborn Viso 100 electrocardiograph was used and proved to be more than satisfactory. Recording was then accomplished without further difficulty, using the following technique. 25-guage needles were used as electrodes. They had aluminum cuffs and these were fixed to the limb leads with aluminum foil. Four leads were placed in each limb of an anesthetized rat.

Leads I, II, and III were recorded. During the first three recordings, they were standardized at 2.0 cm. per two millivolts. The last recording was standardized at 1.0 cm. per millivolt. Tape speed was 50 mm. per second. Rats were anesthetized with anesthesia grade ether during recording. And recording was taken in the supine position (3, 11, 20).

Blood was centrifuged and the serum analyzed by flame photometer using lithium as the standard.

The second phase of the experiment was concerned with the administration of drugs. Desoxycorticosterone
Acetate (Δ4-pregnen-21-ol-3,20-one Acetate) of Sigma Chemicals was given to four adrenalectomized rats. Dosage was given as 10 mg. per rat (10). Suggestions were made that this be placed in a water-alcohol suspension. However, pure sesame seed oil proved to be the best vehicle.

B. Methods

The experiment proceeded in two phases. The first phase studied the effect of adrenalectomy on the electrocardiogram. Accompanying this, serum sodium and serum potassium levels were recorded. The second phase consisted in inducing an hyperkalemic condition in rats and studying the effects of desoxycorticosterone acetate.

Prior to any experimentation, 21 rats were given initial EKG's. There were 10 females and 11 males. Of these, there were 12 young and 9 old rats. The young rats were 3 months old, while the older rats were 6 months old. Weights were recorded. For young rats, the range was 197g to 293g with a mean value of 254±26g. The older rats ranged from 330g to 400g, with a mean weight of 351±21g. Following this initial recording, blood was taken by the method of cardiac puncture. Two methods of entry were studied. Entry was made directly over the heart from the left ventral side, through the 5th and 6th ribs.
Or entry was made to the left of the xiphoid process of the sternum at a small angle.

Andrenalectomy was performed on 11 rats (10, 13, 26). Of these, 6 were young rats and 5 were old. Sex of the rats was determined not to be a factor, so male and female rats were divided as evenly as possible between controls and adrenalectomized rats (13). Entry was through a single middorsal skin incision. The incision was 15mm. in length. This incision was moved to each side for entry through the lateral muscular wall. Small wounds were made in each side near the angle of the last rib with forceps. Once inside the body cavity, the kidneys were quickly located. The adrenal glands were observed imbedded in fat and connective tissue at the anterior poles of the kidneys. The connective tissue was grasped with forceps. Ligature of the suprarenal artery was made with forceps for several minutes. The glands were then excised. Care was taken in removal of the glands so as not to injure the adrenal capsule. Each gland was inspected prior to closure. Lateral musculature wounds were each closed with a 000 Chromic suture. The dorsal skin incision was closed with two 000 Chromic sutures. Of the remaining 10 animals, all were sham adrenalectomized following the above-mentioned technique, except no glands were removed.
EKG's were taken at 24 hours, 6 days, and 7 days. Following surgery, all rats were anesthetized prior to each recording. Weights were again taken. Following this, blood was taken by cardiac puncture.

The second phase of the experiment was conducted in two parts. Eight of the control animals from the previous phase were divided into 2 groups of four animals each. One group was given 7.40 mg. of Potassium Chloride, suspended in 4 ml. of water-sesame seed oil vehicle. This was injected intraperitoneally. The other group served as a control and was given only sesame oil by the same means of injection. In both groups, 4 ml. were administered.

Eight adrenalectomized rats were used in the second part. These were divided into 2 groups of 4 each. One group was injected with 10 mg. of desoxycorticosterone, suspended in one ml. of sesame oil. The other group served as control. In all cases, one ml. of vehicle was injected intraperitoneally.

