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Research Article

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These findings suggest that intense physical work in the heat stimulates higher production of aldosterone than would occur in nonexercising subjects on similar sodium intakes. Similar to the phenomenon of mineralocorticoid escape, such overproduction of aldosterone in the presence of conditions permitting excretion of sodium into the urine could facilitate continued excretion of potassium by the kidney despite serious potassium depletion. As a consequence, the kidney played a role in the genesis of potassium depletion in these subjects.

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Pathophysiology of Intense Physical Conditioning in a Hot Climate

I. MECHANISMS OF POTASSIUM DEPLETION

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ABSTRACT Serial estimations of exchangeable ^{42}K showed that six volunteer subjects undergoing intensive physical conditioning in a hot climate sustained a mean deficit of 517 mEq. This deficit occurred despite a daily potassium intake of 100 mEq. Simultaneous values for lean body mass rose suggesting that potassium deficiency was *not* the result of catabolism. Although sweating was the major avenue by which the deficit occurred, daily excretion of potassium into the urine when each subject was maximally deficient ranged from 46 to 75 mEq and thus was inappropriately high for potassium-depleted subjects. Despite high intakes of sodium and excretion of corresponding quantities into the urine, Na/K ratios in sweat were low thus indicating unsuppressed activity of aldosterone on sweat glands. Moreover, excretion and secretion of aldosterone and in many instances, plasma renin activity, appeared to be high with respect to sodium intake.

These findings suggest that intense physical work in the heat stimulates higher production of aldosterone than would occur in nonexercising subjects on similar sodium intakes. Similar to the phenomenon of mineralocorticoid escape, such overproduction of aldosterone in the presence of conditions permitting excretion of sodium into the urine could facilitate continued excretion of potassium by the kidney despite serious potassium depletion. As a consequence, the kidney played a role in the genesis of potassium depletion in these subjects.

In contrast to subjects undergoing conditioning in the summer months, potassium depletion did not occur in 16 subjects during identical training under cooler environmental conditions.

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INTRODUCTION

Potassium depletion. Intensive physical conditioning in hot climates may be accompanied by serious environmental heat injury (1–4). The importance of this problem in the military population is exemplified by an incidence exceeding 1700 cases per 100,000 men stationed in the southwestern United States during the month of July, 1966 (5). Although dehydration and electrolyte disturbances account for the bulk of such cases, it is widely appreciated that not only military recruits but also apparently healthy young men undergoing conditioning for football in the late summer months are prone to develop severe and often fatal heat stroke.

It has been our experience that heat stroke in these young men often differs in several respects from that observed in older patients. It commonly occurs with intense physical exertion; environmental temperature and humidity need not be extremely high; sweating is commonly evident despite extreme hyperpyrexia; it seems to occur more commonly in individuals of heavy muscular habitus who otherwise appear to be in excellent physical condition and finally rhabdomyolysis, myoglobinuria, and acute renal failure are common complications (2). We have previously considered the possibility that rhabdomyolysis in these men might be the consequence of potassium depletion (2, 3) since the two conditions have been associated (6, 7).

It has been shown (8) that men undergoing basic military training in hot climates may secrete more than 12 liters of sweat daily. Since potassium concentration in sweat averages approximately 9 mEq/liter (9), this vol-

ume of sweat could readily lead to cutaneous potassium losses exceeding 100 mEq. Although intake of potassium is approximately 100 mEq (10), large potassium losses in sweat and continued losses of potassium in urine or stools could facilitate a severe deficit within a short time.

There are other mechanisms whereby work in the heat might lead to potassium deficiency. Excessive production of aldosterone might occur despite a high salt intake (11). Thus, in the presence of aldosterone produced in "pulsed" cycles during intense exercise, subsequent reexpansion of the extracellular volume after ingestion of salt and water might allow sodium to reach the distal nephron where it could exchange for potassium. This is feasible since aldosterone may act on the kidney as long as 8 hr (12).

Finally, excretion of potassium in excess of intake could be catabolic consequent to thermal stress per se (13) or fever generated by muscular work (14). However, in either situation, losses would be proportional to nitrogen and therefore true potassium deficiency would not occur.

Previous experiments examining the consequences of physical conditioning in a hot climate have either been of brief duration, have not imposed the physical stress which prevails under natural conditions, or were done before availability of satisfactory methods to measure aldosterone, plasma renin activity, body composition, and body fluid spaces. Two studies showed that mild potassium depletion occurred during heat exposure in an environmental chamber when potassium intake was marginal (15, 16). Although prolonged study of electrolyte metabolism ordinarily requires the balance technique, such studies under natural conditions would fail consequent to heavy losses of electrolytes and nitrogen in sweat (17). As an alternative, isotope dilution studies enable serial measurement of body composition without the error of balance techniques.

The major objective of this study was to quantitate exchangeable ^{42}K ($^{42}K_e$) serially during the first 32 days of basic military training in hot and cool climates and if potassium depletion occurred, to elucidate its mechanism.

We observed that potassium depletion occurred only in men training in hot climates. Although sweating was the major means of loss, aldosterone production seemed inappropriately high in terms of sodium intake and was probably responsible for failure of the kidney to conserve potassium.

METHODS

Selection of subjects was based upon previous sedentary employment and origin from the northwestern United States to minimize preexisting acclimatization to heat; complete understanding of the purpose, procedures, and possible hazards of the study and satisfactory physical condition as determined by physical examination.

24 subjects were selected. Six of these were studied during the summer months of 1967 (group I), nine during the winter of 1968 (group II), and nine during the early summer of 1968 (group III). One subject of group II withdrew after day 7 and one subject in group III withdrew after day 21.

Diets were prepared from common food lots, weighed, and frozen to provide a constant daily intake representative of that consumed by the average military trainee. Each contained 4180 cal, 146 g protein, 158 g fat, 546 g carbohydrate, and 101 mEq potassium.[1] Sodium and potassium in each lot was determined in triplicate by flame photometry after ashing and acid digestion. All food was consumed *in toto* throughout each study. Supplements of NaCl were administered *per os* as 1% NaCl in distilled water.

The training program is physically exhausting and stereotyped. It does not vary with the season of the year unless extreme conditions of heat or humidity require modification. On training day 10, each subject takes part in a competitive physical proficiency test requiring completion of specific tasks in a minimum time. On days 29, 30, and 31 of the program, all activities are conducted under bivouac conditions. These 3 days are the most physically exhausting of the program. For example, on day 31, each trainee marches 20 miles over rough terrain while carrying a 30 lb. field pack, during which time he is subjected to tear gas attack, helicopter assault, simulated rifle fire, ambush, and artillery fire. After darkness he must negotiate an infiltration course under overhead machine gun fire. The trainees are then returned to the barracks and must complete an additional mile run before retiring at approximately midnight. Reveille is held at the usual time on day 32 at 5:00 a.m.

