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THE FACTORS REGULATING SERUM POTASSIUM AND THEIR DISORDERS

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In health, serum potassium concentration is regulated between 3.5 and 4.5 mEq/L. The recognized influences responsible for this tight regulation include pH, adrenergic receptors, insulin, ion transport, electrical gradients across cell membranes, prostaglandins, renin, aldosterone and the status of renal function.

Disturbances reflecting abnormal regulation of serum potassium concentration have again become a popular topic. There are several important reasons why we should be especially aware of these.

First, increasing numbers of individuals are running for their lives. Not only may they be at risk to develop exercise hyperkalemia with its attendant dangers, but this risk may be increased if certain common drugs are taken that can further impair these regulatory systems. Such drugs include indomethacin, propranolol and spironolactone.

Second, for some unexplained reason, we now recognize that hyporeninemic hypoaldosteronism with its identifying work of hyperkalemia is common. It is especially common in patients with diabetes mellitus.

Third, modest chronic hyperkalemia, while at one time thought not to convey any harmful effects of itself, has now been shown to cause metabolic acidosis.

As an approach to this topic, I would like to discuss exercise hyperkalemia, certain adaptive and prophylactic responses to hyperkalemia that become evident in the trained athlete and the operation of these responses at the cellular level. Finally, I will then attempt to point out how certain disturbances of these responses by primary disease or by pharmacologic intervention can produce the syndrome of hyporeninemic hypoaldosteronism.

EXERCISE HYPERKALEMIA

Contracting muscle cells release potassium ions into their surrounding interstitial fluid (1). Although most of the potassium ions immediately re-enter muscle cells, if exercise is sufficiently intense, there occurs a net release of potassium into venous blood which after mixing in the heart and lung, may occasionally cause important hyperkalemia. In normal persons, the intensity of hyperkalemia during exercise appears to be directly related to the intensity of muscle contractions and may become severe at the point of frank exhaustion.

Moderate degrees of physical work by an untrained individual may result in elevation of serum potassium from 0.3 to as high as 1.5 mEq/L above their baseline values (2,3,4). The quantitative change of serum potassium after exercise is also related to the site of blood sampling. Studies in Mitchell's laboratory (4a) showed that treadmill exercise was associated with greater elevations of serum potassium concentration in femoral venous blood than in blood taken simultaneously from the antecubital vein. It is obvious that since muscle is the principal site from which potassium is released during exercise, blood collected from a non exercising muscle venous bed might even show lower potassium concentrations than that of arterial blood.

In the majority of persons, exercise hyperkalemia is only modest. However, that it can be severe is shown in Figure 1 (2).

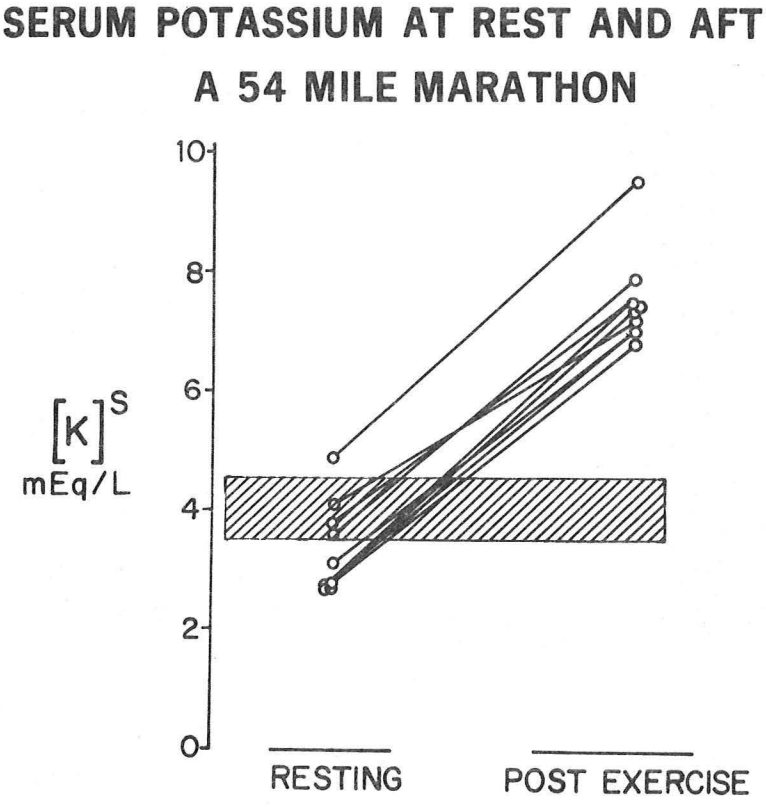

Fig. 1

Striking changes of T-waves have been observed in electrocardiograms recorded immediately after exercise (3,5). Although difficult to prove, sudden death or severe arrhythmias in athletes during massive, exhaustive exercise may on occasion be the result of acute hyperkalemia. This has been especially suspected after completion of exercise when interactions of rapid transients of potassium and pH occur (5a).