Twenty-four hours after injection, all animals were given EKG's, weights recorded, and blood was taken.
PART IV. RESULTS, DISCUSSION, AND CONCLUSION

A. Results

The experiment just outlined produced a number of results and observations, some of which were outgrowths of the original experiment. In studying the effects of hyperkalemia on the EKG, it was necessary to take blood. Cardiac puncture was the method used. Some doubts were raised as to whether puncture would affect the EKG. Would sufficient injury be induced so as to negate any hyperkalemic induced changes? On a separate test animal, EKG's were taken prior to, 2 minutes after, 5 minutes after, and 24 hours after cardiac puncture (Fig. 6). The changes observed are: reversal of the P wave in lead I in all of the subsequent EKG's following puncture; amplitude changes in the T wave; ST segment deviations. All were determined to be of no significance. In leads II and III, 2 minutes and 5 minutes after puncture, large S waves are noted. However, no importance is attached to these increased amplitudes. Thus, no significant changes can be observed during puncture that would interfere with T wave observations.
Cardiac puncture of a test rat before, 2 minutes after, 5 minutes after, and 24 hours after.

Leads (a) Before  (b) 2 minutes after

I

II

III

(c) 5 minutes after  (d) 24 hours after

I

II

III
Blood taken by puncture from all animals was analyzed by a flame photometer for serum sodium and potassium. Serum sodium concentrations, prior to surgery, ranged from 137 to 149 mEq/L. The mean serum sodium is $140.5 \pm 1.9$ mEq/L. Serum potassium, prior to surgery, for all animals ranged from 3.7 to 5.5 mEq/L. The mean serum potassium is $4.5 \pm 0.5$ mEq/L. Use of Student's t-distribution, following a test for difference in means between control and experimental animals, revealed no significant changes at 95% probability.

After surgery, determination of serum electrolyte concentrations were taken on all animals. Among the 9 control animals, no significant serum sodium change is observed when each variate is paired with its normal value. This is again at 95% probability. This was done at 24 hours and 6 days after adrenalectomy. Comparing the difference of means of the controls with the adrenalectomized rats again revealed no significance.

Serum potassium of control animals, when paired with the normal values, showed no change at 95% probability.

On the other hand, serum potassium changes among adrenalectomized rats are significant. In one day, potassium concentrations had achieved a range of 5.2-6.8
with a mean of $5.9 \pm .7$ mEq/L. These values, when paired, varied significantly from the normal values. Comparing these with the values of the controls, using difference of means, also shows variation, indicating the success of adrenalectomy. In three cases, this effect is of particular importance. These particular animals, as was determined later, were only partially adrenalectomized. But, following surgery, they demonstrated noticeable potassium concentration increases. So, at 7 days, all the adrenalectomized rats continued to show significant potassium concentrations with a range of 6.2-7.3 mEq/L and a mean of $6.9\pm .6$ mEq/L.

Measurements were made of weight changes throughout the period of investigation. Employing the tests for paired variates and for differences of mean no significant variations were noted between control and adrenalectomized rats.

Electrolyte manifestations on the EKG were also observed. Measurements were taken of: rate; duration of the P-R, QT, the onset of P to peak of T intervals; amplitudes of P and T; and the variation of the ST segment. During the period of study, no rate changes were observable at 95% probability when control and adrenalectomized
rat rates were paired with their normal values. Rate ranged from 300 to 428 beats per minute with a mean of $350.4 \pm 35.8$. Comparison of control and adrenalectomized rats showed rate varied without significance. The difference in means was used in this determination.

Measurements of the P-R, QT, and onset of P to peak of T intervals also proved to vary randomly. The P-R interval ranged from .04-.06 seconds with a mean of .051 $\pm$ .005. QT ranged from .05-.08 seconds with a mean of .062 $\pm$ .009. And onset of P to peak of T ranged from .08 to .10 seconds with a mean of .091 $\pm$ .008. Control and adrenalectomized rats were all paired with their normal values. The differences of their means were also compared. And this was done with 95% probability using Student's t-distribution.

Amplitude variations between control and adrenalectomized rats also proved to vary randomly. The range and means of all animals are listed in Table I. Control and adrenalectomized rats were paired with their normal values and also the differences of their means were compared. These tests proved insignificant at 95% probability.
TABLE I

Ranges and means of amplitudes of the P wave and T wave on the three leads are listed. Accompanying these are the ranges and means on the three leads of variation of the ST segment. Values are measured in millivolts. (All values are absolute values and do not indicate the direction of the vectors).