For convenience and relative constancy of physical activity, studies were performed on Thursday of each week for 6 consecutive weeks. The control study was performed before training began. Physical activity was light on the control day.

Procedure of study for group I (six subjects). The first study was performed in the summer of 1967. Three subjects (Ch, Jo, and La) received 178 mmoles and three subjects (Re, Ta, and Ti) 355 mmoles of NaCl daily. Water intake was ad lib. After arising at 5:00 a.m., the subjects were moved to a metabolic ward. Each nude subject was weighed to the nearest 50 g on a metabolic scale and immersed in a calibrated body volumeter according to the method of Allen and his associates (18) as modified by Krzywicki and Chinn (19). The mean value of three immersions, recorded during maximal expiration, was used to estimate body volume. Residual lung volume was measured by the method of nitrogen washout (20) and deducted from the total volume measured by immersion. Lean body mass (LBM)[2] was estimated from the formula (19) $LBM = M - [4.878[V - V_R]] - [4.415 \times M]$ wherein M represents body weight in kg; V, total body volume (liters); and V_R, residual lung volume. In subjects of group I, total body water was assumed to be $0.732 \times LBM$ (21). After measurement of body volume, each subject reclined quietly

[1] Estimated from Composition of Foods—Raw, Processed, Prepared. Agriculture Handbook No. 8. U. S. Department of Agriculture. December, 1963.

[2] *Abbreviations used in this paper:* ECV, extracellular fluid volume; LBM, lean body mass; PRA, plasma renin activity.

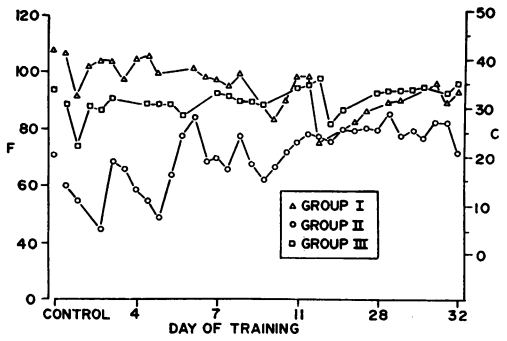

FIGURE 1 Daily maximum dry bulb temperatures recorded during each study.

for 30 min. Blood samples were then collected and other necessary materials administered. At noon, blood samples were collected again for plasma renin activity (PRA).

Since total body sweat could not be collected, an approximation of sodium and potassium losses as well as their concentration ratio, an indirect index of aldosterone activity (22), was estimated from clothing eluates. To facilitate this, clean, dry, distilled H_2O-rinsed clothing was issued on the morning of each study day after measurement of body volume (volumeter filled with deionized H_2O), collected in plastic bags the following morning and subsequently eluted with 6.0 liters of distilled water. Sodium and potassium content of soil varied from 0.86 to 2.2 and 0.13 to 0.21 mEq/100 g respectively and therefore contamination by soil was not considered to contribute significantly to total recoveries. Urine excreted on each study day was collected and stored under refrigeration in polyethylene bottles without a preservative.

Exchangeable potassium ($^{42}K_e$) was estimated by the method of Corsa, Olney, Steenburg, Ball, and Moore (23). ^{42}KCl (Hastings),[3] 1 μCi/kg body weight was administered intravenously. ^{42}K excreted in urine during the following 24 hr was deducted from the administered dose and this value was divided by the mean specific activity of ^{42}K in three consecutive spot-urine collections obtained after 24–26 hr of equilibration. A well-type scintillation detector was utilized for ^{42}K counting.

Aldosterone secretory rates were estimated from the specific activity of the acid-hydrolyzable metabolite in urine collected for 24 hr after injection of aldosterone-2-^{3}H. Aldosterone secretory rates and excretory rates were estimated by the double-isotope dilution method of Kliman and Peterson (24).[4] When recovery of tritium from aldosterone-2-^{3}H in 24 hr urine collections did not exceed 90% of the injected dose, the values for aldosterone secretory rates were discarded. To discount the possibility that part of the aldosterone-2-^{3}H might be excreted in sweat and thereby elevate its secretory rate spuriously by diminishing specific activity of the urinary metabolite, sweat samples were collected during active perspiration into plastic bags sealed over the forearm for several hours after administration of the isotope. These samples were counted in a Packard Tri-Carb, liquid scintillation system (Packard Instrument Co, Downers Grove, Ill.). No radioactivity above background was detected, thus, in agreement with the findings of Jenkins, Rivarola, Brusilow, and Migeon (25), it was concluded that significant quantities of tracer were not lost by this route.

Sodium and potassium were measured by flame photometry, chloride by the potientiometric method of Cotlove, Trantham, and Bowman (26), and total CO_2 in plasma by the manometric method of Van Slyke and Neill (27). PRA was estimated by the method of Boucher, Vegrat, de Champlain, and Genest (28) as modified by Pickens, Bumpus, Lloyd, Smeby, and Page (29).[5]

Procedure of study II (nine subjects). This study was performed during the late winter of 1968. It was patterned similarly to that of group I except as follows: nine subjects were divided into groups of three whose daily intake of sodium was 150, 250, and 350 mmoles. For this and the subsequent study, blood specimens were collected between 4:30 and 5:00 a.m. before the subjects arose. Total body water was estimated from dilution of tritiated water administered orally by estimating its specific activity in vacuum-distilled serum water sampled at 3 hr after ingestion (30). Residual activity of tritium in plasma water remaining from each preceding week was deducted from the administered dose of isotope. Exchangeable ^{42}K was not measured on study day 21. One subject withdrew from this study after day 7.

Procedure of study III (nine subjects). This study was performed during the early summer of 1968. Subjects of this group spent the control day at comparative rest in an air-conditioned metabolic ward. To elucidate the effect of sodium intake on urinary potassium excretion, five subjects received 267 mmoles and four subjects 114 mmoles sodium per day. Sodium intakes were then interchanged on days 5 through 11 and thereafter returned to original quantities.

Extracellular fluid volume (ECV) was estimated from dilution of injected radiosulfate (31). For this procedure, 50 μCi of $Na_2{}^{35}SO_4$ was injected rapidly and its activity measured in plasma at 20 min—using a liquid scintillation detector (Tri-Carb, Packard Instrument Co.) in samples prepared by the method of Mahin and Lofberg (32).

RESULTS

Group I. Daily dry bulb temperatures (Fig. 1) often exceeded 100°F (38°C) during the first 12 days of training.

