CHANGES IN THE FUNCTION AND IONIC COMPOSITION OF THE ALIMENTARY TRACT IN RESPONSE TO DIETARY CATION DEFICIENCES, AND THE POSSIBLE ROLE OF ADRENAL MEDULLARY AND CORTICAL HORMONES IN MEDIATING THESE RESPONSES

by

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Abstract

The possibility that loss of intestinal motility occurs as a result of potassium or sodium depletion has been investigated.

A new technique, based on the passage of a solution containing the dye, gentian violet, was developed for estimating upper bowel motility. Lower bowel motility was not objectively studied. The sodium and potassium content of various portions of the gut from rats on a low sodium, low potassium diet and on a high sodium, low potassium diet have been determined and compared with that of similar portions of the gut of animals on a control diet. The possibility that excess adrenal cortical or medullary hormones may cause or permit electrolyte and motility changes has been studied. The response to dietary potassium restriction in the presence of a high sodium intake were also determined after adrenalectomy, both with and without medullory or cortical hormonal supplementation. The electrolyte pattern of plasma liver and of skeletal muscle from different portions of the body were analysed and compared in order to aid in understanding the overall electrolyte shifts. Analyses of the selected tissues of the body indicated that initial electrolyte concentrations and responses to diets and hormones vary within similar tissues as well as between different organs.

It was not possible to correlate alterations in the gastro-intestinal tract content of sodium and/or potassium with changes in motility.

Dietary potassium deprivation led to depletion of potassium only in plasma, skeletal muscle and certain portions of the gastro-intestinal tract in intact animals. This effect was prevented by adrenalectomy.

Evidence is presented that cortisone can influence the electrolytes of the body by acting in the cells of peripheral tissues as well as on

the kidney and that the high dose administered (4 mgm/day) had direct dietary potassium deficiency actions in addition to permitting depletion to occur in the presence of certain tissues. The hypothesis that excess adrenal cortical hormones cause intestinal immotility through loss of potassium or a gain of sodium in this tissue was not confirmed by the data.

Evidence is presented indicating that adrenalin can partially restore the ability to excrete potassium and the ability of tissues to undergo potassium depletion in adrenalectomized animals on a potassium deficient diet. It does not correct the electrolyte levels in adrenalectomized animals on a control diet. The possibility that adrenalin may play some role in maintaining electrolyte homeostatis is discussed.

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Acknowledgments

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I. A STUDY OF THE EFFECTS OF DIETARY ELECTROLYTE CHANGES ON THE ELECTROLYTE CONTENT OF SELECTED TISSUES IN THE RAT

A. Introduction

The role of potassium in the functioning of smooth muscle and the influence of various conditions and substances on the potassium content of tissues containing smooth muscle have not been extensively investigated. The effects of similar procedures on the electrolytes of skeletal muscle have been subjected to much study. This subject has been reviewed by Manery, '54, Overman, '51, and Danowski, '51. In general a loss of potassium from skeletal muscle is accompanied by an increase of muscle sodium. This exchange of ions does not impair the activity of the skeletal muscle (Heppel, '39). Previous investigators (Kornberg, '46, Skinner, '45, and Henrikson, '51) have reported that animals placed on low potassium diets became anorexic and constipated. Upon post-mortem examination, the gut was described as being hypomotile, and distended with gas and fluid.

From these studies several basic questions arise. Why should the gut become relatively inactive following a lack of dietary potassium? Are the electrolyte changes produced in the gut by potassium deficiency similar to the changes produced in striated muscle? Striated muscle retains its ability to contract, even after a loss of approximately 50 percent of its potassium (Fuhrman, '51). Is the inactivity of the gut due to changes in its electrolyte content? Steinbach, '54, postulated that an increase in the muscle sodium may be inhibitory to contraction. Is hypomotility in the bowel the result of an increase in sodium, a decrease of potassium, or

are both changes required? Does the gastro-intestinal tract respond as a whole to electrolyte imbalance or do its various portions differ in the degree of their response?

It seemed of interest to analyse the effects of potassium depletion, and of other procedures tending to impair motility on the electrolyte content of the gut wall. Some of the animals on the potassium depleted diet were subjected to decreased sodium intake as well, whereas others were placed on a diet of high sodium content. The tissues of potassium deficient animals were compared with those of animals on a normal diet. Liver, and several samples of skeletal muscle also were analysed to compare the degree of potassium depletion with that reported by other workers. The effect of the various diets on gut motility was also investigated.

Chronic dietary electrolyte alterations would appear to constitute a "stress" which might well activate the adrenals. Extensive work has revealed the importance of the adrenal glands (Woodbury, '53, and Drury, '53) in the metabolism of electrolytes and water of the body. The present experiments were designed to study what role the adrenals might play in producing or modifying the changes produced by potassium deficiency. An attempt was made to answer the following questions:

1. Were the adrenals essential for the appearance of any or all of the effects of potassium deficiency; i.e. did adrenalectomy slow or prevent the loss of potassium from tissues caused by low potassium diets?
2. Did cortical or medullary hormones have the greater tendency to return the electrolyte pattern of tissues to that of intact rats on the various diets? Did the hormones have any direct action on electrolyte patterns unrelated to diet?

3. Was the electrolyte pattern of these tissues related to motility?

In order to investigate the effects of both cortical and medullary hormones of the adrenal gland on the electrolytes of the gastro-intestinal tract, cortisone and adrenaline were individually administered to adrenalectomized animals, fed diets varying in potassium content. The effects of these hormones on motility was also investigated. The ability of individual hormones of the medulla and the cortex to maintain life and affect growth of the animals is also reported.

B. Methods

Male albino Wistar rats were used throughout these experiments. The initial weights of the animals were 175 to 200 gm. Diets (Table I) varying in sodium and potassium content were used in the experiments and were offered to the rats ad libitum. The rats were divided into two major sections:

Section I. Intact Animals

Group A. Low potassium, low sodium diet

Group B. Low potassium, high sodium diet

Group C. Control diet.

In each of the several runs of animals in Section I, the animals were grouped as follows:

1. A group of animals subjected to the experimental diet (Table I).
2. Two rats placed on the experimental diet plus added potassium.
3. Two rats placed on the control diet (Table I).

Since no significant variation was seen between animals on Fox Chow (control diet), and the animals on the experimental diet plus added potassium, the data from these animals were combined.

Section II. Adrenalectomized Animals and Hormone Treated Animals

Group D. Adrenalectomized rats on low potassium, high sodium intake (Table I)

Group E. Adrenalectomized rat on control diet

Group F. Adrenalectomized rats on low potassium, high sodium intake plus adrenalin*

Group G. Adrenalectomized rats on control diet plus adrenalin

Group H. Adrenalectomized rats on low potassium, high sodium intake plus cortisone

Group I. Adrenalectomized rat on control diet plus cortisone

Group J. Intact rats on low potassium, high sodium intake plus cortisone

Group K. Intact rats on control diet plus cortisone

Groups A, B, and C were maintained for an average of 35 days. One animal of group A was maintained for 81 days with no significant change in the electrolyte pattern as compared with others in the group. The food, but not water, was removed 24 hours before sacrificing the various animals.

The gut motility of the animals was estimated by force-feeding the animals a one percent solution of gentian violet. The animals were given one cc. of solution per 100 gm. body weight. After 15 minutes, they were anaesthetized with ether and exsanguinated by heart puncture with a heparinized syringe. The abdomen was opened and the sharp demarcation between that part of the small intestine containing gentian violet and the untraversed portion was clamped with a haemostat. The time from the force-feeding of the gentian violet solution to the placing of the haemostat was noted. The entire gut was then removed and the distance the dye had

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* Adrenalin refers to the Adrenalin 1:1000 solution of Parke Davis & Co.

travelled from the pyloric sphincter to the point of demarcation was measured (Table II). The percent distance travelled (Table II, Figure IV) was obtained by dividing the distance the dye travelled by the total length of gut measured from the pyloric sphincter to the ileo-caecal valve, multiplied by 100. The tissues were divided, trimmed of all visible fat and mesentric attachments, and the luminal contents were gently expelled. The samples of skeletal muscle and liver were removed immediately afterwards. All the tissues were gently blotted, placed in tared beakers and weighed. The entire procedure, from the time of heart puncture to final weighing took approximately twenty minutes per animal. The following tissue samples were removed:

1. Right rectus abdominus muscle
2. Right thigh muscle
3. Right lobe of liver
4. Stomach muscle, stripped of mucosa
5. Duodenum
6. Ileum
7. Large intestine
8. Rectum

The mucosa was stripped from the duodenum, ileum, large intestine and rectum of three of the rats in Group A. It is difficult to be certain that all the mucosa had been removed; no significant change between the tissue electrolytes with or without the mucosa was noted. The procedure was abandoned. However the easy and complete removal of the mucosa from the stomach was carried out on all stomach tissues. After the wet weights of the tissues were obtained, the tissues were dried in an oven (temperature 95 to 105° C.) for a minimum of five days. The tissues were then removed, and

the dry weights obtained. The dried tissues were pulverized in a mortar and portions of the powder were used for analysis. The portion for sodium and potassium analyses were digested with nitric acid, redissolved with a minimum amount of one N hydrochloric acid, diluted, and analysed in duplicate on a Jahnke flame photometer using lithium as an internal standard. The tissue chlorides were analysed in duplicate by the Wilson et al, '28, modification of the Van Slyke method, '23.

The exsanguinated blood was centrifuged, the plasma removed and placed in a refrigerator for analysis which was completed withing 24 hours. The sodium and potassium analyses were done on the Jahnke flame photometer using lithium as an internal standard; the chloride analyses were done by the Schales and Schales method.

The rats in Groups D to I were bilaterally adrenalectomized in a single stage operation by a dorso-lumbar approach. Untreated, adrenalectomized rats (Group D and E), due to a high mortality rate, were sacrificed at the end of 14 days. Adrenalin and cortisone treated rats (Groups F to K) were sacrificed at the end of 21 days. The adrenalectomized animals were maintained on their respective diets plus 0.9 percent sodium chloride and one percent glucose in demineralized water.

Two hormones were used in order to investigate the individual roles of the medulla and the cortex since the sites of both adrenaline and cortical hormone production were removed. Of the cortical hormones available, cortisone was chosen because it is known to be one of the hormones produced by adrenal cortex. It was given in the form of cortisone acetate* in a dose of four mg. per day. Adrenalin was administered in a 1:1000 solution;

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* Cortisone acetate — Cortone, Merck and Co., was used.

the dose being 40 micrograms per day per 100 gm. of body weight. Both drugs were injected subcutaneously at 24 hour intervals.

C. Diet

Composition of the synthetic diet with respect to sodium and potassium is shown in Table I. The low potassium synthetic diet was made up as follows: (gm. per 1000 gm. diet).

Starch (Canadian Corn Starch)	665 gm
Casein	270 gm
Fat (Mazola Oil, Crisco)	20 gm
Mineral Mix	12 gm
Calcium Carbonate	7 gm
Vitamins (Litrison)*	2 capsules

Mineral Mix was made up in bulk, and aliquot portions were taken from the diet. The mixture was made up as follows:

Ferric citrate	100 gm
Copper sulphate(hydrated)	13 gm
Manganese sulphate	4 gm
Magnesium sulphate (hydrated)	10 gm
Zinc sulphate	2 gm
Calcium chloride (hydrated)	1 gm
Sucrose	870 gm

Six gm. of sodium chloride per 1000 gm. of diet were added to the diets designated as high sodium low potassium diet (Table I). 3.4 gm. of potassium mono acid ortho phosphate (K_2HPO_4) was added to the synthetic diets when potassium supplement was required.

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* Litrison was kindly supplied by Hoffman La Roche Ltd.

The synthetic diet was analysed for phosphate content. It was found to contain the equivalent amount as found in the control diet.

Calculations

The method of calculations was based on Manery, '39, Manery, '54.

TABLE I

Composition of Diets per 1000 gm. of Diet

Diet	Sodium (mEq.)	Potassium (mEq.)
Low potassium, low sodium	.004	.005
High sodium, low potassium	.20	.005
Control diet	.14	.22

TABLE II

Motility Data

Treatment and Diet	Distance Dye Travelled (cm.)	Total Intestinal Length (cm.)	Time	Percent Distance Travelled
Low Na, Low K	32	80	19 min. 26 sec.	40.0
	39	88	19 38	44.3
	40	90	23 07	44.4
	38	93	19 38	40.9
	40	84	19 21	47.6
	35	83	20 15	42.1
Average	37.3	86.3	20 34	43.2
				1.2
High Na, Low K	61	100	19 40	61.0
	74	91	22 18	81.3
	81	107	19 58	75.7
	61	96	20 51	63.5
	64	87	20	73.6
Average	68.2	96.2	20 33	67.0
				9.2
Control	68	109	21 41	62.4
	69	97	22 20	71.1
	72	109	20 25	66.1
	81	109	22 10	74.3
	53	80	19 50	66.3
	90	115	20 42	78.3
	58	83	19 44	69.9
Average	70.4	100.3	20 58	69.8
				1.9
Adrenalectomized + Low K Diet	55	93	21 14	59.1
	48	84	21 55	57.1
	49	87	21 04	56.3
Average	50.7	88	21 20	57.5
				0.8
Adrenalectomized + Normal Diet	38	106	20 55	35.9

Table II (cont'd)

Motility Data

Treatment and Diet	Distance Eye Travelled (cm.)	Total Intestinal Length (cm.)	Time	Percent Distance Travelled
Adrenalectomized	24	98	24 min. 42 sec.	24.5
+ Low K Diet	24	104	23 51	23.1
+ Adrenalin	24	88	25 47	27.3
Average	24	96.7	24 47	25.0
				1.0
Adrenalectomized	46	103	26 13	44.7
+ Normal Diet	30	105	18 10	28.6
+ Adrenalin				
Average	38	104	22 12	36.7
				8.0
Adrenalectomized	35	112	21 26	31.3
+ Low K Diet	27	92	22 30	29.3
+ Cortisone	21	97	21 55	21.7
	24	103	20 40	23.3
Average	26.8	101	20 53	26.4
				2.3
Adrenalectomized	22	106	23 2	20.8
+ Normal Diet	33	117	22 51	28.2
+ Cortisone	21	109	19 54	19.3
Average	25.3	110.7	22 6	22.8
				2.6
Intact				
+ Low K Diet	29	111	19 2	26.1
+ Cortisone				
Intact	27	105	22 30	25.7
+ Normal Diet	24	99	21 59	24.2
+ Cortisone				
Average	25.5	102	22 15	25.0
				0.7