<table>
<thead>
<tr>
<th>LEADS</th>
<th>P WAVE</th>
<th>T WAVE</th>
<th>ST SEGMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>Mean</td>
<td>Range</td>
</tr>
<tr>
<td>I</td>
<td>.02-.20</td>
<td>.097 ± .049</td>
<td>.00-.30</td>
</tr>
<tr>
<td>II</td>
<td>.05-.25</td>
<td>.133 ± .066</td>
<td>.00-.45</td>
</tr>
<tr>
<td>III</td>
<td>.04-.15</td>
<td>.079 ± .034</td>
<td>.00-.30</td>
</tr>
</tbody>
</table>
Accompanying amplitude changes, changes in the vectors or the direction of the waves and ST segments were measured. Here, no significance could be determined. Values in these cases were tested, using nonparametric statistics. A one-tailed test at 95% probability was employed in determining this insignificance.

Similar measurements were made following injections of KCl and desoxycorticosterone. In the cases of desoxycorticosterone injections, no significant quantitative changes were observed. The values of the above-mentioned ranges and means remained unchanged.

Injection of potassium chloride proved to be fatal in 3 of 4 cases. In the surviving case, notable amplitude and qualitative changes are noted (Fig. 7). Prior to injection, the electrolyte concentrations of the animals appear unchanged. P waves show inversion (negative vectors) in lead III 24 hours and 7 days after surgery. ST segment displacements in all leads except lead I (in the normal condition) are positive or neutral. In lead I, (in the normal condition) a depressed ST segment is observed. T waves are positive in all leads, except in lead II in the normal conditions. T wave amplitude in most cases is small.
FIGURE 7

A control rat 24 hours and 7 days after a sham adrenalectomy. This also shows the effect of injection of 740 mg of KCl. This was injected intraperitoneally.

Leads (a) Normal (b) 24 hours

Leads-(a) Normal (b) 24 hours after injection

(i) Normal

Na=142 mEq/L
K=5.1 mEq/L

Na=141 mEq/L
K=5.1 mEq/L

(c) 7 days

II

III

Na=142 mEq/L
K=5.1 mEq/L

(d) 24 hours after injection

II

III
In the EKG taken 24 hours after injection of KCl, notable changes have occurred. In lead I, P amplitude has increased. The ST segment is depressed. In lead II, a tent-shaped T wave has appeared. And in lead III rounded T waves of increased amplitude are noted. Indications of ST segments also begin to appear on this lead.

All changes observed are of a qualitative nature in adrenalectomized rats. In the normal condition, the ST segment appears, either elevated or depressed. No ST segment per se is observed. Rather, the T wave begins almost immediately after the S wave terminates. The T wave is either missing, diphasic, or of small amplitude (Fig. 6a, 7a, 8a, 9a, 10a, 11a).

Following adrenalectomy, several prominent changes are noted. Definite ST segments appear in leads II and III 24 hours after surgery (Fig. 8). This is approximately .01 seconds in duration. No change has appeared in the QT interval, as has been discussed above. The T wave is more rounded and symmetrical. In lead III, the T waves approximate a tent-shape. These changes reflect the changes observed with injected KCl. With the appearance of these waves in the adrenalectomized rats, it has frequently been observed that the ST segment appears on the
Typical EKG's of a rat showing the EKG's before adrenalectomy and 24 hours after adrenalectomy. Symmetrical T waves appear in leads II and III 24 hours after surgery. Note the potassium concentrations.

Leads (a) Normal            (b) 24 hours after adrenalectomy

I

II

III

\[ \text{Na}=138 \text{ mEq/L} \]
\[ \text{K}=4.7 \text{ mEq/L} \]

\[ \text{Na}=136 \text{ mEq/L} \]
\[ \text{K}=5.8 \text{ mEq/L} \]
isoelectric line. This is indicated in leads II and III of Fig 8b. However, this is not observed in all cases (Fig. 9b-c, 11b-c). Six or seven days after adrenalectomy no added changes are observed. The above-mentioned changes just appear to become more distinct (Fig. 10c, 11c)

In 3 cases, incomplete adrenalectomy is observed. The ST segments are elevated in the normal condition. Following adrenalectomy (Fig 9b), distinguishable ST segments and rounded T waves appear. However, by six days these changes begin to diminish and again approach normal. The ST segment became less distinct. T wave changes also diminished. Comparison of lead III 24 hours and 6 days shows a definite change toward normal - the diphasic condition (Fig 9b-c). Administration of desoxycorticosterone appears to have hastened the reappearance of the normal condition (Fig. 9d). Subsequent autopsy has revealed small hypertrophied fragments of adrenal glands. These were of diminutive size in comparison to the normal gland, but apparently they began functioning within a week. This is also mentioned in the literature (13).