Serial measurements of body composition are shown in Tables I A and I B. Total $^{42}K_e$ fell in each subject. The average maximum deficit for $^{42}K_e$ in those receiving 355 mmoles NaCl was 517 mEq (range: 451–567) and in those receiving 178 mmoles NaCl 507 mEq (range: 370–572 mEq). Losses of potassium were greater on day 4 in subjects receiving the higher sodium intake. $^{42}K_e$/kg LBM fell in each subject during the period of potassium depletion and rose again as total $^{42}K_e$ rose.

The observation that LBM rose in each subject (Table I) suggests that potassium losses were not consequent to protein catabolism. All subjects perspired heavily during the first 12 days of training but much less there-

[3] Hastings Radiochemical Works, Inc, Friendswood, Tex.

[4] Performed by New England Nuclear Corp, Boston, Mass.

[5] Kindly performed by Dr. Norman Kaplan, The University of Texas (Southwestern) Medical School, Dallas, Tex.

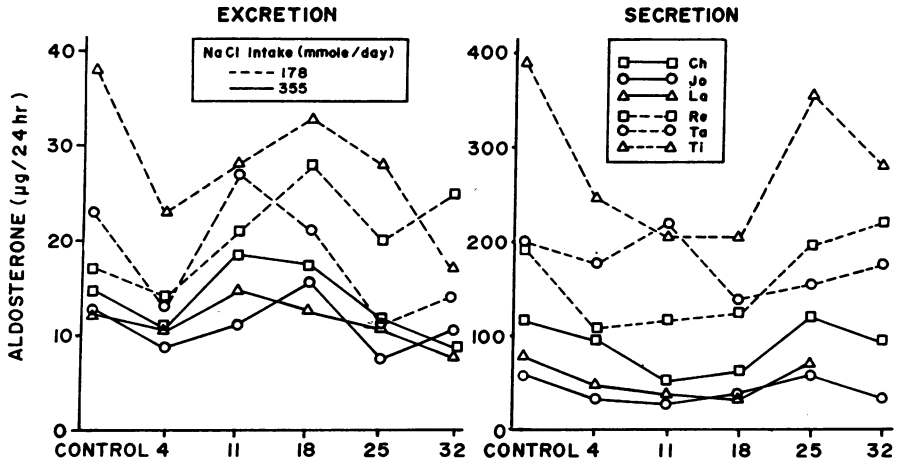

FIGURE 2 Excretion and secretion of aldosterone in subjects of group I.

after as hot environmental conditions abated. Recoveries of potassium from clothing extracts and urine on each study day (Table II) showed that exclusive of unaccountable sweat losses, their sum frequently approached or exceeded total potassium intake. Although potassium recoveries from clothing are at best approximations and are indicative of losses only on study days, extrapolation of these data to the entire period of study would account for the deficit measured by $^{42}K_e$. For example, the mean deficit of $^{42}K_e$ for the entire group on day 11 was 422 mEq. To establish this deficit required a mean daily loss of only 38 mEq in excess of intake. The sum of unrecovered potassium losses in dripped sweat, that which adhered to the skin or that excreted in feces could easily account for such a daily deficit.

Excretion of potassium in the urine (Table II) was higher than than anticipated for potassium-depleted subjects (33). Thus, on study days 4, 11, and 18, urinary potassium excretion varied between 52 and 77 mEq. No clear relationship was discernable between potassium excretion in urine to either sodium intake or sodium excretion.

No subject became frankly hypokalemic (Table II). The plasma concentration of Na, Cl, and total CO_2 remained normal.

Aldosterone excretion and secretion are shown in Fig. 2. Subjects ingesting 178 mmoles NaCl clearly excreted and secreted more aldosterone than those ingesting 355 mmoles of NaCl. Compared with initial values, aldosterone secretory rates were lower on study days 4, 11, and 18. This pattern of aldosterone secretion corresponded to that of potassium depletion. Although aldosterone excretion was lower on study day 4, subsequent values did not follow the pattern of aldosterone secretion.

Ratios of excreted to secreted aldosterone measured by this analytical method normally approximate 0.1 (34–36). Although ratios were slightly elevated on the control day in those subjects ingesting 355 mmoles NaCl, higher values were observed in all subjects on days 11 and 18 (Fig. 3). These values were appreciably higher (ranging from 0.36 to 0.42) in individuals receiving high NaCl intakes. By contrast, the highest values observed in the subjects on lower sodium intakes ranged from 0.15 to 0.23.

To assess inferentially the biologic effect of aldosterone on sweat glands, mean concentration ratios of Na/K in clothing were calculated on each study day and are shown in Table II. All subjects showed a lower Na/K ratio in sweat on day 4 which was significantly different from control values ($P < 0.01$). Mean values for this ratio were not significantly different between the two groups despite the difference of NaCl intake.

Plasma renin activity (PRA) is shown in Fig. 4. Although normal subjects demonstrate wide variations, their average values are usually less than 300 ng/100 ml in the recumbent position and less than 500 ng/100 ml after standing. By these criteria, 15 of 18 values in recumbent subjects receiving 175 mmoles NaCl, and 10 of 18 in those receiving 350 mmoles NaCl were elevated after activity. 9 of 18 values in subjects receiving 178 mmoles NaCl were greater than 500 ng/100 ml as were 6 of 18 in those ingesting 355 mmoles NaCl.

Increased values for PRA were observed in all subjects after activity on the control day and day 11. On subsequent study days, anticipated increases of PRA after activity were not commonly observed.

Group II. In contrast to the first study, environmental temperature was generally cool (Fig. 1). Comparison of individual sequential measurements of $^{42}K_e$, $^{42}K_e$/LBM and total body water in these subjects showed no relationship to NaCl intake. Therefore, all data were grouped and averaged values are shown in

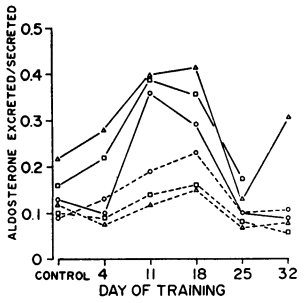

FIGURE 3 Serial ratios of excreted to secreted aldosterone in subjects receiving 355 mEq (——) and 178 mEq (- - - -) NaCl daily. Symbols refer to subjects as indicated in Fig. 2.

Table III. In contrast to the findings in group I, total $^{42}K_e$ remained normal in group II. By day 32, the average gain of $^{42}K_e$ was 386 mEq and similarly $^{42}K_e$/kg LBM rose. A net gain of $^{42}K_e$/kg LBM by the end of the training cycle suggests an increase of muscle mass. Comparison of the difference between mean values for total body weight and lean body mass on the control day (10.2 kg) and day 32 (8.4 kg) supports the latter contention. The greater gain of total body water than lean body mass suggests that the excess was located in the extracellular compartment.