TABLE III

Mortality Data

Treatment and Diet	Percent Survival	Duration of Experiment (days)
Low Na, Low K	100	35 (average)
High Na, Low K	100	35 (average)
Control	100	35 (average)
Adrenalectomized + Low K Diet	50	14
Adrenalectomized + Normal Diet	17	14
Adremalectomized + Low K Diet + Adrenalin	50	21
Adremalectomized + Normal Diet + Adrenalin	50	21
Adrenalectomized + Low K Diet + Cortisone	67	21
Intact + Low K Diet + Cortisone	50	21
Adrenalectomized + Normal Diet + Cortisone	75	21
Intact + Normal Diet + Cortisone	100	21

TABLE IV

Blood Analyses

Treatment and Diet	No. of Samples	mEq. per litre		
		Sodium	Potassium	Chloride
Low Na, Low K	10	149.3 ±1.2	2.64 ±0.2	100.4 ±1.5
High Na, Low K	5	147.9 ±4.5	3.02 ±0.2	98.1 ±4.0
Control	10	150.9 ±0.7	4.45 ±0.2	107.9 ±1.9
Adrenalectomized + Low K Diet	3	152.6 ±1.6	5.77 ±0.1	113.4 ±2.6
Adrenalectomized + Normal Diet	1	152.8	5.1	114.5
Adrenalectomized + Low K Diet + Adrenalin	3	157.4 ±0.7	1.84 ±0.4	84.5 ±2.6
Adrenalectomized + Normal Diet + Adrenalin	3	150.2 ±3.8	2.63 ±0.7	91.8 ±0.5
Adrenalectomized + Low K Diet + Cortisone	4	161.4 ±1.9	1.59 ±0.2	94.3 ±2.9
Intact + Low K Diet + Cortisone	1	150.8	1.22	91.0
Adrenalectomized + Normal Diet + Cortisone	3	161.5 ±2.8	3.03 ±0.7	101.3 ±1.1
Intact + Normal Diet + Cortisone	2	156.7	1.90	96.0

TABLE V

THIGH MUSCLE.

Treatment and Diet	ANALYTICAL DATA								DERIVED DATA						
		mEq./Kgm. WET WEIGHT			mEq./Kgm. DRY WEIGHT								mEq./Kgm. INTRACELLULAR WATER		
	No. of Tissues	Na	K	Total	Na	K	Total	% Water	Total mEq/Kgm Tissue Water	No. of Tissues	Tissue Cl	Water in Cl Space	Cellular Water	Na	K	Total
Low Na, Low K Diet	5	48.9 ±3.1	87.8 ±3.2	136.7	186.7 ±8.4	335.5 ±2.6	522.2	738.2 ±8.4	185.2	5	14.6 ±3.2	134.1 ±8.5	604.1 ±14.1	46.7 ±5.8	145.4 ±8.1	182.1
High Na, Low K	5	45.9 ±1.8	80.7 ±2.1	126.6	185.6 ±4.6	326.4 ±4.2	512.0	752.7 ±5.7	168.2	5	11.7 ±0.8	107.6 ±8.1	644.6 ±7.0	46.2 ±3.3	124.7 ±3.4	170.9
Control	7	23.7 ±2.6	117.8 ±2.0	141.5	85.2 ±4.3	447.5 ±7.1	532.7	753.3 ±3.4	187.8	7	14.2 ±1.1	118.4 ±7.7	634.9 ±9.4	8.4 ±3.5	184.9 ±4.6	193.3
Adrenalectomized + Low K Diet	3	28.9 ±2.5	108.3 ±2.5	137.2	127.9 ±10.1	480.7 ±9.3	608.6	774.7 ±2.8	177.1	3	19.7 ±2.1	157.3 ±14.1	617.4 ±13.1	71.3 ±3.7	174.1 ±7.0	245.4
Adrenalectomized + Normal Diet	1	41.4	118.2	159.6	174.2	496.6	670.8	761.9	209.5	1	13.4	106.4	655.5	36.2	179.4	215.6
Adrenalectomized + Low K Diet + Adrenalin	3	58.4 ±0.9	91.3 ±0.9	149.7	251.9 ±6.2	393.9 ±7.0	645.8	764.2 ±4.2	195.9	3	15.9 ±1.7	166.1 ±20.9	602.2 ±22.7	52.2 ±5.2	151.1 ±4.0	203.3
Adrenalectomized + Normal Diet + Adrenalin	3	29.5 ±0.7	107.0 ±4.6	136.5	139.1 ±1.9	503.5 ±4.5	642.6	787.6 ±8.3	173.3	3	17.6 ±2.3	174.6 ±23.6	612.9 ±15.5	4.2 ±6.8	173.6 ±3.5	177.8
Adrenalectomized + Low K Diet + Cortisone	4	49.1 ±2.0	95.5 ±3.4	144.6	197.9 ±8.6	384.8 ±8.9	582.7	752.0 ±3.7	192.3	4	19.0 ±1.9	183.0 ±17.1	569.0 ±16.6	33.7 ±6.6	167.7 ±6.8	201.4
Intact + Low K Diet + Cortisone	1	58.0	97.9	155.9	245.0	413.7	658.7	763.3	204.2	1	15.9	158.6	604.7	55.6	161.6	217.2
Adrenalectomized + Normal Diet + Cortisone	3	48.6 ±0.7	94.7 ±0.6	143.3	195.0 ±1.4	380.3 ±5.6	575.3	750.7 ±3.2	190.9	3	22.8 ±5.9	204.8 ±6.2	545.9 ±7.2	26.9 ±1.2	172.4 ±1.8	199.3
Intact + Normal Diet + Cortisone	2	48.6	86.2	134.8	258.8	422.9	681.7	797.0	169.1	2	28.7	268.1	528.7	11.3	160.9	172.2

TABLE VI

ABDOMINAL MUSCLE

Treatment and Diet	No. of Tissues	ANALYTICAL DATA: mEq./Kgm. WET WEIGHT Na	K	Total	mEq./Kgm. DRY WEIGHT Na	K	Total	% Water	Total mEq/Kgm Tissue Water	DERIVED DATA: No. of Tissues	Tissue Cl	Water in Cl Space	Cellular Water	mEq./Kgm. INTRACELLULAR WATER Na	K	Total
Low Na, Low K	11	45.6 ±1.2	83.6 ±1.8	129.2	176.7 ±6.0	323.9 ±5.1	500.6	741.8 ±4.0	174.2	7	18.7 ±1.3	170.9 ±11.9	573.5 ±11.6	31.3 ±5.3	144.4 ±5.1	175.7
High Na, Low K	5	50.7 ±2.3	71.0 ±2.2	121.7	219.9 ±9.1	289.2 ±4.2	509.1	754.8 ±4.5	161.2	3	19.9 ±3.2	173.0 ±26.7	577.8 ±24.0	46.8 ±6.2	125.5 ±5.8	172.3
Control	10	34.8 ±2.2	106.1 ±3.4	140.9	143.5 ±9.8	436.0 ±11.4	579.5	755.7 ±3.3	186.4	10	18.4 ±1.5	155.4 ±12.0	600.3 ±10.6	17.8 ±3.7	175.8 ±5.2	193.6
Adrenalectomized + Low K Diet	3	37.5 ±2.0	101.1 ±2.3	138.6	170.7 ±9.7	460.3 ±5.2	631.0	783.7 ±7.7	176.9	3	19.3 ±2.5	153.8 ±18.2	629.8 ±22.4	21.3 ±1.5	159.6 ±7.8	180.9
Adrenalectomized + Normal Diet	1	38.7	110.4	149.1	167.8	478.2	646.0	731.0	204.0	1	21.9	174.0	557.0	20.8	196.6	217.4
Adrenalectomized + Low K Diet + Adrenalin	3	50.6 ±1.0	77.9 ±0.2	128.5	226.1 ±3.2	350.9 ±1.0	576.8	776.2 ±1.3	165.6	3	21.4 ±1.2	230.9 ±19.7	545.2 ±19.1	32.1 ±2.7	132.6 ±5.4	164.7
Adrenalectomized + Normal Diet + Adrenalin	3	45.6 ±2.1	110.6 ±2.4	156.2	212.8 ±4.6	517.5 ±4.7	730.3	786.2 ±6.7	198.7	3	19.4 ±1.8	191.7 ±18.5	594.3 ±15.1	27.3 ±6.5	185.2 ±4.8	212.5
Adrenalectomized + Low K Diet + Cortisone	4	50.5 ±2.0	80.0 ±2.7	130.5	199.0 ±10.3	313.7 ±5.7	513.4	745.4 ±4.4	175.1	4	23.1 ±2.1	229.3 ±4.6	522.4 ±24.2	25.6 ±9.4	153.5 ±11.4	179.1
Intact + Low K Diet + Cortisone	1	53.6	78.1	131.7	230.8	336.3	567.1	767.9	171.5	1	26.3	262.7	505.2	26.1	154.0	180.1
Adrenalectomized + Normal Diet + Cortisone	3	45.7 ±2.5	80.2 ±2.8	125.9	182.5 ±6.2	321.1 ±4.8	503.6	750.1 ±5.4	167.8	3	21.8 ±1.2	195.6 ±11.4	554.5 ±10.5	24.2 ±5.4	143.7 ±5.1	167.9
Intact + Normal Diet + Cortisone	2	48.8	95.1	143.9	232.6	445.6	678.2	788.1	182.6	2	27.5	271.9	516.2	10.0	182.1	192.1

TABLE VII

STOMACH

Treatment and Diet	No. of Tissues	ANALYTICAL DATA mEq./Kgm. WET WEIGHT Na	K	Total	mEq./Kgm. DRY WEIGHT Na	K	Total	% Water	Total mEq/Kgm Tissue Water	DERIVED DATA No. of Tissues	Tissue Cl	Water in Cl Space	Cellular Water	mEq./Kgm. INTRACELLULAR WATER Na	K	Total
Low Na, Low K Diet	10	57.6 ±2.4	66.2 ±1.7	123.8	239.5 ± 8.5	285.9 ± 7.4	525.4	765.0 ± 6.0	161.8	4	52.6 ±1.8	491.4 ±20.3	281.5 ±26.5	-46.3 ±16.6	233.0 ±26.7	186.7
High Na, Low K	5	74.6 ±3.6	65.8 ±5.9	140.4	366.6 ±7.2	316.3 ±14.1	682.9	795.1 ±6.9	176.6	3	52.3 ±0.4	493.2 ±26.5	294.8 ±17.5	11.3 ±30.6	235.6 ±26.4	246.9
Control	10	53.6 ±1.1	69.5 ±1.3	123.4	247.3 ±5.9	316.9 ±5.5	564.2	773.6 ±7.3	159.5	7	55.2 ±3.3	473.3 ±36.7	310.7 ±35.3	71.3 ±10.4	252.6 ±23.4	181.3
Adrenalectomized + Low K Diet	3	72.0 ±0.9	66.8 ±0.7	138.8	351.4 ±4.5	326.0 ±5.5	677.4	795.2 ±2.4	174.5	3	61.1 ±0.8	489.4 ±4.8	305.8 ±2.6	14.0 ±18.3	206.6 ±2.5	220.6
Adrenalectomized + Normal Diet	1	63.8	80.0	143.8	273.8	342.4	615.6	766.5	187.6	1	60.8	487.4	482.5	-40.1	272.9	232.8
Adrenalectomized + Low K Diet + Adrenalin	3	83.8 ±3.6	62.6 ±2.1	146.4	397.7 ±3.3	297.0 ±5.1	694.7	789.0 ±10.7	185.6	3	62.1 ±2.7	667.7 ±25.3	121.3 ±31.4	-237.7 ±100.1	572.9 ±169.0	335.2
Adrenalectomized + Normal Diet + Adrenalin	3	76.6 ±0.9	63.8 ±1.8	140.4	385.9 ±6.0	321.2 ±7.8	707.1	801.5 ±4.0	175.2	3	59.3 ±0.4	586.7 ±3.0	214.8 ±7.0	-60.3 ±6.0	290.8 ±19.4	230.5
Arenalectomized + Low K Diet + Cortisone	4	86.2 ±1.0	71.7 ±2.7	157.9	364.2 ±3.2	302.4 ±9.8	666.6	763.3 ±1.5	206.9	4	60.9 ±0.6	588.6 ±23.1	174.7 ±22.3	-91.6 ±45.2	425.1 ±56.9	333.5
Intact + Low K Diet + Cortisone	1	83.9	81.6	165.5	417.8	383.6	701.4	787.1	210.3	1	59.0	588.6	198.5	-33.8	407.6	373.8
Adrenalectomized + Normal Diet + Cortisone	3	74.3 ±2.7	74.3 ±0.7	148.6	298.9 ±0.8	313.4 ±8.3	612.3	762.6 ±4.5	194.9	3	61.5 ±1.4	561.4 ±10.2	201.2 ±13.9	-94.2 ±28.3	363.7 ±21.4	269.5
Intact + Normal Diet + Cortisone	2	66.9	52.3	119.2	336.6	254.7	591.3	804.3	148.2	2	63.3	602.4	201.9	-154.5	384.4	229.9