The cause of K-release from contracting muscle cells.

Three mechanisms have been proposed (6) to explain exercise hyperkalemia (1) depolarization of the cell membrane, (2) decomposition of glycogen, under the assumption that by some unknown mechanism, potassium is chemically associated with glycogen and (3) acidosis. Quite obviously, other factors could even be more important. For example, since K is always released from contracting muscle even during non-exhaustive exercise, and rapidly transported back into muscle cells, failure of those factors facilitating re-uptake must also be important.

Tibes and his coworkers, (6) proposed that acidosis resulting from exercise was the factor most likely responsible for release of potassium. Although depolarization of the muscle membrane has been proposed as one mechanism to explain potassium release during exercise, Grob (7) showed that depolarization in a normal subject does not cause elevation of venous plasma potassium concentration during exercise. The authors also proposed that decomposition of glycogen and high-energy phosphates would be responsible only for increased concentration of lactate, hydrogen ion and probably orthophosphate. Based upon evidence that exercise induced-changes of most electrolyte concentrations are similar to those which occur as a result of metabolic or respiratory acidosis without exercise, they proposed that acidosis per se might be responsible for electrolyte patterns seen under these circumstances. Thus during muscular activity, not only is there an increase in potassium, but also sodium, calcium, magnesium, orthophosphate, lactic acid and hydrogen ion concentrations. It is notable that chloride concentration does not change. In addition, because of the increased intracellular osmolality resulting from degradation of glycogen or sugar phosphates, movement of water occurs from inflowing arterial plasma thereby increasing concentrations of many substances in the plasma simply by hemoconcentration (8). All of these substances increase their concentration in proportion to that of total protein with the exception of potassium and phosphorus. These substances increase substantially more than could be accounted for by simple hemoconcentration. Tibes and his co-workers studied three groups of normal subjects, six men who were highly conditioned competitive athletes, six completely untrained subjects and six who were semitrained, implying that they ran three to five hours per week. They introduced a catheter into the femoral vein and sampled blood at regular intervals during maximum exercise. They showed that release of potassium and phosphorus was significantly less in the highly

trained subjects as compared to those who were semitrained or not trained at all. The authors determined the ratio of venous potassium and phosphorus, measured at any given instant during exercise, and utilizing the Henderson-Hasselbalch Equation used the simultaneous venous pH to predict intracellular pH. Thus, potassium phosphate (PK6.64) is an effective buffer within the pH range of effluent muscle blood and presumably cell contents during work. This relationship is illustrated in Figure 2.