Recovery of potassium in clothing eluates on the first 3 study days ranged from 2 to 6 mEq and consequently for the remainder of this study only undershirts were

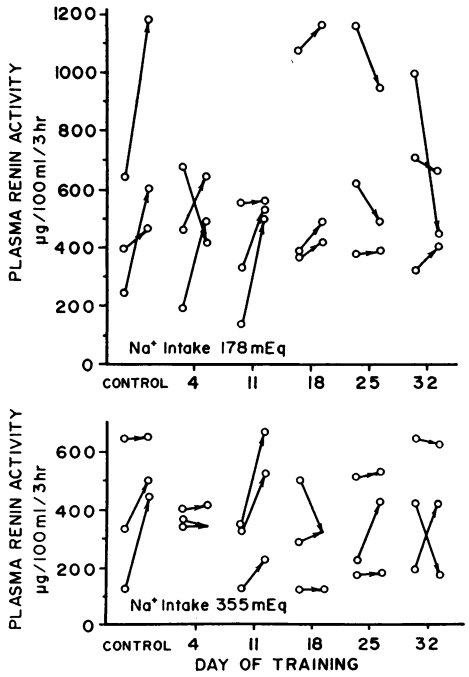

FIGURE 4 Group I. Weekly values for plasma renin activity determined early in the morning and at noon.

TABLE I

The Pathophysiology of Physical Conditioning in a Hot Climate. I. Potassium Depletion

Subject	Day of training	Potassium (mEq) $^{42}K_e$	Potassium (mEq) $^{42}K_e$/kg LBM	Weight	Lean body mass
				kg	*kg*
Group I A, NaCl intake, *355 mmoles*					
Ch	Control	2971	43.9	70.85	67.75
	4	2662	39.9	71.40	66.69
	11	2400	34.9	73.20	68.75
	18	2744	40.5	73.15	67.74
	25	3203	46.0	73.85	69.70
	32	—	—	73.25	69.68
Jo	Control	2840	49.4	61.85	57.52
	4	2470	41.3	63.95	59.85
	11	2483	42.0	65.35	59.12
	18	2768	45.4	65.75	61.04
	25	2598	41.4	66.45	62.75
	32	3027	50.1	66.10	60.37
La	Control	3651	54.7	74.12	66.76
	4	3079	45.0	76.35	68.45
	11	3176	45.6	78.25	69.58
	18	3102	44.6	78.05	69.59
	25	3436	48.7	79.55	70.57
	32	3508	49.5	79.30	70.88
Group I B, NaCl intake, *178 mmoles*					
Re	Control	2953	56.1	64.35	52.64
	4	2807	48.8	66.30	57.56
	11	2386	38.4	67.60	62.17
	18	3214	50.6	68.65	63.58
	25	3340	52.1	69.50	64.16
	32	3344	52.7	69.95	63.41
Ta	Control	3139	55.7	58.90	56.32
	4	2748	47.5	60.95	57.89
	11	2869	49.0	62.45	58.80
	18	2688	45.4	63.20	59.19
	25	2853	46.9	64.50	60.85
	32	3450	58.0	64.15	59.45
Ti	Control	3959	53.4	84.60	74.16
	4	3655	47.7	85.30	76.57
	11	3425	45.2	86.15	75.71
	18	3459	45.5	86.40	76.09
	25	3978	51.9	85.90	76.68
	32	4144	55.4	85.80	74.80

Group I consecutive weekly values for total exchangeable ^{42}K ($^{42}K_e$), exchangeable ^{42}kg lean body mass ($^{42}K_e$/kg LBM), body weight and lean body mass (LBM).

eluted to obtain ratios of Na/K. Compared with the value on the control day, the average ratio was significantly lower only on day 32 ($P < 0.01$) (Table IV).

Mean values for urinary potassium excretion were not different from those observed in group I (Table II). Sodium excretion in urine corresponded closely to dietary intake.

TABLE II

Electrolytes in Urine, Sweat, and Plasma‡

Day of study	Urine K^+	*Sweat K^+	Urine Na^+	*Sweat	Plasma (mEq/liter) Na^+	K^+	Cl^-	HCO_3^-
	mEq/day	*mEq/day*	*mEq/day*	*Na/K*				
Group IA, Na^+ intake, *355 mmoles/day*								
Control	66	29	308	4.6	145	3.5	107	25
	(60–70)	(23–40)	(185–382)	(2.6–6.5)	(143–146)	(3.4–3.6)	(105–110)	(23–26)
4	57	38	203	2.9	143	4.0	106	24
	(41–75)	(35–42)	(187–226)	(2.6–3.6)	(143–144)	(3.5–4.1)	(99–110)	(24–25)
11	61	19	211	4.1	144	3.8	109	24
	(46–79)	(10–30)	(195–230)	(2.8–4.9)	(142–147)	(3.6–4.0)	(104–115)	(19–27)
18	77	24	248	3.3	144	3.9	108	27
	(69–87)	(19–31)	(227–264)	(1.9–4.1)	(144–144)	(3.6–4.4)	(106–111)	(24–28)
25	79	25	227	2.1	141	3.7	106	26
	(72–87)	(17–39)	(204–240)	(0.3–3.2)	(140–142)	(3.5–4.0)	(105–108)	(24–28)
32	49	14	183	2.2	143	3.6	108	22
	(48, 50)	(9–20)	(162–198)	(1.7–2.9)	(142–144)	(3.5–3.6)	(107–108)	(21–24)
Group IB, Na^+ intake, *178 mmoles/day*								
Control	46	27	108	7.9	143	3.8	107	25
	(33–56)	(22–34)	(46–151)	(3.0–15.3)	(142–144)	(3.6–4.0)	(106–108)	(25–25)
4	72	35	80	3.9	142	4.1	106	23
	(68–79)	(24–42)	(49–118)	(3.0–4.7)	(141–142)	(3.9–4.2)	(105–107)	(22–25)
11	52	28	92	3.2	144	3.7	110	22
	(48–56)	(18–42)	(83–97)	(2.5–3.6)	(140–148)	(3.5–4.0)	(107–112)	(21–24)
18	67	21	100	3.1	141	3.8	105	23
	(58–72)	(11–32)	(83–122)	(2.7–3.3)	(141–142)	(3.7–4.0)	(104–107)	(22–27)
25	72	20	111	2.4	142	3.7	107	25
	(58–89)	(12–35)	(81–112)	(2.0–3.1)	(141–144)	(3.6–3.8)	(104–109)	(20–28)
32	51	27	73	2.2	143	3.5	109	21
	(45–57)	(11–50)	(36–96)	(1.9–2.5)	(142–144)	(3.4–3.6)	(108–109)	(21–22)

Weekly values for electrolytes in urine, clothing eluates, and plasma from subjects of group I.