TABLE VIII

DUODENUM

Treatment and Diet	No. of Tissues	ANALYTICAL DATA: MEq./Kgm. WET WEIGHT Na	K	Total	mEq./Kgm. DRY WEIGHT Na	K	Total	% Water	Total mEq/Kgm Tissue Water	DERIVED DATA: No. of Tissues	Tissue Cl	Water in Cl Space	Cellular Water	mEq./Kgm. INTRACELLULAR WATER Na	K	Total
Low Na, Low K	11	54.7 ±1.8	93.7 ±1.3	148.4	233.2 ±5.1	403.6 ±7.7	636.8	769.0 ±2.8	193.0	4	37.7 ±1.1	352.4 ±13.4	413.9 ±14.8	8.4 ±10.9	221.9 ±9.1	230.3
High Na, Low K	5	51.9 ±2.2	80.1 ±1.4	132.0	250.4 ±3.5	395.9 ±4.4	646.3	788.9 ±2.7	167.3	3	27.3 ±2.0	244.7 ±12.1	534.4 ±11.5	36.9 ±0.4	154.4 ±0.5	191.3
Control	10	52.3 ±1.5	92.4 ±2.3	144.7	232.0 ±6.1	409.6 ±7.8	641.6	774.2 ±4.6	186.9	5	41.2 ±0.7	348.6 ±18.4	425.9 ±16.0	8.5 ±8.8	216.7 ±15.2	225.2
Adrenalectomized + Low K Diet	3	57.4 ±2.2	94.2 ±8.6	151.6	281.8 ±3.4	461.7 ±8.6	743.5	796.2 ±3.2	190.4	3	41.0 ±1.8	328.3 ±7.9	467.9 ±10.7	13.7 ±3.5	197.6 ±11.3	211.3
Adrenalectomized + Normal Diet	1	40.7	115.6	156.3	189.2	537.7	726.9	785.0	199.1	1	35.5	281.9	503.1	-6.6	226.8	220.2
Adrenalectomized + Low K Diet + Adrenalin	3	64.5 ±1.6	91.8 ±2.1	156.3	320.8 ±2.1	456.2 ±8.2	777.0	798.9 ±2.2	195.6	3	45.1 ±5.8	485.3 ±66.4	313.6 ±20.3	-59.7 ±39.8	313.1 ±58.7	253.4
Adrenalectomized + Normal Diet + Adrenalin	3	59.0 ±1.8	111.3 ±4.3	172.3	299.1 ±7.0	563.4 ±4.9	862.5	802.4 ±7.9	214.7	3	39.5 ±8.8	390.2 ±8.9	412.2 ±4.5	1.9 ±5.4	267.6 ±10.8	265.7
Adrenalectomized + Low K Diet + Cortisone	4	63.5 ±1.7	103.4 ±2.0	166.9	257.9 ±5.6	420.4 ±7.1	678.3	754.1 ±1.4	221.3	4	42.7 ±2.1	411.5 ±12.7	342.7 ±12.2	-7.4 ± 1.7	301.2 ±14.5	293.8
Intact + Low K Diet + Cortisone	1	57.7	103.4	161.1	281.1	503.7	784.8	794.8	202.7	1	36.4	362.7	432.1	4.4	238.1	242.5
Adrenalectomized + Normal Diet + Cortisone	3	62.7 ±2.9	113.6 ±3.1	176.3	252.7 ±6.8	458.1 ±4.0	710.8	763.8 ±2.1	230.8	3	44.6 ±3.7	409.1 ±24.5	354.6 ±24.0	19.7 ±6.3	318.4 ±29.9	338.1
Intact + Normal Diet + Cortisone	2	69.4	104.1	173.5	376.5	548.5	825.0	808.3	214.6	2	44.7	421.4	386.8	7.5	267.7	275.2

TABLE IX

ILEUM

Treatment and Diet	No. of Tissues	ANALYTICAL DATA mEq./Kgm. WET WEIGHT Na	K	Total	mEq./Kgm. DRY WEIGHT Na	K	Total	% Water	Total mEq/Kgm Tissue Water	DERIVED DATA No. of Tissues	Tissue Cl	Water in Cl Space	Cellular Water	mEq./Kgm. INTRACELLULAR WATER Na	K	Total
Low Na, Low K	8	54.3 ±2.9	85.6 ±1.0	139.9	193.0 ±9.8	307.2 ±6.7	510.2	723.1 ±6.1	193.5	5	32.5 ±1.8	291.2 ±9.4	424.5 ±5.9	34.1 ±9.8	200.7 ±6.9	234.8
High Na, Low K	5	51.7 ±1.8	84.6 ±1.5	136.3	211.4 ±9.8	334.8 ±7.0	546.2	754.7 ±7.5	180.6	4	32.6 ±2.4	293.3 ±13.8	460.5 ±21.5	15.0 ±4.5	181.8 ±9.6	196.8
Control	5	58.2 ±1.9	90.9 ±2.9	149.1	261.5 ±7.4	407.8 ±11.5	669.3	777.1 ±5.0	191.9	5	34.4 ±2.8	322.3 ±27.3	474.8 ±30.5	23.4 ±5.1	192.7 ±17.1	216.1
Adrenalectomized + Low K Diet	3	59.0 ±1.8	98.2 ±1.7	157.2	284.6 ±1.6	474.6 ±9.2	759.2	792.8 ±5.1	198.3	3	34.8 ±0.8	278.9 ±6.8	513.9 ±5.7	30.2 ±5.7	188.0 ±2.3	218.2
Adrenalectomized + Normal Diet	1	53.6	104.1	157.7	270.9	474.9	745.8	780.9	201.9	1	51.9	411.4	369.5	-26.8	276.0	249.2
Adrenalectomized + Low K Diet + Adrenalin	3	69.1 ±0.1	89.4 ±4.1	158.5	354.1 ±9.3	457.5 ±7.7	811.6	804.9 ±3.9	196.9	3	46.3 ±1.1	482.5 ±3.9	322.4 ±1.6	-28.2 ±1.1	273.8 ±14.0	245.6
Adrenalectomized + Normal Diet + Adrenalin	3	65.0 ±2.0	102.8 ±1.8	167.8	312.7 ±8.9	494.8 ±4.7	807.5	792.4 ±2.6	211.8	3	37.1 ±4.1	366.8 ±41.1	425.6 ±42.1	14.3 ±6.5	244.3 ±25.7	258.6
Adrenalectomized + Low K Diet + Cortisone	4	59.8 ±2.1	95.4 ±1.1	155.2	216.6 ±8.9	345.6 ±4.8	562.2	723.9 ±2.1	214.4	4	34.3 ±1.8	333.6 ±13.2	390.3 ±11.8	12.1 ±2.9	243.9 ±10.2	256.0
Intact + Low K Diet + Cortisone	1	58.9	99.2	158.1	249.6	420.1	669.7	763.9	207.0	1	34.9	348.7	415.2	12.5	238.0	250.5
Adrenalectomized + Normal Diet + Cortisone	3	60.2 ±0.8	108.3 ±0.9	168.5	225.0 ±3.1	404.6 ±7.9	629.6	732.3 ±6.1	230.8	3	35.1 ±1.3	314.8 ±10.9	417.4 ±13.2	19.7 ±6.4	257.4 ±7.4	277.1
Intact + Normal Diet + Cortisone	2	62.9	96.2	159.1	288.1	429.1	717.2	773.0	205.8	2	40.9	386.6	386.4	4.1	248.9	253.0

T A B L E X

L A R G E I N T E S T I N E

Treatment and Diet	No. of Tissues	ANALYTICAL DATA mEq./Kgm. WET WEIGHT Na	K	Total	mEq./Kgm. DRY WEIGHT Na	K	Total	% Water	Total mEq/Kgm Tissue Water	DERIVED DATA No. of Tissues	Tissue Cl	Water in Cl Space	Cellular Water	mEq./Kgm. INTRACELLULAR WATER Na	K	Total
Low Na, Low K	11	50.9 ±1.1	84.4 ±2.0	135.3	206.4 ±4.9	342.2 ±9.2	548.6	752.7 ±5.5	179.6	4	34.6 ±1.9	322.1 ±15.0	432.3 ±14.2	6.5 ±17.2	187.2 ±13.1	193.7
High Na, Low K	5	53.1 ±1.0	82.5 ±1.4	135.6	216.0 ±5.6	336.0 ±6.2	552.0	751.8 ±8.6	180.4	3	44.8 ±1.3	401.9 ±2.4	347.9 ±20.4	20.7 ±2.1	227.3 ±16.1	228.0
Control	10	52.5 ±2.3	91.0 ±2.6	143.5	223.6 ±9.5	386.7 ±8.7	610.3	756.4 ±8.4	189.7	4	40.1 ±2.5	351.9 ±31.8	413.9 ±36.5	5.5 ±8.9	234.2 ±31.1	239.7
Adrenalectomized + Low K Diet	3	57.9 ±1.5	89.3 ±2.0	147.2	307.3 ±1.4	474.5 ±7.9	781.8	811.7 ±5.3	181.3	3	37.1 ±1.0	297.3 ±5.2	514.5 ±3.6	22.7 ±5.3	170.1 ±1.2	192.8
Adrenalectomized + Normal Diet	1	45.2	102.6	147.8	235.7	535.0	770.7	808.2	182.9	1	36.0	285.2	523.0	1.3	193.3	194.6
Adrenalectomized + Low K Diet + Adrenalin	3	77.9 ±0.5	84.8 ±2.3	162.7	400.2 ±10.5	434.8 ±10.2	835.0	804.9 ±4.4	202.1	3	42.6 ±2.7	459.5 ±38.9	345.4 ±36.4	9.4 ±15.2	246.8 ±17.9	256.2
Adrenalectomized + Normal Diet + Adrenalin	3	57.3 ±1.1	98.2 ±3.9	155.5	287.2 ±8.0	517.5 ±6.7	804.7	801.5 ±2.6	194.0	3	39.0 ±2.0	386.0 ±21.3	415.4 ±23.7	-4.2 ±6.4	235.9 ±19.3	231.7
Adrenalectomized + Low K Diet + Cortisone	4	67.5 ±1.6	93.2 ±1.0	160.7	263.4 ±5.1	372.5 ±2.6	635.9	747.5 ±3.1	215.0	4	41.4 ±1.4	399.3 ±13.4	348.2 ±10.5	47.5 ±8.5	266.4 ±6.4	313.9
Intact + Low K Diet + Cortisone	1	70.2	85.0	155.2	248.0	300.3	548.3	716.8	216.5	1	33.4	333.8	383.0	49.1	220.9	270.0
Adrenalectomized + Normal Diet + Cortisone	3	54.8 ±1.5	92.6 ±0.5	147.4	201.0 ±8.5	381.3 ±7.1	582.3	760.4 ±2.9	193.8	3	32.1 ±1.0	332.6 ±12.6	427.8 ±9.7	-14.2 ±4.5	213.6 ±5.6	199.4
Intact + Normal Diet + Cortisone	2	60.5	90.3	150.8	284.8	426.7	711.5	787.8	191.4	2	39.9	378.4	409.4	-0.1	218.9	218.8

TABLE XI

RECTUM

Treatment and Diet	No. of Tissues	ANALYTICAL DATA mEq./Kgm. WET WEIGHT Na	K	Total	mEq./Kgm. DRY WEIGHT Na	K	Total	% Water	Total mEq/Kgm Tissue Water	DERIVED DATA No. of Tissues	Tissue Cl	Water in Cl Space	Cellular Water	mEq./Kgm. INTRACELLULAR WATER Na	K	Total
Low Na, Low K	11	61.2 ±1.0	80.7 ±1.4	141.9	229.3 ±7.3	346.5 ±7.9	575.8	767.4 ±10.0	184.9	4	37.4 ±2.1	349.1 ±19.7	414.6 ±20.9	43.1 ±6.0	196.4 ±14.6	239.5
High Na, Low K	5	58.1 ±3.4	75.4 ±4.4	133.5	264.1 ±6.0	342.2 ±3.2	606.3	780.0 ±11.6	171.2	3	31.2 ±2.2	274.4 ±18.5	478.3 ±18.5	43.7 ±3.9	173.4 ±7.5	217.1
Control	10	56.1 ±1.9	91.5 ±2.4	147.6	245.8 ±8.8	395.5 ±7.3	641.3	773.6 ±4.5	190.8	4	41.5 ±1.4	359.1 ±23.7	417.0 ±27.7	12.6 ±8.4	230.1 ±20.2	242.7
Adrenalectomized + Low K Diet	3	63.3 ±2.1	93.8 ±2.3	157.1	334.1 ±6.8	498.6 ±7.1	832.7	799.7 ±16.5	196.4	3	35.6 ±1.4	284.9 ±7.5	514.8 ±14.7	36.8 ±7.5	180.5 ±8.4	217.3
Adrenalectomized + Normal Diet	1	61.9	94.4	156.3	311.8	475.3	787.1	801.4	195.0	1	26.2	207.4	594.0	49.8	157.1	206.9
Adrenalectomized + Low K Diet + Adrenalin	3	69.6 ±1.0	85.5 ±2.8	155.1	362.3 ±8.9	444.6 ±5.0	806.9	807.7 ±4.5	192.0	3	44.4 ±1.6	478.9 ±28.4	328.8 ±24.0	-23.4 ±15.3	259.1 ±12.7	235.7
Adrenalectomized + Normal Diet + Adrenalin	3	63.4 ±0.1	91.7 ±3.0	155.1	346.1 ±10.8	499.6 ±6.7	845.7	816.4 ±6.9	190.0	3	40.8 ±1.7	403.1 ±16.8	413.3 ±13.8	-3.5 ±4.3	219.5 ±7.3	216.0
Adrenalectomized + Low K Diet + Cortisone	3	70.1 ±1.3	89.4 ±1.9	159.5	273.1 ± 8.0	347.8 ±5.8	620.9	742.7 ±9.5	214.8	3	36.2 ±6.8	303.1 ±18.4	439.6 ±26.8	46.8 ±0.6	204.2 ±16.5	251.0
Intact + Low K Diet + Cortisone	1	79.4	117.2	196.6	325.9	481.5	807.4	756.5	259.9	3	28.1	280.7	475.8	76.1	245.5	321.6
Adrenalectomized + Normal Diet + Cortisone	3	63.0 ±1.5	108.6 ±2.5	171.6	252.2 ±4.0	434.0 ±3.5	686.2	749.8 ±7.6	228.9	3	39.0 ±1.3	349.8 ±13.9	399.9 ±10.5	13.4 ±4.7	269.2 ±9.5	282.6
Intact + Normal Diet + Cortisone	2	65.3	88.1	153.4	330.6	439.1	769.7	798.8	192.0	2	45.3	425.4	373.4	38.0	235.1	273.1