In the second half of the experiments, oil and desoxycorticosterone were administered to adrenalectomized rats. In all cases, notable peaking of the T wave is
EKG's of a rat with incomplete bilateral adrenalectomy. After 6 days, the initial hyperkalemic effect is disappearing. This is also indicated by the apparent leveling off of the potassium concentration. Administration of desoxycorticosterone acetate hastens the return to normal.

Leads (a) Normal (b) 2½ hour adrenalectomy

I

II

III

\[Na=140 \text{ mEq/L}\]
\[K=4.8 \text{ mEq/L}\]

Na=140 mEq/L
K=5.7 mEq/L

(c) 6 day adrenalectomy (d) desoxycorticosterone

I

II

III

\[Na=141 \text{ mEq/L}\]
\[K=5.2 \text{ mEq/L}\]
The expected effects of adrenalectomy are demonstrated here. Serum potassium continues to rise. ST segments become apparent in most leads. Injection of oil produces no change.

Leads (a) Normal

(b) 24 hour adrenalectomy

III

$Na = 141 \text{ mEq/L}$
$K = 4.7 \text{ mEq/L}$

$Na = 135 \text{ mEq/L}$
$K = 6.5 \text{ mEq/L}$

(c) 6 day adrenalectomy

(d) with oil

III

$Na = 147 \text{ mEq/L}$
$K = 6.8 \text{ mEq/L}$
A typical adrenalectomized rat is depicted. T wave changes and the appearance of ST segments should be observed. The rat is then given desoxycorticosterone acetate. Mild changes are observed.

Leads (a) Normal (b) 24 hour adrenalectomy

I

II

III

Na=144.1mEq/L
K=2.8 mEq/L

Na=142mEq/L
K=5.4 mEq/L

(c) 6 day adrenalectomy (d) desoxycorticosterone

I

II

III

Na=134 mEq/L
K=7.0 mEq/L
present prior to injection (Fig. 8a-b-c, 9a-b-c). Administration of oil appears to have no effect on the shape of the T wave (Fig 10).

Comparison of the three leads before desoxycorticosterone injection, with those following injection, reveals several things: T wave amplitude and shape remain unchanged in lead I; in lead II, the T wave is definitely diphasic and almost absent; lead III shows a decrease in amplitude of the T wave; the ST segment becomes depressed in lead II and less elevated in lead III. ST segment duration appears to diminish (Fig 11).
B. Discussion

In these experiments, several observations can be made in regard to cardiac puncture, electrolyte concentration, and the electrocardiogram.

Cardiac puncture appears to be more fatal to older rats in this group. All but one of the rats, dying from puncture, was old. Autopsy revealed, in some cases, unsealed puncture wounds in the atrial wall. Puncture was, in most cases, through the rib cage, increasing the possibility of piercing the atrium, but this method was also used on the younger rats. This leads to the supposition that the atrial wall in the older rats failed to seal after puncture. This may suggest further investigation of the effects of age in relation to ischemia or heart injury.

The rats of this sample population also demonstrated depressed sodium and potassium concentration. According to the Handbook of Biological Data, the normal range of values for rat sodium levels should be 143-156 mEq/L and 5.4-6.4 mEq/L for potassium levels. Comparing these values with the sample population, leads one to possibly conclude that the rats have reestablished a
sodium/potassium equilibrium less than normal. This would be reflected by an absent or diphasic T wave. The low, diffuse T wave is a characteristic of hypokalemia. Possibly these manifestations in the EKG reflect a hypokalemic situation, even with accompanying hyponatremia. However, these characteristics could also be caused by a very long and diffuse repolarization phenomena that is theorized in small animals (19).