* Based upon recovery from clothing eluates.

‡ Mean and range.

Serum potassium concentration remained normal with the exception of five isolated values which ranged from 3.3 to 3.4 mEq/liter. Serum sodium concentration rose and attained a value of 152 mEq/liter on day 32. This was not related to NaCl intake. Mean values for chloride and bicarbonate concentration in plasma were normal throughout the study.

Aldosterone excretion and secretion (Fig. 5) varied widely on the control day. On day 4, values were higher in all subjects whose sodium intake was 150 mmoles. Subsequently, there was no apparent relationship between aldosterone excretory rates and sodium intake. However, aldosterone secretion, except for an isolated value on day 4, was consistently higher in subjects whose Na intake was 150 mmoles. There was little apparent difference in values for subjects receiving 250 or 350 mmoles of NaCl suggesting maximum suppression of aldosterone secretion by a NaCl intake of 250 mmoles under these conditions.

As in group I, ratios of excreted to secreted aldosterone tended to be higher in subjects receiving higher sodium intakes. However, in contrast to results of study

TABLE III

*Group II, Body Composition**

Day of study	Weight	LBM	$^{42}K_e$	$^{42}K_e$/LBM	TBW
	kg	*kg*	*mEq*	*mEq/kg*	*liter*
Control	73.5 ±4.1	63.3 ±3.2	3330 ±184	53.3 ±2.0	48.2 ±2.8
4	73.7 ±3.9	65.0 ±3.2	3395 ±147	52.4 ±1.1	48.9 ±2.8
11	74.7 ±3.9	64.9 ±3.3	3383 ±136	52.4 ±1.8	48.0 ±2.2
18	75.2 ±3.8	66.3 ±3.4	—	—	48.9 ±2.0
25	75.4 ±3.8	66.4 ±3.5	3586 ±137	54.4 ±1.4	51.5 ±2.4
32	75.2 ±3.7	66.8 ±3.6	3716 ±147	56.4 ±1.5	52.1 ±2.2

Group II, serial values for body weight, lean body mass (LBM), total exchangeable ^{42}K ($^{42}K_e$), exchangeable ^{42}K/kg lean body mass ($^{42}K_e$/LBM), and total body water.

* Mean ±SEM.

TABLE IV

*Group II, Electrolytes in Urine, Plasma, and Sweat**

Day of study	Urine K excretion	Plasma concentration mEq/liter				Sweat
	K	Na	K	Cl	HCO_3	Na/K
	mEq/day					
Control	77 ±8	145 ±0.6	3.8 ±0.1	106 ±0.5	26.6 ±0.5	3.3 ±0.3
4	58 ±4	142 ±0.4	3.9 ±0.1	106 ±0.6	24.5 ±0.5	4.1 ±0.6
11	82 ±5	148 ±0.6	3.7 ±0.1	108 ±0.4	24.9 ±0.6	4.7 ±1.0
18	68 ±5	146 ±0.4	3.7 ±0.1	108 ±0.7	24.6 ±0.6	2.6 ±0.4
25	62 ±3	148 ±1.1	3.7 ±0.1	109 ±0.7	24.6 ±0.5	2.8 ±0.6
32	64 ±4	152 ±0.7	3.8 ±0.1	108 ±0.8	23.9 ±0.6	1.3 ±0.2

Group II, serial values for potassium excretion in urine, plasma electrolyte concentrations, and Na/K ratios in clothing eluates.

* Mean ±SEM.

I where values as high as 0.42 were observed, values in study II did not exceed 0.18.

As in the first study, PRA (Fig. 6) was not clearly predictable with respect to NaCl intake or physical activity.

Group III. Maximum dry bulb temperatures during this study were unseasonably low (Fig. 1). As a consequence, the subject's sweat production was much less than anticipated. Data on body composition are shown in Table V. Determination of $^{42}K_e$ was possible only on the control day and days 4 and 11 due to subsequent unavailability of ^{42}K. $^{42}K_e$ rose in all subjects during during the first 11 days of training. LBM also rose and therefore $^{42}K_e$/kg LBM remained essentially unchanged. Mean body weight and LBM rose in both groups. On day 11, subjects of group A, whose NaCl intake on days 5 through 11 had been increased to 267 mmoles, demonstrated an average gain of 1.2 kg in body weight and 1.8 kg LBM. That these changes bore little relationship to alteration of NaCl intake is suggested from similar changes in body weight and LBM in group B whose NaCl intake was lower during the same period. These observations are also supported by a similar trend in mean values for total body water. Although extracellular volume rose more in group A the difference between the groups was not statistically significant.

Subsequent to day 11, the effects of different NaCl intakes were more apparent. In this study, all subjects took part in the physical proficiency test on day 17 insteady of day 10. Subjects of group A showed lower body weight on day 18 than day 11 whereas those of group B did not ($P < 0.05$).

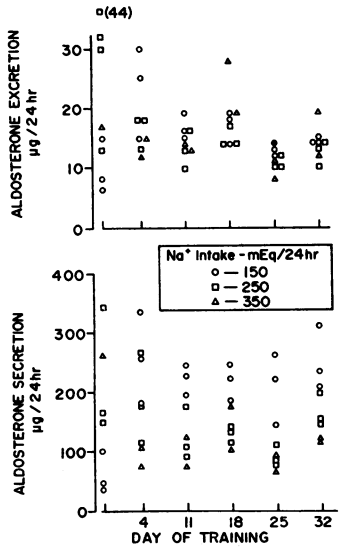

FIGURE 5 Weekly values for excretion and secretion of aldosterone in all subjects of group II.

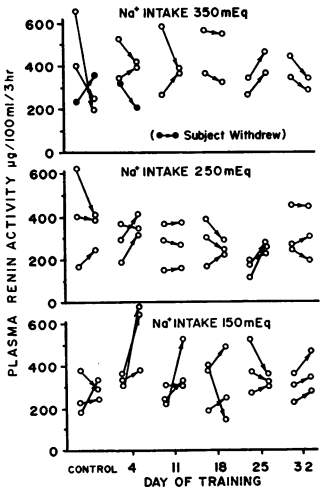

FIGURE 6 Weekly values for plasma renin activity determined before arising and at noon in all subjects of group II.