TABLE XII

LIVER

Treatment and Diet	No. of Tissues	ANALYTICAL DATA mEq./Kgm. WET WEIGHT Na	K	Total	mEq./Kgm. DRY WEIGHT Na	K	Total	% Water	Total mEq/Kgm Tissue Water	DERIVED DATA No. of Tissues	Tissue Cl	Water in Cl Space	Cellular Water	mEq./Kgm. INTRACELLULAR WATER Na	K	Total
Low Na, Low K	10	36.5 ±1.6	100.5 ±4.4	137.0	122.7 ±5.4	325.0 ±7.5	447.7	702.3 ±7.7	195.1	6	29.1 ±1.0	258.9 ±10.6	441.2 ±11.7	-6.4 ±5.9	241.1 ±15.5	234.7
High Na, Low K	5	36.5 ±2.3	88.9 ±2.8	125.4	128.3 ±5.2	310.0 ±7.9	438.3	713.8 ±3.5	175.7	3	27.6 ±0.1	263.1 ±22.3	445.3 ±24.0	-7.7 ±0.8	207.9 ±1.3	200.2
Control	10	34.9 ±1.0	80.8 ±2.9	115.7	122.8 ±3.7	288.7 ±8.0	411.5	715.2 ±3.6	161.8	8	29.5 ±1.2	252.6 ±8.1	463.3 ±8.1	-10.1 ±2.1	176.2	166.1
Adrenalectomized + Low K Diet	3	38.8 ±2.5	99.2 ±0.7	138.0	152.3 ±4.2	391.1 ±12.8	543.4	745.8 ±9.7	185.0	3	23.1 ±1.4	185.0 ±7.1	560.1 ±16.9	18.0 ±3.0	175.5 ±6.1	193.5
Adrenalectomized + Normal Diet	1	52.6	100.4	153.0	196.4	374.8	571.2	769.1	198.9	1	25.0	198.2	570.9	38.0	173.6	211.6
Adrenalectomized + Low K Diet + Adrenalin	3	46.1 ±0.6	101.1 ±3.4	147.2	185.3 ±6.8	406.1 ±7.0	591.4	750.8 ±9.2	196.1	3	22.4 ±3.0	241.2 ±32.1	509.6 ±30.5	13.4 ±13.2	198.7 ±10.2	212.1
Adrenalectomized + Normal Diet + Adrenalin	3	47.4 ±0.8	110.5 ±5.2	157.9	194.3 ±5.1	452.0 ±1.2	646.3	755.5 ±11.1	209.0	3	25.4 ±3.2	251.0 ±32.8	504.6 ±30.9	17.3 ±8.0	219.5 ±16.9	236.8
Adrenalectomized + Low K Diet + Cortisone	4	51.6 ±3.1	106.5 ±1.3	158.1	156.4 ±8.0	326.4 ±9.9	482.8	669.7 ±15.1	236.1	4	28.6 ±3.2	274.1 ±27.0	398.6 ±34.0	13.9 ±4.6	272.3 ±23.9	286.2
Intact + Low K Diet + Cortisone	1	36.6	102.1	138.7	133.4	371.9	505.3	725.5	191.2	1	20.4	203.5	522.0	10.2	195.0	205.2
Adrenalectomized + Normal Diet + Cortisone	3	50.6 ±0.2	98.6 ±1.6	149.2	159.2 ±6.2	309.4 ±6.1	468.6	680.8 ±11.2	219.2	3	24.5 ±0.8	223.3 ±2.0	457.6 ±10.3	30.3 ±2.4	214.4 ±8.3	244.7
Intact + Normal Diet + Cortisone	2	47.2	111.0	157.2	179.2	429.6	608.8	736.7	213.4	2	20.2	189.1	547.6	31.2	201.9	233.1

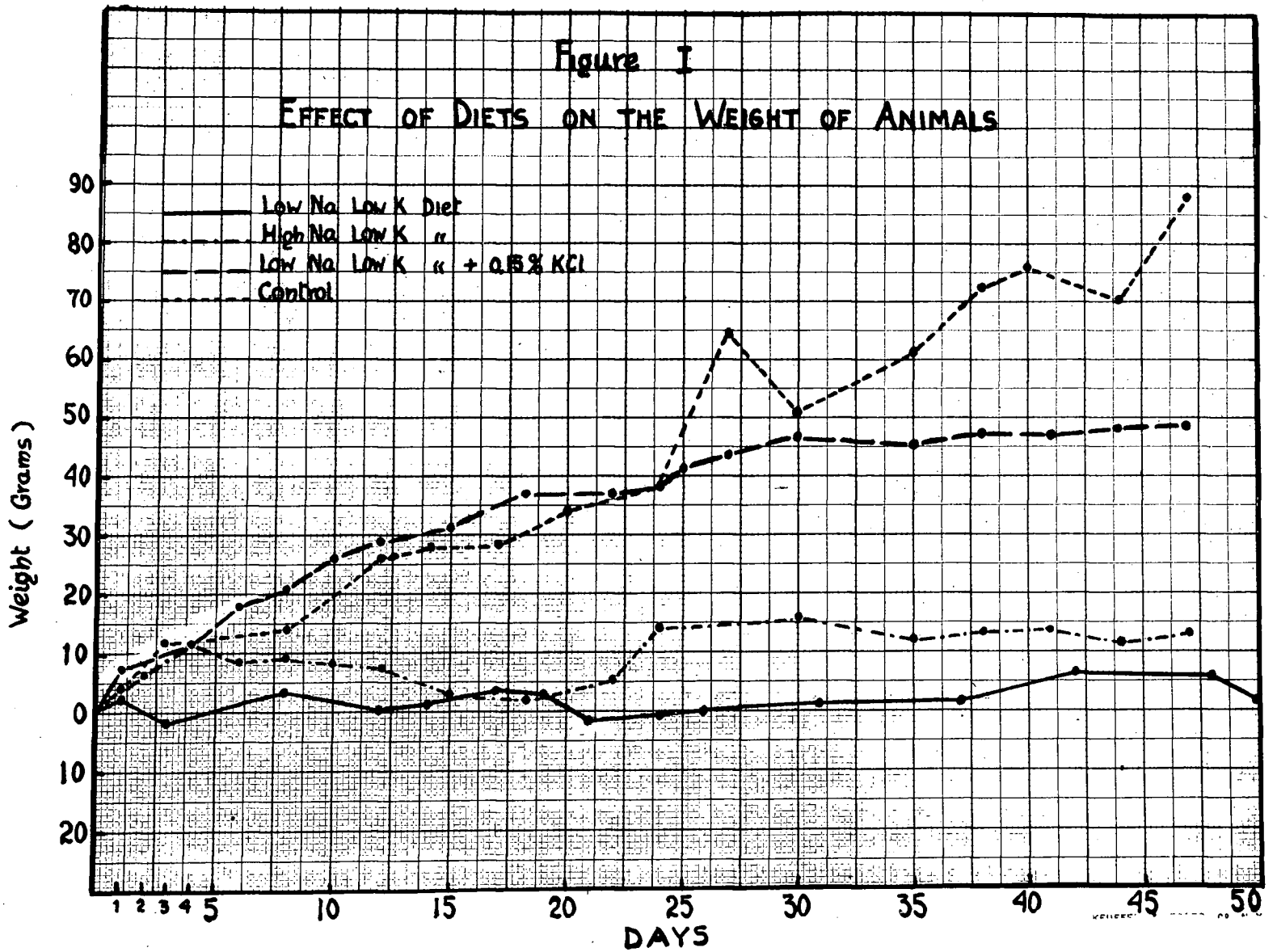


Figure I
Effect of Diets on the Weight of Animals
Low Na Low K Diet
High Na Low K "
Low Na Low K " + 0.15% KCl
Control
Weight (Grams)
90
80
70
60
50
40
30
20
10
0
10
20
1 2 3 4 5 10 15 20 25 30 35 40 45 50
DAYS

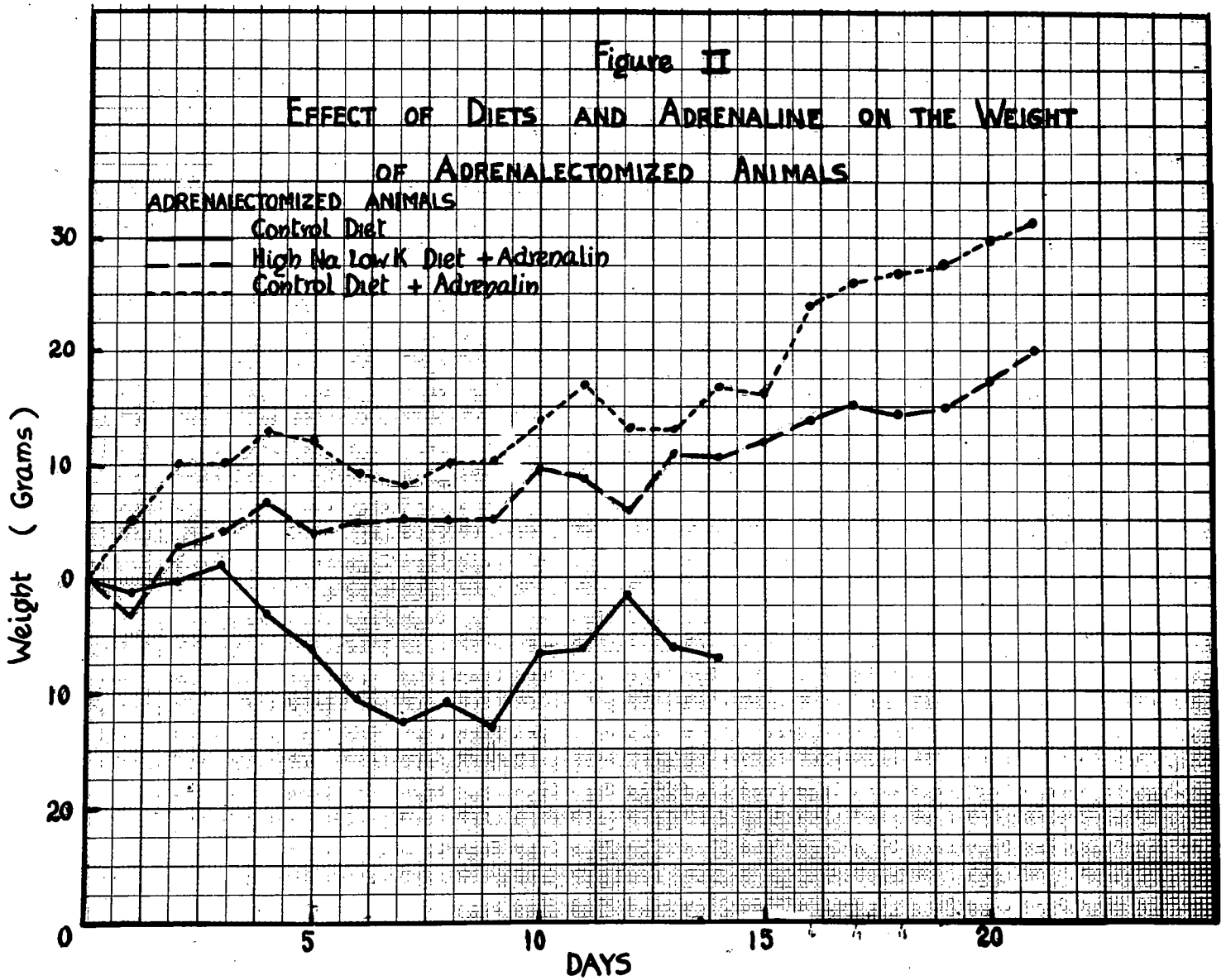
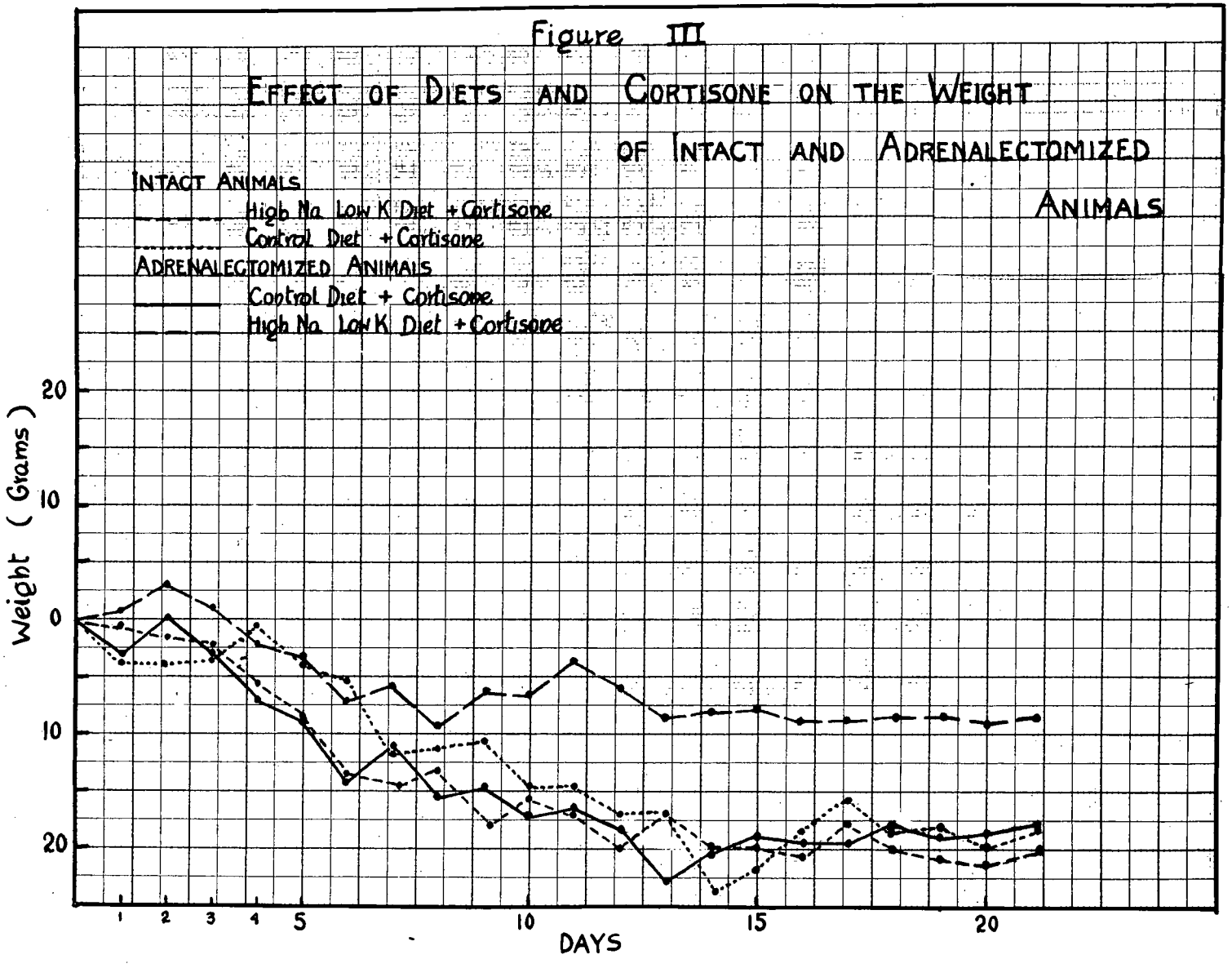
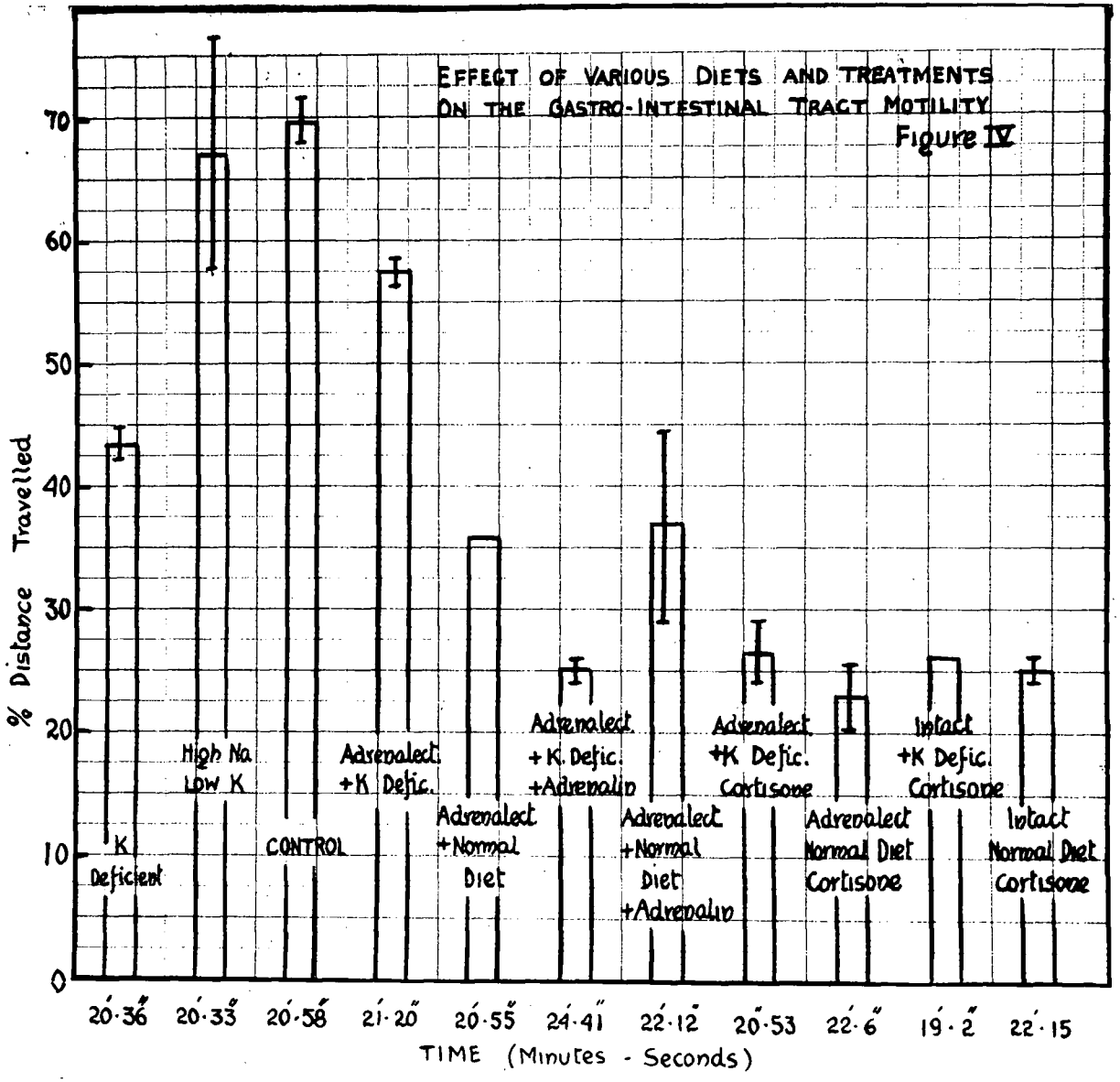