Another electrolyte phenomena observed, was the hypertrophy of adrenal fragments into functional organs. Three animals demonstrated this. Hyperkalemia was observed to progress in the animals, but at a slower rate. (This cannot be verified, since the sample was too small to conduct any meaningful statistics). However, they survived. Adrenalectomy was assumed to be complete since the glands were examined immediately after surgery. It could be theorized from these facts that the hyperkalemia occurred while the gland fragments grew until they could assume function of electrolyte balance or microscopic, secondary adrenal bodies were present as mentioned by Gaunt. In any case, a lag time is suggested, leading to the question as to the quantity of gland required to sustain an adrenalectomized animal.
No effects were observed in the rate, duration, or amplitude. But the values obtained were taken rather early. This was indicated by several facts: (1) The increased potassium concentration after the first day was not sufficiently high enough to elicit high peaked T waves. However, T waves with notable changes in shape were present. (2) P-R interval changes occur at potassium concentrations of 8.0 mEq/L in man. In man, sodium ranges between 136 and 145 mEq/L, and potassium has a range of 3.5 to 5.0 mEq/L. So, it should be evident, from the values given above for the rat, that the beginning of P-R interval changes in rats might occur at much higher levels; (3) In most cases, the P wave is present and has good amplitude. If potassium levels were high enough, the P wave would have had a wide duration or would have disappeared completely. If values were obtained continuously and for longer periods of time, then there is a good chance that the expected duration changes would have occurred. Thus, most of the experiment was involved with the early changes in potassium concentrations and was consequently involved with the early obscure changes associated with potassium intoxication.
The appearance of the T wave does corroborate the reports that the T wave is the primary indicator of potassium imbalance. No significant changes could be found in the QRS complex. As mentioned, no changes could be noted in regard to P-R, QT, or onset of P to peak of T. However, the appearance of a definite ST segment bears note. Study of normal rat EKG's led to the theory that rat repolarization was to diffuse and the T wave inscription so discrete that the ST segment would not appear. Mention has been made of the insignificance of heart rate. These facts are important in light of the appearance of an ST segment. Without decrease of heart rate, an ST segment appears. One would expect ST segment appearance with slower heart rate when repolarization is so diffuse. The lower potassium concentration now has new importance. Maybe the increase in potassium is only bringing the serum potassium concentrations to a normal level, thus, an appearance of an ST segment. If experimentation had continued, possibly the ST segment would have disappeared as would be expected in acute hyperkalemic situations. The low serum potassium would also help to explain the absence of symmetrically peaked T waves when potassium increased.
Peaking is an early manifestation and only the normal round wave appears. This seems to add further to the belief that the sodium/potassium balance is at a lower level of equilibrium.

The shape of the T wave and lack of peaking, however, may present difficulty. One could mention the case of KCl injection and the appearance of only rounded T waves (Fig. 7). Then one could say that this is the expected acute hyperkalemic condition. But consideration should be given to the fact that KCl was injected 24 hours before the EKG was given. It was mentioned in the literature that KCl produced its maximum effect 2 hours after oral administration (7). Edelman discussed perfusion of toad hemibladders which produced maximum KCl responses 30 minutes after immersion in KCl solutions (4). One can then conclude that what is observed is only an after effect. But, why did the EKG not return to normal? This can be explained by the fact that 3 to 5 days are required before a new potassium balance between intake and excretion can be established in man (12). So the rounded T wave observed may only be an after effect of maximum potassium intoxication.

Discussion now centers on the effect of desoxy-corticosterone acetate. Changes back to normal were
observed. However, these were not as complete as expected. In lead I, no change was observed at all. Several possibilities exist: the hormone might have been observed after its peak activity; the activity per se of desoxycorticosterone acetate might have been less than expected; the concentration may have been insufficient.

Of the three possibilities, the last two may be eliminated when one considers that miniscule amounts are present in the body and these are sufficient to produce the desired effect. So, again the period after injection appears to have been too long to observe the maximum effect.
C. Conclusion

This thesis was intended to establish a correlation between the control of serum potassium by the adrenal glands and the manifestations of any changes in T waves on the rat electrocardiogram. It can be concluded that adrenalectomy will have electrocardiographic effects on the T wave. The changes herein observed consist of: appearance of an ST segment; emergence of a rounded T wave from an absent or diphasic condition; and an appearance of tent-shaped T waves at higher concentrations.

The second phase of the experiment involved the study of injections of KCl and desoxycorticosterone acetate. The tent-shaped T waves observed with KCl and the return to normal observed with desoxycorticosterone are theorized to have been records of post maximum effect and not records of maximum effect as expected.

So with better technique, a longer period of examination, greater monitoring with the EKG, and the use of more normal rats, the above-mentioned correlation might be better established.