TABLE V
Group III, Body Composition

Day of study	$^{42}K_e$	$^{42}K_e$/LBM	LBM	Weight	TBW	ECV
	mEq	*mEq/kg*	*kg*	*kg*	*liter*	*liter*
Group A, NaCl intake, *114 mmoles/day**						
Control	3874 ±162	55.3 ±1.2	70.0 ±2.7	80.6 ±2.8	51.2 ±2.3	15.3 ±0.9
4	4096 ±188	58.0 ±1.7	70.6 ±2.4	80.8 ±2.4	52.4 ±2.0	15.8 ±0.6
11	4155 ±181	57.3 ±1.6	72.4 ±1.8	82.0 ±2.6	53.9 ±2.3	17.9 ±0.7
18	—	—	70.6 ±2.3	81.0 ±2.4	53.3 ±2.2	14.9 ±0.8
25	—	—	71.1 ±2.6	82.0 ±2.5	53.8 ±2.3	17.5 ±0.7
32	—	—	70.9 ±2.6	81.2 ±2.5	52.0 ±2.3	15.3 ±0.5
Group B, NaCl intake, *267 mmoles/day*‡						
Control	2823 ±458	51.6 ±2.8	53.7 ±6.4	61.4 ±4.2	42.0 ±2.8	13.6 ±0.6
4	2969 ±402	52.8 ±3.0	55.5 ±5.0	62.9 ±3.9	44.7 ±2.0	14.4 ±0.8
11	3134 ±438	53.9 ±4.0	57.3 ±4.2	63.8 ±3.6	46.1 ±2.2	15.1 ±0.5
18	—	—	56.2 ±4.7	63.9 ±3.6	45.3 ±1.9	16.3 ±0.5
25	—	—	59.9 ±5.6	64.7 ±3.4	45.5 ±1.6	16.4 ±0.7
32	—	—	57.9 ±4.1	64.4 ±3.2	45.8 ±1.3	16.2 ±0.7

Group III, serial values for total exchangeable ^{42}K($^{42}K_e$), exchangeable ^{42}K/kg lean body mass ($^{42}K_e$/LBM), lean body mass (LBM), body weight, total body water (TBW), and extracellular fluid volume (ECV).
* NaCl intake days 8 through 14 = 267 mmoles.
‡ NaCl intake days 8 through 14 = 114 mmoles. All values are means ±SEM.

On day 32, which followed 3 days of intense physical activity while on bivouac, body weight was lower in all subjects than on day 25. Although the mean weight loss in group A was greater than group B, the difference was small and not significant. On day 32, all those ingesting 114 mmoles NaCl showed lower total body water and extracellular fluid volume than on day 25. In contrast, this did not occur in those on 267 mmoles NaCl ($P < 0.05$).

Values for extracellular fluid volume on the control day and day 25 provide the best comparison for actual changes in these subjects which would not be complicated by the effects of physical activity on the previous day. Thus, comparison of extracellular volume on day 25 with the control day shows a mean rise of 14.4% ($P < 0.001$) in group A and 20.6% ($P < 0.05$) in group B.

Individual values for electrolyte recovery from clothing, urinary potassium excretion, and plasma electrolyte concentrations showed no relationship to NaCl intake and therefore are presented as mean values for the entire group (Table VI).

Average combined recovery of potassium from clothing and urine did not exceed 72 mEq/day. Sodium-potassium ratios in clothing extracts attained their lowest value on day 32. Mean concentration of sodium in plasma rose as training progressed. Plasma potassium concentrations ranging from 3.1 to 3.4 mEq/liter were observed on several occasions in four subjects. These were unrelated to NaCl intake. All subjects of group III showed a progressive rise of plasma potassium concentration after day 4.

Mean aldosterone excretion in group A was not significantly different from that of group B on the control day (Table VII). On day 4, group A excreted significantly greater quantities of aldosterone than the subjects of group B ($P < 0.05$). On day 11 all those whose NaCl intake was increased from 114 to 267 mmoles showed diminished aldosterone excretion. In contrast, two of three subjects whose NaCl intake was reduced from 267 to 114 mmoles (group B) showed modest increases on day 11. On day 17, all subjects took part in the physical proficiency test. The following day, physical activity was moderately heavy and all subjects of group A showed significantly higher aldosterone excretion than previously ($P < 0.01$) whereas those of group B did not. On day 25, activity was comparatively light and although one subject of group A excreted 38 μg of aldosterone, there was no significant differences between the groups. Day 32 followed 3 days of heavy work. Compared with day 25, mean aldosterone excretion on day 32 was considerably higher in group A but only slightly higher in group B.

Aldosterone secretory rates followed the same general pattern as the excretory rates (Table VII). Thus, on the control day the mean value in group A was higher but not significantly different from that of group B. On day 4, group A again demonstrated a higher

TABLE VI

Group III, Electrolytes in Clothing Extracts, Urine, and Plasma*

Day of study	Clothing extract		Urine K excretion	Plasma electrolytes mEq/liter			
	K total	Na/K		Na	K	Cl	HCO_3
	mEq		*mEq/day*				
Control	8.0 ±1.4	6.54 ±0.77	64 ±5	148 ±0.2	3.7 ±0.0	106 ±0.5	25.0 ±0.3
4	5.9 ±0.5	2.93 ±0.19	47 ±6	148 ±1.0	3.5 ±0.1	105 ±0.6	24.5 ±0.2
11	—		49 ±4	142 ±0.6	3.7 ±0.1	109 ±0.5	24.8 ±0.2
18	9.8 ±0.9	1.91 ±0.26	61 ±3	152 ±0.5	4.2 ±0.1	106 ±0.6	25.2 ±0.4
25	12.2 ±1.2	3.19 ±0.31	50 ±3	154 ±0.8	4.4 ±0.1	106 ±0.3	24.6 ±0.5
32	14.3 ±1.1	1.75 ±0.22	58 ±5	153 ±0.7	4.1 ±0.1	107 ±0.7	24.8 ±0.2

Serial values for potassium recovery from clothing eluates, Na/K concentration ratios in clothing eluates, urine potassium excretion/24 hr, and electrolyte concentrations in plasma.

* Mean ±SEM.