Figure II
EFFECT OF DIETS AND ADRENALINE ON THE WEIGHT
OF ADRENALECTOMIZED ANIMALS
ADRENALECTOMIZED ANIMALS
Control Diet
High Na Low K Diet + Adrenalin
Control Diet + Adrenalin
Weight (Grams)
30
20
10
0
10
20
0
5
10
15
20
DAYS

Figure III


EFFECT OF DIETS AND CORTISONE ON THE WEIGHT OF INTACT AND ADRENALECTOMIZED ANIMALS
INTACT ANIMALS
High Na Low K Diet + Cortisone
Control Diet + Cortisone
ADRENALECTOMIZED ANIMALS
Control Diet + Cortisone
High Na Low K Diet + Cortisone
Weight (Grams)
20
10
0
10
20
1
2
3
4
5
10
15
20
DAYS


EFFECT OF VARIOUS DIETS AND TREATMENTS
ON THE GASTRO-INTESTINAL TRACT MOTILITY
Figure IV
% Distance Travelled
0
10
20
30
40
50
60
70
K Deficient
High Na Low K
CONTROL
Adrenalect. +K Defic.
Adrenalect +Normal Diet
Adrenalect +K. Defic. +Adrenalin
Adrenalect +Normal Diet +Adrenalin
Adrenalect +K Defic. Cortisone
Adrenalect Normal Diet Cortisone
Intact +K Defic. Cortisone
Intact Normal Diet Cortisone
20·36"
20·33"
20·58"
21·20"
20·55"
24·41"
22·12"
20·53"
22·6"
19·2"
22·15
TIME (Minutes - Seconds)

D. Limits and Sources of Errors

The magnitude of changes observed in the tissue sodium and potassium content greatly exceeded the possible sources of errors in chemical determination, or in procurement of specimens. In the case of the chloride determination, there was less agreement in duplicate samples, but this error was random and probably would not significantly alter the results.

The use of the chloride ions for the determination of extracellular space is questionable (Amberson et al, '38, Manery and Hastings, '39, Crismon et al, '43, and Conway, '45). As yet there is no ideal chemical available for determining extracellular space. The boundaries and nature of the extracellular space are still poorly defined. The mechanism of movements of electrolytes from extracellular space into the cells are based on hypothesis rather than unequivocal proof. The influences of hormonal imbalance and alteration of water retention on the extracellular fluid is even less clearly understood. Recently White et al, '55, have studied the influence of adrenalectomy on extracellular fluid. These workers concluded that current methods for determining extracellular fluid in vivo are not sufficiently accurate to permit comparison of total intra- and extracellular electrolytes before and after adrenalectomy. Although the derived data of Section I and II were recorded, no attempt was made to interpret these results. As a result of the inability to derive any secure information concerning the intracellular concentration of electrolytes, one is faced with the task of obtaining alterations in the total tissue electrolytes that are significantly different in order to give some demonstration of the effects of various experimental procedures. Grollman, '54, has performed chronic experiments on adrenalectomized dogs and obtained significant changes in the total tissue electrolytes. These changes were not

dependant on any assumption regarding the coincidental changes in the relative volumes of the extracellular and cellular compartments based on chloride determinations.

Another possible source of error is the variable fat content of the tissues. However, even after several extractions with ether and other "fat" solvents, some lipid residue remains. This is because the individual members of the lipid group show large individual variations in their solubility (Hawk et al, '48). Substances like cholesterol, and compound lipids, like the phospholipids, glycolipids, would be extracted as well as neutral fats. These substances form an intricate part of the tissue structure. Removal of these substances may introduce a greater error in electrolyte determination than is present by including the small amount of neutral fat that may remain with the tissue after the macroscopically visible fat, if any, has been removed. Cotlive et al, '51, have done fat determinations on skeletal tissues of potassium deficient and control animals and found the total fat extract to be less than one percent. Thus the fat content of the tissues analysed was not considered to be an important factor in causing an error in the results.

The blood content of the tissues may be a source of incorrect estimation of the electrolyte values. However, there is no simple accurate technique available for carrying out tissue blood determinations. Manery et al, '38, and Gardner et al, '50, have reported that in animals which were decapitated, or as in the present study, bled by heart puncture, many tissues do not contain a measureable amount of blood. Blood determinations were not carried out on the tissues in the present investigation.

The question arises as to whether the low potassium diets may be so poorly palatable as to lead to starvation. Evidence against this possibility

is seen in the weight charts. The control animals on the diet with added potassium had normal weight gains. While the animals on low potassium diets did not gain weight, none of the animals involved showed a marked loss of weight. The weights of the diets consumed were recorded at regular intervals, but due to loss of diet from the cages, the recordings were not accurate. Though the animals on the low potassium diet became anorexic towards the latter portion of the experiments, there was a continued consumption of the diet.

Section I

EFFECT OF DIETARY CATION CHANGES ON THE ELECTROLYTES OF SELECTED TISSUES OF THE BODY

Results

1. Effect of Diet on the Weight of the Animals

The animals were studied at a stage of development normally accompanied by active growth (Controls, Figure I). This weight gain was completely prevented by placing the animals on a low potassium diet, whether the sodium content of the diet was restricted or increased (Figure I). Addition of 0.15 percent potassium chloride to the low potassium diet resulted in restoration of the growth curve to a normal pattern.

2. Effect of Diet on Gut Motility

Animals on a low sodium, low potassium diet showed a highly significant decrease (43.2 percent) in their gut motility as compared with the controls (69.8 percent) (Table II and Figure IV). The animals on a high sodium, low potassium diet showed no significant difference in the motility (67.0 percent) compared with the controls. There was a significant difference between the gut motility of the animals on a low sodium, low potassium diet and the animals on a high sodium, low potassium diet.

3. Electrolyte Analyses

a) Plasma Electrolytes

From Table IV, it can be seen that alterations in the electrolyte content of the diet had no effect on the sodium levels of the plasma. The potassium and chloride levels were significantly lowered in the rats fed

low sodium low potassium, and high sodium low potassium diets as compared with the controls. There was no significant difference between the potassium and chloride levels of either group of rats on the low potassium diets. The plasma electrolytes of the controls and the potassium deficient animals are in agreement with the results reported by Schwartz, '53, and others. Therefore altering sodium intake had no significant effect on the sodium, potassium or chloride levels of plasma.

b) Skeletal Muscle Electrolytes

Skeletal Muscle of the Control Animals Significant differences were observed in the content of the various electrolytes when skeletal muscle from the thigh was compared to that of the abdomen (Table V and VI). The abdominal muscle contained more sodium (34.8 mEq. per Kg. wet weight) and less potassium (107.1 mEq. per Kg. wet weight) than the thigh muscle (23.7 mEq. per Kg. sodium wet weight and 117.8 mEq. per Kg. potassium wet weight). The abdominal muscle also contained a significantly higher level of chloride ions. This may be due to a higher content of chloride-rich tissue in the abdominal muscle. The ionic pattern of the control thigh muscle was in general agreement with that reported by Lowry et al, '42, Darrow, '46, and Muntwyler et al, '50. The difference between our data and that of other workers was no greater than has been shown to exist between controls of different strains of animals of different ages (Lowry et al, '42).

Effect of Altering Sodium and Potassium Intake on Skeletal Muscle In addition to their initial differences in ionic patterns, the electrolyte content of thigh and abdominal muscle differed in the degree of alteration produced by changes in electrolyte intake. On decreasing the potassium intake of the rats, approximately 30 percent of the initial potassium content of the tissues was lost and was only partially replaced

by sodium in both the abdominal and thigh muscle as has been reported by several workers (Heppel, '39, Conway et al, '48). The shift was quantitatively different for the two muscle samples. The thigh muscle exchange was 25.2 mEq. per Kg. sodium increase for a 30 mEq. per Kg. potassium decrease. In the abdominal muscle, the content of sodium uptake in exchange for potassium loss was even less complete (10.8 for 22.5). As shown by Holliday, '55, an increase in sodium ingestion accentuated the muscle changes produced by potassium deficiency. However, the increase in sodium intake did not affect skeletal muscle uniformly. The exchange of sodium for potassium in the thigh muscle was 22.2 for 37.1, values which are not significantly different from those found with a low sodium intake. The abdominal muscle sodium:potassium exchange ratio was 15.9:22.5. For the same degree of potassium loss, the sodium uptake was significantly increased.

The voluntary muscle of the body did respond to a potassium deficiency regardless of the amount of sodium intake. However, the electrolytes of skeletal muscle from different parts of the body responded differently when the electrolyte intake was altered. The thigh muscle, which had more potassium initially, experienced a greater potassium depletion in response to a potassium deficiency, than did abdominal muscle, and also a correspondingly greater sodium intake. However, when the dietary sodium was increased, an altered degree of sodium - potassium exchange was found in the abdominal muscle, rather than the thigh muscle. These differences between muscle of thigh and abdominen were largely due to differences in the proportion of extracellular material which they contained since shifts in calculated cellular electrolytes were more nearly identical in the two muscles than shifts in tissue electrolytes.

c) Gastro-Intestinal Tract Electrolytes

Electrolytes of Rats on Control Diet The data presented in Tables VII to XI indicate that the electrolyte and the water content of the various segments of the gastro-intestinal tract responded differently to the dietary regimes and were also different from striated muscle. The total electrolyte content, per kilogram of wet weight of various segments of the gut in the control animals with the exception of the stomach, is approximately the same. The concentration of cations in the stomach was lower than the rest of the gut, possibly as a result of removal of the mucosa. With the exception of the stomach, the various sections of the intestinal tract contained a higher total concentration of electrolytes than striated muscle; the ileum showing the highest concentration. This high tissue electrolyte concentration is due to the low content of non-electrolyte-containing solids, since calculated in terms of mEq. per kilogram tissue water no differences between striated muscle and gut are observed. The sodium concentration per kilogram wet weight of gastro-intestinal tract was approximately the same (52.3 - 58.2 mEq. per kilogram) throughout the gut, with the duodenum containing the highest concentration. In contrast, striated muscle had a lower and more variable sodium concentration, (thigh muscle, 23.7 mEq., abdominal muscle 34.8 mEq. per kilogram wet weight). The potassium levels per kilogram wet weight of various portions of intestinal tract were quite uniform (90.5 - 92.4) except for stomach which contained a markedly lower content of potassium (69.5). From these data it is not possible to decide whether stomach smooth muscle actually contains less potassium than other intestinal muscle or if the mucosa generally possesses a high potassium content. The striated muscle had a higher and more variable potassium content (117.8

mEq. per kilogram in thigh muscle and 106.1 mEq. per kilogram in abdominal muscle).

Effects of Low Potassium, Low Sodium Diet

Alterations in Sodium On placing the animals on a low sodium, low potassium diet, there was no significant change in the sodium content (59.0 - 61.2 mEq. per kilogram wet weight) of the stomach, duodenum, large intestine or rectum, but there was a significant decrease of sodium in the ileum. This response is in marked contrast to the striated muscle which showed a highly significant increase in sodium content in the presence of potassium deprivation.

Alterations in Chloride Tissue chloride was significantly decreased in the duodenum and large intestine, but unaffected in other regions of the bowel.

Alterations in Potassium. The potassium levels in the gut of the animals on a low sodium, low potassium diet did not change in stomach muscle or duodenum. There was a significant decrease of potassium in the ileum, large intestine and rectum; the ileum having the greatest decrease. The decrease in potassium content of ileal tissue, unlike that of large intestine and rectum, was not accompanied by a decrease in cellular potassium levels since there was a marked cellular dehydration. The decrease in potassium in these tissues was significantly smaller (approximately eight percent of the initial value) than was shown to occur in the striated muscle (approximately 30 percent).

Thus the various segments of the gastro-intestinal tract responded differently when the diet was low in both sodium and potassium. The electrolyte pattern of the upper portion of the intestinal tract (stomach muscle and duodenum) was not affected despite changes in motility. The

lower portions of the bowel had potassium loss, but in contrast to skeletal muscle, there was no corresponding sodium uptake. The ileum was unique in that although it lost both sodium, potassium and water, these changes in tissue electrolyte concentrations were not accompanied by similar changes in calculated cellular electrolyte concentrations.

Effects of High Sodium, Low Potassium Diet

Alterations in Sodium On placing the rats on a high sodium, low potassium diet there was a highly significant increase in the sodium content of the stomach (366.6 mEq. per kilogram) compared to the controls (247.3 mEq. per kilogram), and to the animals on low sodium, low potassium diet (239.5 mEq. per kilogram). The duodenum showed some increase of sodium content in terms of tissue dry weight (250.4 mEq. per kilogram) as compared to the controls (232.0 mEq. per kilogram) and the animals on the low sodium, low potassium diet (233.2 mEq. per kilogram). The high sodium, low potassium intake had no significant effect on the sodium level of the large intestine or rectum as compared to the controls. However, the sodium content did tend to be higher per kilogram dry weight than in animals with dietary restrictions of both sodium and potassium. There was a decrease in the sodium content of the ileum, indicating that increasing the dietary sodium content did not prevent the decrease in sodium which potassium depletion had produced. Thus the ileum was unable to retain its sodium content in the presence of a potassium deficiency regardless of the level of sodium intake.

Alterations in Potassium The potassium levels in the duodenum of the rats on a high sodium, low potassium diet decreased so that now the duodenum as well as more anal regions became deficient. Again there was no change in the stomach muscle. It should be recalled that these tissues were as

motile as controls in spite of their potassium loss.

In summary, in rats subjected to dietary potassium deficiency, the stomach and duodenum showed no change in ionic pattern when the sodium intake was also restricted. Ileum, large intestine and rectum lost significant quantities of potassium on both diets, but showed no increase in sodium content. The ileum actually lost sodium on both diets. No relation between these changes and motility was apparent.

d) Liver Electrolytes

Gardner et al, '50, and Heppel, '39, have shown that placing rats on a low potassium diet does not cause the liver to lose potassium. The results in Table XII shows that liver potassium was actually increased in our rats on a low potassium diet, even when the sodium content of the diet was high, and that a dietary decrease of both sodium and potassium caused a highly significant increase of potassium concentration (325.0 mEq. per kilogram dry weight) compared to the controls (288.7 mEq. per kilogram dry weight).

Gardner et al, '50, reported a significant increase in liver sodium in their potassium deficient rats. Our results showed no significant alteration in the liver sodium.

Since the sodium levels did not alter, and the potassium levels were increased without an accompanying increase in cellular water, the animals on the low potassium diet showed increases in the total electrolyte content of the liver per kilogram wet weight. Thus placing an animal on a low potassium diet caused a paradoxical increase in liver potassium.

Section II

EFFECTS OF VARYING DIETARY ELECTROLYTE INTAKE, ADRENALIN AND CORTISONE ADMINISTRATION TO ADRENALECTOMIZED AND INTACT RATS

Results

1. Effect of Diet and Hormone Treatment on the Weight of Animals (Figure I to III)

All adrenalectomized, hormone-treated animals were maintained on a high sodium intake, both from the diet (Table I) and from 0.9 percent sodium chloride as the sole source of fluid intake. This was done to aid the maintenance of animals after adrenalectomy. Further, as was indicated in the intact animals, the high sodium intake can cause a greater alteration in the tissue electrolytes during dietary potassium deprivation.

The untreated adrenalectomized rats lost weight on a high sodium, low potassium diet, as well as on a control diet (Figure II). The adrenalin-treated adrenalectomized rats on the control diet (Figure II) experienced a gain in weight (+33.1 gm.) almost equal to the weight gain (approximately 37 gm.) of the intact control animals for the same period of time. A similar, though more variable effect was obtained in adrenalin treated animals on low potassium intake. Thus adrenalin was capable of producing a weight gain in the animals. Whether this weight gain is due to normal growth or water retention will be discussed (page). Both the intact and adrenalectomized rats lost weight when treated with cortisone. Among the cortisone treated animals, the adrenalectomized animals on the low potassium diet, lost the least weight (-8.5 gm.), as compared with the intact animals on the control diet (-18.0 gm.), intact animals on low potassium diet (-20.0 gm.) and adrenalectomized rats on control diet (-17.4 gm.).

Therefore the results indicate that in the dosages administered, adrenalin causes a gain in weight whereas cortisone causes a weight loss.

2. Effect of Diet and Hormone Treatment on Gut Motility

(Table II, Figure IV)

Adrenalectomy The gut motility of untreated, adrenalectomized animals (57.5 percent) on a high sodium low potassium diet was not significantly different from that of intact animals (67 percent) on the same diet. Thus the presence or absence of the adrenal glands had no significant effect on gut motility when a high sodium, low potassium diet was used. The decreased motility of the single, adrenalectomized animal on a normal diet may have been due to its nearly moribund state.

Adrenalin Administration of adrenalin to adrenalectomized rats reduced the gut motility as compared with other adrenalectomized rats not receiving hormonal treatment. Thus adrenalin, as might be expected from its inhibitory effects on intestinal muscle *in vitro*, did not improve motility.

Cortisone Cortisone treatment decreased motility (26.4 - 22.8 percent) in both intact and adrenalectomized rats as compared with similar animals not receiving hormonal treatment. The decrease in motility was the same for adrenalectomized and intact animals regardless of electrolyte content of diet. Therefore it appears that cortisone exerts a direct action on the gastro-intestinal tract.

3. Effect of Diet and Hormone Treatment on Mortality

(Table III)

The adrenalectomized rats on a normal diet had the highest mortality.

The temperature of the animals' room was about 15° C. and this may have contributed to the limited survival of these rats. Similarly the adrenalectomized rats on a high sodium, low potassium intake had a tendency to die sooner and were therefore sacrificed earlier than the animals that were undergoing hormonal treatment.

The animals receiving adrenalin had a prolonged life span compared to the untreated rats. These animals also appeared to be more vicious and vigorously resisted the subcutaneous injections of the adrenalin.

The cortisone treated animals also had a prolonged life span compared to the untreated rats. These animals appeared quite docile and languid. From the small series of rats used, it is not possible to say whether adrenalin or cortisone was capable of maintaining life longer for adrenalectomized rats.

4. Electrolyte Analyses

a) Plasma Electrolytes (Table IV)

A significant increase in the plasma potassium and chloride levels occurred in adrenalectomized animals in spite of a high sodium, low potassium diet, but there was no change in plasma sodium. Other workers (White et al, '55) have reported a drop in plasma sodium in adrenalectomized rats. However, maintaining the animals on a high sodium diet and on a 0.9 percent sodium chloride as drinking water, prevented the drop in plasma sodium.

Adrenalin in adrenalectomized rats on a high sodium, low potassium diet caused an increase in plasma sodium and a decrease in plasma potassium and chloride compared with the plasma level of these ions in the same diet. Exogenous adrenalin in the adrenalectomized rats on a control diet had no

effect on sodium, but did cause a drop in the potassium and chloride (Table IV) even below the levels found in the intact rat. Therefore, adrenalin alone seemed to be capable of reversing the electrolyte changes of adrenalectomy (high potassium and chloride), and could stimulate the plasma electrolyte pattern of hypochloremic hypokalemic alkalosis.

Cortisone in the adrenalectomized rats caused a marked increase in plasma sodium and a decrease in potassium and chloride, compared with the corresponding values in untreated adrenalectomized rats as well as intact rats on similar diets. However, the reduction in plasma potassium and chloride with cortisone administration was much less marked in animals fed adequate amounts of potassium.

Cortisone in the intact rats caused no increase in plasma sodium, but reduced the plasma potassium and chloride even more than in the cortisone treated adrenalectomized rats. Thus cortisone seemed to produce a greater change in the blood electrolytes if the adrenals were intact.

In summary, both adrenalin and cortisone caused an increase in plasma sodium and a decrease in plasma potassium and chloride in adrenalectomized rats on a high sodium, low potassium diet. However, the sodium increase was greater with cortisone and the chloride decrease was more significant when adrenalin was used.

b) Skeletal Muscle Electrolytes

The skeletal muscle was considered in detail to provide a basis for comparison with the gastro-intestinal tract. Also the effects of the various procedures have been studied on skeletal muscle by other workers. Therefore these data permit a comparison of the status of these animals with those of other investigators who used similar conditions.

Effects of Adrenalectomy

Normal Diet Due to the high degree of martality in the group of

adrenalectomized animals on the control diet and the desire to avoid variation due to post-mortem changes, results from only one animal are presented. The results are comparable to similar data for adrenalectomized rats reported by Darrow et al, '48.

Adrenalectomy led to an increase of sodium and potassium content in both abdominal and thigh muscle. The increase in sodium (+89 mEq. sodium per kilogram dry weight) of thigh muscle was greater than that of abdominal muscle (+24.3 mEq. sodium per kilogram dry weight). The increase in potassium in the two muscles are not markedly different (thigh muscle 49.1 mEq. per kilogram dry weight potassium, abdominal muscle 42.2 mEq. per dry weight).

Low Potassium Diet. Since the untreated, adrenalectomized animals were sacrificed only fourteen days after adrenalectomy, the question arose as to whether these animals had sufficient time for the potassium deficient diet to produce its effect. In similarly-fed adrenalectomized rats, Darrow et al, '48, reported levels of 10.9 mM. sodium per 100 gm. and 47.0 mM. potassium per 100 gm. of muscle tissue. These workers sacrificed their animals fourteen days after adrenalectomy, at which time the muscle of their intact animals did show the electrolyte pattern characteristic of potassium deficiency. The results for thigh muscle shown in Table V (12.8 mEq. sodium per 100 gm. and 48 mEq. potassium per 100 gm. dry weight of tissue) are similar to those of Darrow et al. Thus adrenalectomy prevents the development of potassium deficiency in muscle as well as in plasma. The muscle and the plasma potassium of the adrenalectomized rats actually remained high instead of the usual decrease seen on a potassium deficient diet. The effects of adrenalectomy on plasma and muscle electrolytes were not prevented by the diet. The increase of muscle sodium was small compared

with the concentrations found in intact controls on a normal diet. These results are in marked contrast to the intact animals on the low potassium diet where there was a highly significant increase of muscle sodium along with a marked decrease of potassium. Thus both adrenalectomy and the high sodium, low potassium diet tend to cause an increase in muscle sodium. The failure of muscle sodium to be additively elevated, when these two experimental procedures are combined, remains unexplained. This situation contrasts with that of other tissues (gastro-intestinal tract, liver) where the anticipated additive effects were obtained.