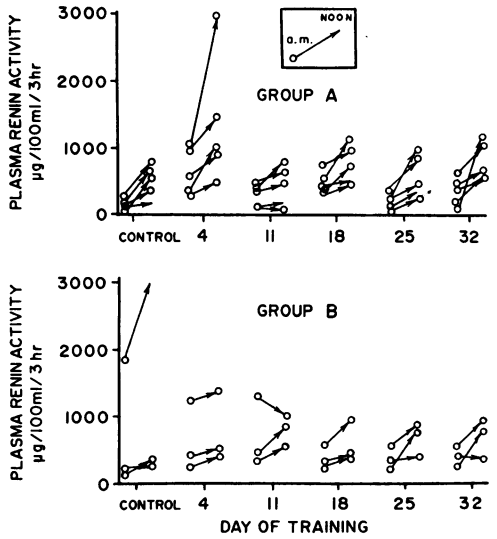

FIGURE 7 Serial values for plasma renin activity before arising and at noon in subjects of group III.

value which was of questionable significance ($P < 0.1$). On day 11, all subjects of group A, whose NaCl intake was increased from 114 to 267 mmoles, showed suppression of aldosterone secretion to 24% of its mean value on day 4. In contrast, in the two subjects of group B whose secretory rates were measureable on day 11, aldosterone secretion decreased to 81 and 87% of their values measured on day 7, despite the lower NaCl intake. On all subsequent study days, group A showed significantly higher values than group B.

Ratios of excreted to secreted aldosterone rose in all subjects of group A whose NaCl intake was increased whereas the two subjects of group B whose NaCl intake was lowered showed no change.

PRA in subjects of group A, whether measured in the supine or erect positions, were never statistically different on any day of training from those in group B (Fig. 7). Individual values were commonly greater than normal.

TABLE VII

*Group III, Excretion and Secretion of Aldosterone**

	Day of training	Control	4	11	18	25	32
Group A, NaCl intake, *mmole/day*		114	114	267	114	114	114
$n = 5$	Excretion	13.4 ±1.9	21.2 ±3.2	12.0 ±3.1	35.8 ±2.8	22.2 ±3.8	43.2 ±6.1
	Secretion	131 ±27	300 ±52	73 ±14	259 ±39	160 ±26	392 ±63
Group B, NaCl intake, *mmole/day*		267	267	114	267	267	267
$n = 3$	Excretion	9.7 ±0.3	9.0 ±1.9	12.7 ±2.2	13.0 ±0.5	16.3 ±0.5	19.7 ±2.2
	Secretion	64 ±5	126 ±31	118‡	95 ±8	70 ±8	148 ±24

Serial mean values for excretion and secretion of aldosterone in subjects of group III. Note cross-over of NaCl intake between each group from day 4 through day 11.

* µg/24 hr, mean ±SEM.

‡ Mean of two values.

DISCUSSION

These studies show that intense physical training in a hot climate (group I) lead to an average total body potassium deficit of 517 mEq. This occurred despite an adequate potassium intake. Simultaneous estimations of LBM, permitting more meaningful assessment of body potassium deficit, showed that the average maximum loss of $^{42}K_e$/LBM was 10.6 mEq/kg, representing an average total body deficit of 20%. In contrast, 16 other subjects studied during cooler weather but otherwise under nearly identical conditions (groups II and III) did not become potassium-deficient. In group I, $^{42}K_e$/LBM barely returned to control values during the period of study. In subjects of group II, studied in cool weather, $^{42}K_e$/LBM rose 3.1 mEq/kg during a comparable period of training ($P = 0.055$). These data suggest that subjects of group I were still slightly potassium-deficient after 32 days of training.

Plasma potassium concentration did not closely reflect the total body potassium deficit as measured by $^{42}K_e$, so that subjects of group I who became potassium-depleted did not show frank hypokalemia. That serum potassium concentration may be normal in the presence of potassium depletion is well known (37, 38). Elevation of serum potassium concentration from low values to the range observed in our subjects was reported by Kassirer and Schwartz (39) after correction of alkalosis by administration of NaCl to potassium-depleted volunteers without alteration of body potassium stores. Thus, relatively high intakes of NaCl in our subjects might have facilitated urinary excretion of bicarbonate which prevented metabolic alkalosis and thereby prevented hypokalemia. We have no explanation for the highly significant rise of serum potassium concentration during the last 3 study days in all subjects of group III.

Although heavy sweating was the major cause of potassium loss, excretion in the urine ranged from 46–75 mEq/day when maximum deficits were observed. This is higher than ordinarily anticipated in subjects whose depletion occurred primarily by extrarenal mechanisms. Huth, Squires, and Elkinton (33) showed that subjects experimentally depleted of potassium by dietary means excreted less than 15 mEq/day in their urine. Thus, efficient potassium conservation by the kidney could have prevented or ameliorated potassium depletion in subjects of group I.

Such inappropriate excretion of potassium in the urine could be explained by the action of aldosterone produced in sufficient quantity to exert a renal tubular effect in the presence of high sodium excretion rates. According to this hypothesis, aldosterone production would be stimulated by the sequence of intense exercise in the heat, contraction of effective arterial volume,

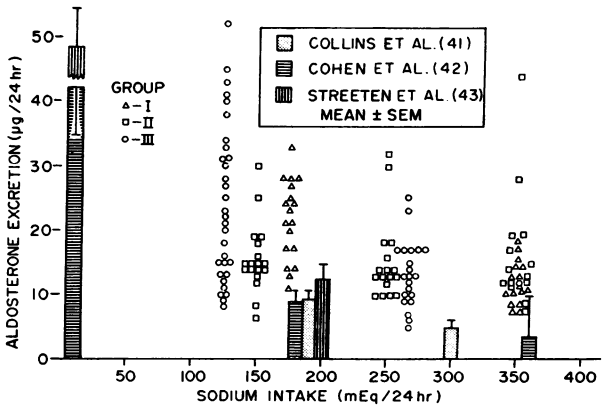

FIGURE 8 Aldosterone excretion compared with sodium intake for all subjects. Bars represent mean values reported by other investigators.

and production of renin. Aldosterone activity could persist even though its production had fallen consequent to restoration of effective arterial volume, since activity of the previously secreted aldosterone on the renal tubule can continue up to 8 hr (12). In the presence of sustained aldosterone activity, reexpansion of effective arterial volume by ingestion of NaCl and water could permit sodium to reach the distal tubule where exchange could occur and thereby explain inappropriate excretion of potassium into the urine as observed in these subjects.

Additional evidence suggesting unsuppressed aldosterone activity despite high sodium intakes was low Na/K concentration ratios in sweat (22, 40).

Aldosterone excretion in all subjects we studied is compared with mean values obtained by similar quantitative methods (24) published by several other investigators (41–43) (Fig. 8). Aldosterone excretion in relation to sodium intake appeared to be higher in our subjects than anticipated in normal individuals not subjected to comparable stress. Moreover, this relationship seemed to be especially pronounced when sodium intake was high. The latter contention is exemplified in a study of normal subjects by Cohen and his associates (42) in which sodium intake was nearly identical with that of our subjects in group I. Those authors reported aldosterone excretory rates ranging from 2 to 6 µg/24 hr when sodium intake was 360 mEq. By contrast, aldosterone excretion in three subjects reported herein whose sodium intake was 355 mEq ranged from 8 to 19 µg/24 hr.