Effects of Replacement with Medullary and Cortical Hormones of the Adrenal Gland on Skeletal Muscle

Adrenalin A comparison of the muscle electrolyte levels in adrenalin treated adrenalectomized animals on a normal diet and on a low potassium diet, to those of intact animals on similar diets revealed that adrenalin was able to restore the muscle electrolyte levels of adrenalectomized rats towards those of intact rats only in the case of the rats on the potassium deficient diet. In contrast, on a diet containing potassium there was no marked correction of the abnormalities in muscle electrolyte produced by adrenalectomy, with the exception of the sodium levels of the thigh muscle. In addition, adrenalin caused marked hydration of tissues in the animals on a control diet. Therefore adrenalin alone, without dietary alterations, did not mobilize the excess potassium from tissues after adrenalectomy even though it did produce hypokalemia. It appears that adrenalin permits the low potassium diet to exert its usual effects on tissue potassium rather than itself directly altering tissue electrolyte levels.

Cortisone In the intact animals and the adrenalectomized animals, regardless of diet, cortisone caused effects similar to the low potassium

diet in untreated intact animals. In general, cortisone caused the skeletal muscle to have a smaller loss of potassium than was caused by the potassium deficient diet alone. The potassium depletion produced by cortisone was not enhanced by the presence of a deficiency in the diet and is resumably a direct action of the hormone. There is some indication that the presence of the adrenals interfered with potassium depletion by cortisone. These experiments do not support the hypothesis that cortical hormones act simply by permitting the effects of a low potassium diet to be manifest.

In summary, it can be seen that both adrenalin and cortisone can alter the electrolytes of skeletal muscle. Both hormones, in the dosage used, were incapable of correcting the water and electrolyte disturbances of adrenalectomy. Cortisone, in the dosage used, reduced the high plasma and tissue levels of potassium seen after adrenalectomy to levels beneath those seen in the intact control animals. Adrenalin reduced plasma potassium levels and enabled the low potassium diet to produce its usual depletion of tissue potassium. Cortisone duplicated these changes by a pharmacological action of its own independent of the diet.

c) Gastro-Intestinal Tract Electrolytes (Table VII to XI)

Effect of Adrenalectomy

Control Diet The data of the adrenalectomized animals on the control diet are available for only one animal. This analysis is presented in the tables, but no attempt was made to evaluate the results.

Low Potassium Diet When compared with intact animals on the same potassium deficient diet, adrenalectomy produced no further significant change in the total electrolyte content or the tissue water levels of the stomach. Potassium deprivation after adrenalectomy caused a marked increase

in the total electrolyte content per kilogram dry weight in the remainder of the gastro-intestinal tract. This effect is similar to that seen in skeletal muscle under comparable circumstances. Actually there was a markedly greater increase in total electrolytes in the tissues aboral to the duodenum than in the striated muscle. This increase in total cations was quantitatively different in the various portions of the intestines with the increase being lest in the duodenum of the adrenalectomized rat (+97.2 mEq. per kilogram dry weight), as compared with the remainder of the intestines(213 - 229.8 mEq. per kilogram dry weight).

In general, the tissue potassium content was relatively more elevated after adrenalectomy than was the sodium content, so that, in spite of dietary restrictions, potassium depletion was prevented in these tissues as in striate muscle. In summary, adrenalectomy showed no effect on the stomach, prevented the depletion of tissue potassium by a deficient diet in those segments of the gastro-intestinal tract where it had previously occurred, and elevated the sodium content of all segments except the stomach.

Effects of Replacement with Medullary and Cortical Hormones of the Adrenal on Gastro-Intestinal Tract

Adrenalin Treated Adrenalectomized Rats The adrenalectomized rats treated with adrenalin, when compared with untreated adrenalectomized rats showed an increase of sodium in the stomach, duodenu, ileum, large intestine and rectum, beyond that caused by adrenalectomy alone whether dietary potassium was restricted or not. As in skeletal muscle, adrenalin treatment of adrenalectomized rats on a potassium deficient diet produced a decrease in the potassium content throughout the entire gastro-intestinal tract, toward the levels seen in intact rats on the same diet. The potassium depletion was not significant in all cases and was not as great

as that seen in intact animals on the potassium deficient diet. The change in potassium content was least in the duodenum. Thus adrenalin caused a greater increase in tissue sodium than was caused by adrenalectomy alone, and partially opposed the action of the potassium deficient diet, reducing the degree of tissue potassium depletion in those portions of the gut where it occurred. Thus, although adrenalin decreased the motility of the gastro-intestinal tract, it did not produce a corresponding reduction in potassium content.

Cortisone Treated Intact Rats When intact animals were treated with cortisone, regardless of diet, there was an increase of sodium throughout the gastro-intestinal tract. The potassium levels of all portions of the gastro-intestinal tract(with the exception of the stomach) were increased to varying degrees. This action of cortisone was not accentuated by the low potassium diet (one animal). Thus in the intact animal treated with cortisone, the gastro-intestinal tract (except for the stomach) was seen to have an opposite electrolyte shift to skeletal muscle, in that cortisone decreased potassium content in skeletal muscle but increased it in the gastro-intestinal tract. Both skeletal muscle and alimentary tract responded to cortisone in characteristic responses regardless of dietary potassium intake. There was decreased gastro-intestinal motility in cortisone-treated animals even though the potassium content of the tissue was elevated.

Cortisone Treated Adrenalectomized Animals Cortisone administration caused an alteration in the electrolyte patterns of the gut, as compared with that of untreated adrenalectomized rats. The sodium content of the stomach increased, while the potassium levels in all tissues decreased toward normal values regardless of diet. Though cortisone caused a

decreased in its motility, the sodium and potassium content of the tissues of the gastro-intestinal treact was not reduced as compared with intact controls.

In the cortisone treated adrenalectomized animals fed a potassium deficient diet, the gastro-intestinal tract contained less potassium than that of animals fed the control diet, but not all the differences were significant. In all segments, excpet duodenum and large intestine, the reduction in potassium content with cortisone treatment and deficient potassium intake was sufficient to lower the levels of that of intact control animals on the same diet. Similarly, in all tissues except duodenum and rectum, tissue potassium after cortisone treatment and normal potassium intake was lowered to the levels observed in intact control animals on the same diet. Thus, in the gastro-intestinal tract, cortisone restored potassium levels of adrenalectomized rats to those found in intact animals on comparable diets, except in duodenum.

On the potassium deficient diet, cortisone restored the sodium levels which had been elevated by adrenalectomy to those found in intact controls in this diet, except that the sodium level of the large intestine was not reduced to control values. On the control diets, sodium levels were reduced to normal by cortisone in all tissues except stomach, in which there was some residual elevation of sodium, and ileum, in which the sodium concentration was depressed below control levels.

The lack of relationship between potassium levels and motility was again indicated by the fact that cortisone produced extreme reductions in motility irrespective of diet or the presence or absence of the adrenal gland, but did not correspondingly decrease the potassium levels of the gastro-intestinal tract. Furthermore, in contrast to effects observed in

skeletal muscle, the potassium deficient diet did have effects in addition to those produced by cortisone alone. In the gastro-intestinal tract of adrenalectomized rats, cortisone partially restored the ability of the various tissues to lose potassium when on a potassium deficient diet, in addition to correcting most of the increases in tissue potassium caused by adrenalectomy.

d) Liver Electrolytes

Effect of Adrenalectomy

Adrenalectomy caused an increase of sodium and potassium in the liver as compared with intact animals on similar diets. The greatest increase occurred in the animals on the control diet.

Effect of Replacement with Individual Hormones of the Adrenal Gland

Adrenalin Treated Adrenalectomized Rats Adrenalin caused a significant increase of liver sodium and no change in potassium content in adrenalectomized animals on potassium deficient diets as compared with untreated adrenalectomized animals on the same diet. Conversely, adrenalin caused no increase in sodium, but an increase of potassium in the liver of adrenalectomized animals on a control diet. Adrenalin did not return the liver cation levels to those of intact animals. In fact, it caused a further retention of cations. It seems possible that adrenalin may reduce potassium in plasma in animals on a control diet partially by depositing it in liver. Dury, '53, has previously shown that adrenalin in proper amounts can cause an increase in liver potassium.

Cortisone Treated Intact Rats When cortisone was administered to animals with intact adrenals, there was a rise of both sodium and potassium in the liver to levels above those seen in untreated intact rats on a similar diets. The interpretation of these electrolyte disturbances is not

clear.

Cortisone Treated Adrenalectomized Rats Cortisone caused a dehydration of the liver in adrenalectomized animals as compared with untreated adrenalectomized animals and intact animals on similar diets. Thus diet had no effect on the dehydrating action of cortisone. In relation to dry weight, cortisone reduced the tissue potassium levels, which had been enhanced by adrenalectomy. It did not reduce tissue sodium values.

Thus adrenalin alone intensified the liver sodium and potassium retention caused by adrenalectomy. In intact rats, cortisone caused a similar increase of liver sodium and potassium but caused a reduction of potassium and had no marked effect on sodium in livers of adrenalectomized rats as compared with those of untreated adrenalectomized rats.

E. Discussion

The basic problems initially proposed will be discussed in the light of the present results under the following headings:

1. The role of the electrolytes in motility.
2. The comparison of the electrolyte changes in the gut with that of striated muscle and liver.
3. The role of the hormones in the pattern of alterations of electrolytes seen in potassium and/or sodium deficiency.

Role of Electrolytes in Motility

Limitations of the method of assessment of motility The problem of measuring the gastrointestinal motility of rats led to the investigation of various techniques of recording gut movement in vivo. The balloon recording devices (Gruber et al, '35) and the intraluminal pressure devices (Quigley et al, '52) were found to give too great a variability in their results, if results were obtainable. Other workers, (Chapman et al, '50), have emphasized the great variation in results obtained with balloon techniques. Also the effect on motility of the introduction of a foreign object into the fluid or semi-fluid contents of the small intestine is difficult to evaluate. The use of a mixture containing a high percentage of charcoal and acacia (Northup et al, '52) also would introduce a large mass of foreign material into the alimentary tract. Furthermore, the absorptive properties of charcoal may have an adverse influence on the electrolyte levels of the gastro-intestinal tract. In our experiments a dilute solution of gentian violet was used to follow the movement of solutions through the gastro-intestinal tract. The gentian violet solution was analysed for sodium and potassium content and was found to be free of these ions. Thus the results were not influenced by the introduction of exogenous

ions in the test solution. The possibility exists that minor decreases in the electrolyte content of the gut wall might be produced by uptake of water from or loss of ions into the dilute contents of the lumen. This effect would be restricted to those portions of the bowel which were transversed by the dye solution. It is not expected that the magnitude of these changes would be appreciable. Since the same solution was used in test and control animals, the composition of this fluid cannot account for differences in these results. In particular it seems unlikely that potassium depletion was responsible for impaired motility where this occurred but that this effect was masked by a greater loss of potassium into the test solution in control animals. If potassium depletion actually was responsible for impairment of motility, then dilution of the test "solution" should reduce the intestinal motility of all animals to the same level, since the final potassium content was the same in all animals both experimental and control. The present procedure gave excellent reproducible results and appeared to provide a valid estimate of upper intestinal motility in vivo (Table II). It would seem likely that if any segment of the upper intestinal tract showed significant decrease in motility this would be manifested as an overall decrease in transit of the dye solution. However, the technique did not permit a direct evaluation of variations in motility in different portions of the upper intestine and provided no indication of the activity of the lower bowel.

The large intestine and rectum of the animals on a low sodium, low potassium diet were distended with a larger quantity of faeces than was present in the control animals. This suggests that the lower part of the gastro-intestinal tract may also have been in a state of hypomotility.

However, no objective method of noting the extent of this inactivity was developed.

The adrenalectomized animals and those that received the hormones contained yellowish semi-fluid material throughout their gastro-intestinal tracts. Again, the motility of the upper portions of the tracts were evaluated with the gentian violet solution. The lower parts of the tracts were assumed to be hypomotile due to their marked distensions.

Changes in Electrolytes of Stomach Muscle in Relationship to Motility. There was no variation in the potassium level of the stomach, regardless of diet or treatment. Therefore the overall loss of motility could not be correlated with any potassium changes in the stomach. The tissue sodium level of the stomach was increased under certain conditions (intact animals on a high sodium, low potassium diet; adrenalin treated animals). Steinbach, '54 in a review article, suggests that sodium uptake decreases the force of a maximal contraction of skeletal muscle. However, the stomach muscles of the animals on a high sodium, low potassium diet, though increased in sodium content, were apparently normal in motility. At least, no overall change in motility in the upper bowel could be detected. Therefore the possibility that increased sodium concentration may be inhibitory was not supported by these results in the case of smooth muscle.

The stomach muscle, differed from the other samples of gastro-intestinal tract in that the mucosa was consistently stripped from it. This raises the possibility that the changes in potassium level seen in the rest of the gastro-intestinal tract may be due to alterations only in the mucosa rather than the smooth muscle, though this appears unlikely. Our methods do not differentiate between mucosa and smooth muscle of the gastro-intestinal

tract aboral to the stomach.

Changes in Electrolytes in the Duodenum and Ileum in Relation to Activity

The duodenum and ileum like the stomach, in general, showed very few instances in which potassium depletion occurred. Specifically, the duodenum had no loss of potassium or of sodium in any of the experimental procedures even in those groups that showed diminished intestinal activity. The possibility that a high tissue sodium may inhibit motility is not supported by this data, since the intact animals on a high sodium, low potassium diet did not have a loss of motility, even though the duodenum sodium content was increased. Similarly, the duodenum of the adrenalectomized animals on a low potassium diet contained a significant increase of sodium, and again, there was little indication of inhibition of motility. Finally, there were elevations in potassium content in some groups of hormone-treated animals but their intestinal motility was not different from other such groups with normal potassium levels. Therefore, as in the stomach, the duodenum showed no correlation between electrolyte levels and motility.

The ileum was unique in that in several procedures sodium and potassium were both decreased. The depletion of both cations did not invariably produce an alteration of motility. For instance, motility was decreased on the K deficient diet when sodium was also restricted, but not when the dietary sodium content was elevated, although the pattern of ionic change in the ileum was the same in both instances. Similarly, there is no indication that an increase in cation levels alters motility. In fact adrenalectomy alone causes an elevation in both sodium and potassium content of the ileum without causing an appreciable decrease of motility.

In view of the possibility that the overall changes which were recorded

in motility might have been due to diminished activity and altered electrolyte content in but one segment, it seems worthwhile to inquire if such an explanation can be excluded by the data. These data taken together exclude the possibility that decreases in potassium or in sodium in any segment might be correlated with loss of motility since there was loss of motility without depletion of sodium or potassium in any segment except the ileum in the doubly deficient diet, but a similar alteration of ileum electrolyte content on the low K, high sodium diet did not cause loss of motility. In no instance where motility was impaired (intact animals on doubly deficient diet) was there an increase in tissue potassium in any segment of the bowel. The possible role of increased sodium can likewise be eliminated since it occurred only in the stomach and duodenum and then on a high sodium diet where no loss of motility was recorded.

Changes in Electrolytes of Large Intestine and Rectum in Relation to Motility In no experimental procedure was the sodium level of the large intestine or rectum significantly lower than the levels of the intact control animals which had normal motility. Several procedures did cause an increase of tissue sodium. However, there was no correlation between these increases in tissue sodium and the decreases in motility which were noted in the upper intestine of some groups. Furthermore, although both increases and decreases in potassium content occur in the lower bowel, there is no correlation between either of these changes and motility changes elsewhere in the large intestine or rectum as indicated by its distension.

The problem as to why the gut should become relatively inactive, whereas the striated muscle retains its ability to contract, when the animals are

subjected to adrenalin or cortisone treatment or to low sodium, low potassium diets remains unanswered. The casuistic theories of Vaughn Williams, '54 Darrow, '50, and Henriksen, '51, thatparalytic ileus or gut distention is due to the loss of potassium from the gastro-intestinal tract seem to be incorrect. The data indicate that, though both adrenalin and cortisone can cause a marked reduction in gut motility, they do not cause a drop in the potassium levels of the tissue. In fact, in intact animals, cortisone produces an increase in the potassium content of the gastro-intestinal tract. While large doses of cortisone-like compounds can cause loss of motility this is not accomplished by depletion of potassium in these tissues.

The possibility that the increased sodium content of the alimentary tract might be inhibitory was definitely disproven for the upper portions of the gastro-intestinal tract. Alterations in the cation content of the lower bowel can not be correlated with changes of motility, since objective measurement of activity in this region was not achieved. Clinically, the infusion of potassium solution corrects the symptoms of paralytic ileus (Darrow, '45). It would be of interest to analyse the gastro-intestinal tissues after a potassium infusion in various conditions associated with impaired intestinal mobility to determine whether or not the motility would be restored to normal and to observe any tissue electrolyte changes which might accompany this procedure.

The Comparison of the Electrolyte changes in the Gut with that of Striated Muscle and Liver It is commonly assumed that the electrolyte content of one tissue and its responses to different treatments are representative of other tissues of the body. In agreement with Woodbury's results our data indicate that the responses to a given experimental

procedure of various tissues of the body are not uniform. For example, cortisone, in our intact rats, decreases skeletal muscle potassium but increases intestinal potassium. The results demonstrate that the two samples of skeletal muscle, five samples of gastro-intestinal tract, and the liver all contained different initial levels of sodium, potassium and chloride ions, and these responded differently to the various experimental procedures. It is possible that the various tissues may have contained differing amounts of extracellular material, especially connective tissue. This could account for differences in the initial levels of electrolytes in the same type of tissue. If this were the sole source of variation, calculated cellular cation contents should be similar in all tissues. This was not the case, since all gastro-intestinal tissues had higher calculated cellular potassium values than did skeletal muscle. Since the calculation of cellular content is based on the assumption that the chloride space is a measure of extracellular space, conclusions must be tentative until this assumption is verified or disproven. However, the electrolyte changes in the various types of tissue produced by the various procedures differ far too much from one another to be explained by differences in gross tissue structure.

The interpretation of tissue electrolyte changes in terms of underlying intracellular ionic alterations is difficult. The changes in total tissue electrolyte can result from changes in water or electrolyte content of cells or from changes of the extracellular content of tissues. From a functional point of view intracellular changes are of primary interest. Unfortunately the available methods do not allow accurate assessment of these changes. Nevertheless dubious assumptions are commonly accepted in an effort to arrive at an estimate of cellular ionic concentrations.

The results of such calculations must be evaluated with a great deal of reserve.

Role of Hormones in the Pattern of Alteration of Electrolytes seen in Sodium and/or Potassium Deficiency.

Effects of Adrenalectomy In adrenalectomized animals, both sodium and potassium content were increased in all tissue examined with the exception of the stomach. After adrenalectomy dietary potassium reduction did not have its usual effect on the electrolyte pattern of the tissues. This suggests that some portion of the adrenal gland is necessary for the depletion of plasma and muscle potassium during dietary potassium deficiency. Further, since the increases in tissue potassium following adrenalectomy were general and occurred even in the face of diminished potassium intake. The lack of tissue potassium depletion under these circumstances as a result of failure to excrete the potassium released by tissue catabolism seems to be an acceptable hypothesis.

Response of Plasma and Tissues to Cortisone Cortisone caused a hypochloremic, hypokalemic state in the animals regardless of diet. However, on investigating the individual tissues, a more complex picture appeared. In skeletal muscle, the electrolyte changes due to cortisone were independent of potassium intake. This suggests that cortisone can reduce muscle potassium by direct action. Thus the hypothesis that low potassium diets exert their influences by causing an excessive release of adreno-cortical hormones is compatible with this evidence.

Cortisone produced different changes in the gastro-intestinal tract electrolytes of intact as compared with adrenalectomized animals. The gastro-intestinal electrolytes of the adrenalectomized animals were also different from those of striated muscle. In cortisone treated adrenalectomized

rats the potassium free diet produced further potassium depletion in the gut in addition to that caused by cortisone alone, and the levels recorded approximated to those found in intact animals on similar diets, whereas dietary potassium deficiency did not enhance the potassium depleting effect of cortisone in skeletal muscle of adrenalectomized animals. These results suggest that hypercorticism alone could account for the potassium depletion of skeletal muscle seen in dietary potassium deficiency but is inadequate to explain the potassium depletion of the bowel produced by a deficient potassium intake, although cortisone is necessary for dietary potassium restriction to produce its usual effect in adrenalectomized animals. Although the effects of cortisone on plasma and skeletal muscle electrolytes might be attributed to improved renal capacity to excrete potassium, and a decreased rate of sodium excretion, this mechanism cannot explain the increased potassium content of gastro-intestinal tissues and liver in cortisone-treated intact animals. Here some direct alteration of the tissue distribution of electrolytes must be involved. This finding is perhaps worthy of emphasis since it further extends the evidence, presented by Woodbury, '53, that cortical steroids have direct extra-renal actions.

In addition, some of the data suggest strongly that cortisone can act directly on the kidney to cause additional potassium excretion. There seems to be no other explanation for the cortisone induced potassium depletion in all tissues and the plasma of adrenalectomized animals on an adequate potassium intake. If cortisone simply enabled the kidney to make homeostatic adjustments more efficiently (in this case to a potassium load derived from tissue catabolism) then it would not lower tissue or

plasma levels below those in the intact animal.

The needs of the body for cortical steroids vary widely depending upon the activity and the environment of the organism. The dose which would induce hypercorticism under optimal conditions, that is a dose which might be classified as pharmacological, may barely satisfy the needs of an organism vigorously engaged in a homeostatis response to stress or an organism lacking hormonal secretions. Therefore the electrolyte response to the same dose of hormones under the varying circumstances of hypercorticism, eucorticism, or hypocorticism, may be entirely different and the stress induced by dietary potassium deficiency might have been expected to increase the amount of cortisone required for controlling potassium metabolism. However, some of the effects of the doses of cortisone used here (e.g. weight loss, lowering of plasma potassium) are usually considered to be evidence of pharmacological effects. A pharmacological dosage was not undesirable for the purpose of testing theories of motility because other workers claim that symptoms seen in gut distention and paralytic ileus are due to excessive activation of the adrenal cortex. However, high dosage makes interpretation of other effects uncertain in relation to normal physiology. For example, the difference in the response between intact and adrenalectomized animals might be attributed to the use of a fixed dose of cortisone. Furthermore, the direct action of cortisone on tissue electrolytes and on renal excretion demonstrated in this study may be the result of the high dosage used.

In any case the data contradict the theory that excess adrenalcortical steroids are the cause of paralytic ileus following operative procedures,

as a result of their effects on intestinal potassium. In no case did a dose of cortisone which was so large as to produce weight loss intestinal hypomotility and pronounced potassium loss from skeletal muscle, cause any depletion of gastro-intestinal potassium beneath levels in intact animals. Why cortisone in this dosage, antagonized the effects of adrenalectomy on gastro-intestinal potassium content but caused additional changes in skeletal muscle potassium remains an enigma.

Responses of Plasma and Tissue to Adrenalin The animals were treated with adrenalin simply to provide controls for complete replacement therapy. It was rather unexpected that adrenalin should cause adrenalectomized animals to gain weight and to prolong their lives. The drop in plasma potassium produced by adrenalin has been reported by Rogoff et al, '50. He concludes that adrenalin can function as well as steroid components of the cortex in maintaining normal blood plasma potassium levels. It would be of interest to investigate further the effects of chronic pharmacological doses of adrenalin on intact animals, and on the prolonged maintenance of adrenal-ectomized rats. The doses of adrenalin used in the experiment were pharmacological in that they caused edema formation, and a hypokalemia. In future experiments it would also seem desirable to investigate the effects of physiological doses of adrenalin on the maintenance of adrenal-ectomized rats.

In adrenalectomized animals, adrenalin in the presence of a low potassium diet, lowered the electrolyte concentration of skeletal muscle to the values found in intact animals, an effect which could not be accomplished by dietary potassium restriction alone. Adrenalin alone did not prevent the changes initiated by adrenalectomy. Adrenalin permits the low potassium diet to exert its usual effects on skeletal muscle potassium content despite

adrenalectomy. The possibility remains that the potassium deficient diet does cause a depletion in this tissue by a direct action provided that the adrenal medulla is functional, without the effect being mediated via one of the adrenal hormones. The adrenal medulla may be essential for the renal excretion of potassium which accompanies potassium depletion during dietary potassium restriction.

In the gastro-intestinal tract, adrenalin had a different effect than in the skeletal muscle. Here adrenalin in the presence of the low potassium diet could not completely correct the electrolyte changes caused by adrenalectomy. Furthermore, it caused an even greater increase of the sodium content of the alimentary tract. Thus the adrenalin combined with low potassium diet could partially but not completely correct the electrolyte changes caused by adrenalectomy in the gastro-intestinal tract. This suggests that the presence of the adrenal medullary hormone alone is not sufficient to permit potassium depletion to occur in the lower bowel of intact animals deprived of dietary potassium. This suggestion is in agreement with the previously mentioned possibility that cortical steroids are essential for the development of potassium depletion in the bowel. However, these data are inconsistent with the theory that potassium depletion from skeletal muscle during deficient dietary intake is the result of hypercorticism, since adrenalin alone is capable of permitting depletion to occur in this tissue.

One other conclusion can be drawn from the data concerning the effects of adrenalin on tissue and plasma electrolytes. Most of the effects of adrenalin on potassium levels could be explained in terms of "improved" renal potassium excretion. However, there is a suggestion that there is actually an increase in tissue potassium, especially in liver, when adrenalin

is administered to adrenalectomized animals with an adequate potassium intake. The simplest explanation of this observation would be a direct action of adrenalin on the tissues leading to potassium accumulation.

Anatomically, the site of production of adrenalin and cortisone are related, but chemically the two structures bear no relationship to one another. This gives rise to an interesting problem as to how two chemicals so dissimilar in structure, can exert certain similar reactions (e.g. hypokalemia, hypomotility) in the body. As yet, no metabolic pathway has been identified for the synergistic action of these two hormones.

F. Summary and Conclusions

1. The cation content of various portions of the gut from rats on a low sodium, low potassium diet and on high sodium, low potassium diet, have been determined and compared with those of similar portions of the gut of animals on a control diet. The responses to a high sodium,low potassium diet after adrenalectomy both with and without medullary or cortical hormonal supplementation was also determined. The electrolyte patterns of liver and of skeletal muscle from different portions of the body were similarly analysed and compared.

2. A new technique based on the passage of a solution containing the dye, gentian violet, was developed for estimating upper bowel motility, but the procedure did not permit evaluation of motility of the lower bowel.

3. In none of the circumstances studied was it possible to correlate alterations in the gastro-intestinal tract content of sodium and/or potassium with motility. The problem as to why the gut should become relatively inactive when subjected to various procedures remains unsolved.

4. Careful analyses of the selected tissues of the body indicate that initial electrolyte concentration and responses to diets and hormones vary within similar tissues and between different organs. Evidence is presented to show that not all differences could be the result of initial differences in extracellular material.

5. Adrenalectomy prevented dietary potassium deficiency from decreasing tissue potassium. Evidence indicating that adrenalectomy results in impaired ability to excrete potassium is discussed.

6. Although an excess of cortisone did cause diminished alimentary tract motility, and loss of potassium from striated muscle, the hypothesis that adrenal cortical hormones cause immotility through a loss of potassium or

a gain of sodium was disproven.

7. Evidence is presented that cortisone can influence the electrolytes of the body by acting on the cells of peripheral tissues as well as on the kidney and that a high dose administered has direct as well as permissive effects.

8. Evidence is presented indicating that adrenalin can partially restore the ability to excrete potassium and the ability of tissues to undergo potassium depletion in adrenalectomized animals on a potassium deficient diet. The possibility that adrenalin may play an important role in maintaining electrolyte homeostasis is discussed.

9. The possibility is suggested that the cortex and medulla of the adrenal gland may exert synergistic influences on the electrolytes of the body.

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