Higher secretory rates of aldosterone also appeared to occur in many of our subjects as compared with values obtained by others (44, 45) when physical or heat stress was not a factor (Fig. 9).

Ratios of excreted to secreted aldosterone were unusually high in our subjects during hot weather and

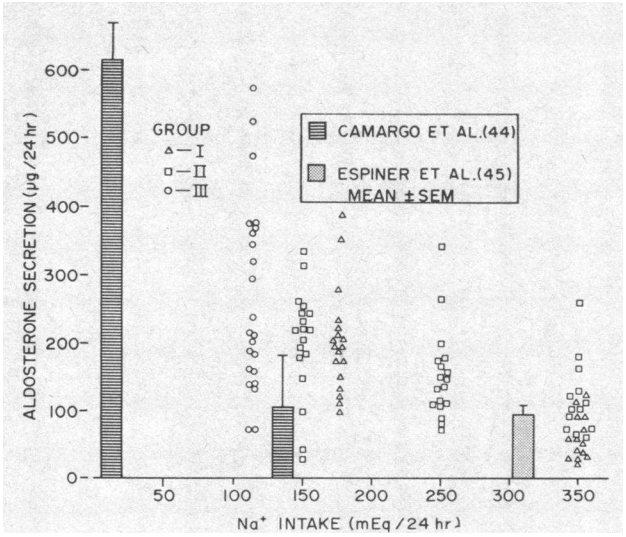

FIGURE 9 Aldosterone secretion compared with sodium intake for all subjects. Bars represent mean values reported by other investigations.

were related to a high sodium intake. The latter relationship was also noted during cooler weather but was not as pronounced. Under normal circumstances, the ratio of excreted to secreted aldosterone is not affected by sodium chloride intake (34–36). Neither the mechanism nor the significance of this observation is clear.

Since physical stress stimulates release of renin, it would be anticipated that PRA after exercise would be high in men undergoing such training. While the anticipated high values often occurred, many were normal. Moreover, certain subjects demonstrated relatively high PRA when supine and in many cases, paradoxically lower values at noon despite intense physical activity during the intervening period. High values before arising suggest that factors controlling secretion of renin, such as diminished effective arterial volume, might have been operative.

Extracellular volume was measured serially in subjects of group III and as demonstrated previously (46), rose appreciably after several weeks of conditioning. Thus, expansion of total body water and extracellular volume, increased production of aldosterone and low concentration ratios of Na/K in sweat support the concept of physiological hyperaldosteronism in a state of "mineralocorticoid escape" as proposed by Conn (40).

A major question concerns the mechanism whereby men training under such conditions might repair their deficit of potassium. Most short-term physiological studies of heat acclimatization have shown that the volume of sweat produced in response to a given heat load increases with acclimatization (47). Consequently, if potassium concentration in sweat remains relatively constant under the influence of either acclimatization (48) or aldosterone (22), or even rises as claimed by some (49), continued heat stress would be accompanied by progressively larger losses of potassium in sweat. However, studying the response to *long-term* acclimatization, Adam and his coworkers (50) observed a decreased sweat volume response to a given heat load. It is our contention that this might well be related to greater efficiency of muscular work consequent to conditioning per se which would be associated with less metabolic heat production per unit or work and in turn, require less sweating to dissipate heat.

Collins (51) has published evidence that aldosterone decreases the quantity of sweat produced in response to a given heat load. Thus, if potassium concentration in sweat is not changed by aldosterone or acclimatization, diminution in sweat volume would curtail potassium losses. Although our subjects partially repaired their potassium deficit by the end of the study period, we could not ascertain the precise mechanism. Aldosterone secretion in group I eventually rose. However, environmental temperature fell simultaneously and therefore either process might have been responsible for decreased sweat production.

It has been our experience as well as others (52) that most cases of heat stroke and rhabdomyolysis occur in the 2nd wk of basic training. This corresponds to the period of maximum potassium depletion observed in our subjects. Thus, if potassium depletion and the occurrence of environmental heat injury are related temporally, consideration must be given to the possibility that the two are related etiologically.

While it is well appreciated that the response of the adrenal cortex is necessary for acclimatization to heat, it is possible that aldosterone per se is critically important under extreme heat stress. Potassium depletion, probably independently of plasma potassium concentration, is known to blunt aldosterone production (53, 54) in response to extracellular volume contraction or sodium depletion. Indeed, mean values for excretion and especially secretion of aldosterone in our subjects training in hot weather (group I) fell with potassium depletion even though frank hypokalemia did not occur. This pattern stands in sharp contrast to that observed in subjects of group II studied in cool weather.

Braun and his associates (55) have produced evidence suggesting that aldosterone may be of critical importance in the hemodynamic response to heat stress. Thus, volunteer subjects showed significantly smaller increments of pulse rate and core temperature to a given work load in the heat after administration of aldosterone. Although their findings differ from those published in older but similar studies examining the effects of desoxycorticosterone (DOCA) (56), recent

evidence suggests that aldosterone, but not DOCA, exerts a positive inotropic effect on the heart (57).

Perhaps independently of diminished aldosterone production, potassium deficiency per se may be associated with profound circulatory disturbances which could compromise man's ability to tolerate work in the heat. These include hypotension, impaired circulatory responses to change of posture (58), and diminished vascular responsiveness to catecholamines (59).

Muscle temperature may rise as high as 105.8°F during hard work (60). It seems reasonable to postulate that increased muscle blood flow during work mediates transport of heated blood to the surface of the body for dissipation to the environment. Adequate dissipation of heat thus produced requires propulsion of blood from muscle to skin which in turn depends upon an adequate pumping action of the heart. Besides experimental evidence already cited that aldosterone is inotropic (57), observations in our laboratory indicate that potassium-depleted dogs show findings of acute left ventricular failure with exercise (61).

Although it has been observed that potassium depletion may be associated with rhabdomyolysis, its possible mechanism has not been elucidated. We have recently shown that exercise hyperemia in the isolated gracilis muscle preparation of the dog is virtually abolished by potassium depletion (62) and further, such exercise leads to frank rhabdomyolysis. Thus, if the latter experimental observations are pertinent to potassium-depleted man under conditions of extreme physical stress, failure of exercise hyperemia in the face of continued muscular contraction could induce ischemic necrosis of skeletal muscle. Moreover, failure of cardiac output to rise appropriately with muscular work could impair normal mechanisms by which heat is dissipated with the consequence of hyperpyrexia.

It may be speculated therefore that potassium depletion might play an important role in the pathogenesis of both environmental heat injury and rhabdomyolysis under these conditions.

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