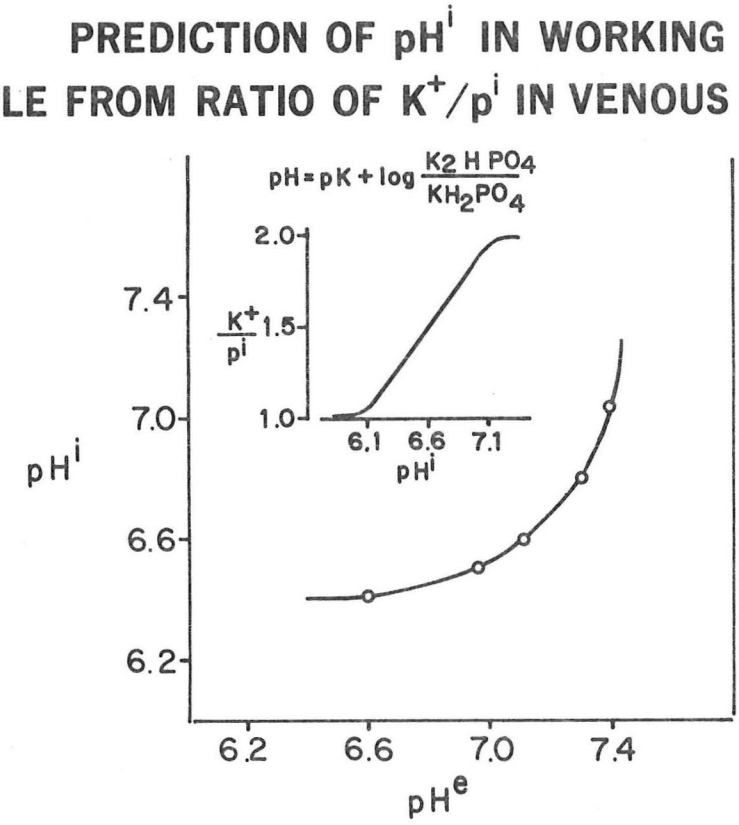

Fig. 2

As blood pH falls, the ratio K/P should approach one. As the pH rises, it should approach two. From the ratio, internal pH of the cell could be predicted. As would seem predictable, there was also an extremely close inverse curvilinear relationship between the severity of hyperkalemia and lactate accumulation in venous blood (Figure 3).

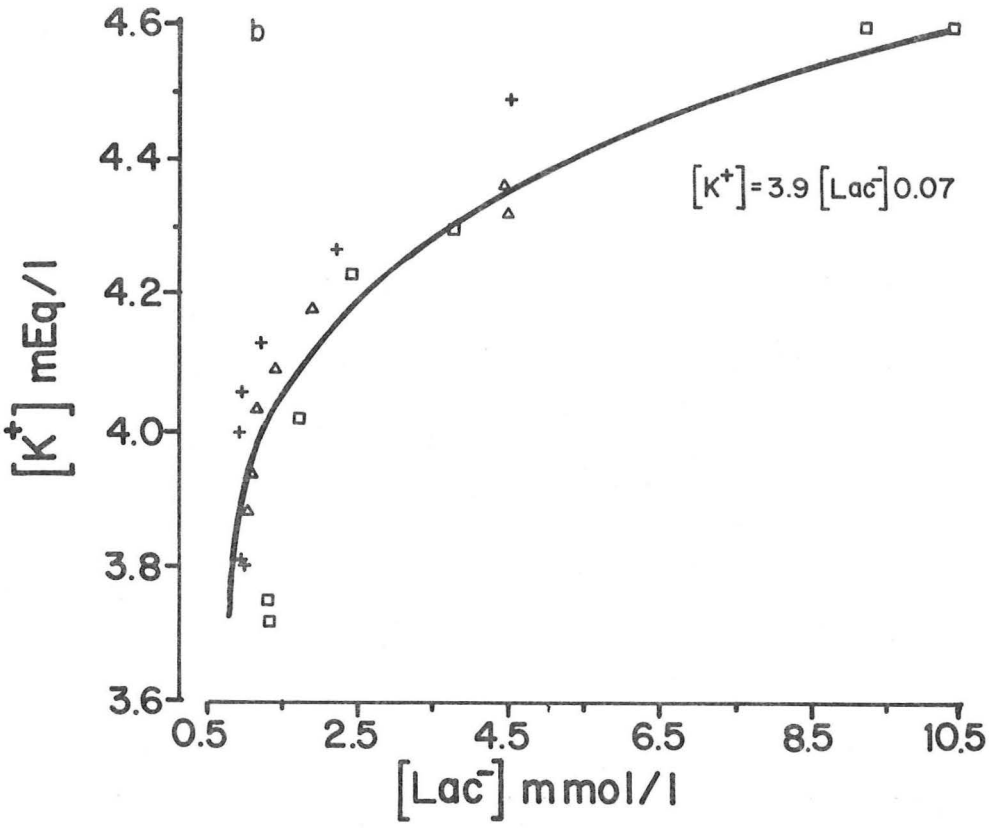

Fig. 3

For reasons that are unclear, sustained effort such as that of an ordinary long-distance race (10,000 meters or 26.2 mile marathon), does not cause comparable metabolic acidosis as that following intermittent, repetitive bursts of exhaustive exercise (9). In the former, the well-trained runner will finish with a total serum CO_2 content of approximately 20 mEq/L and a whole blood lactate concentration of 4 mmoles/L. In contrast, arterial pH as low as 6.9 and blood lactate as high as 30 mmoles/L have been observed in olympic runners after intermittent, exhaustive exercise. Unfortunately, serum potassium concentrations were not reported in those studies. This difference in metabolic responses during sustained compared to intermittent, repetitive, exhaustive exercise might account for the alleged higher frequency of sudden deaths in basketball or football players than in long-distance runners.

The concept that intracellular acidosis is responsible for movement of potassium and phosphate from the cell (6) and that this phenomenon is less intense in highly trained than untrained individuals correlates well with certain other phenomena that occur as a result of training(10). For example, a highly trained individual shows a substantial increase in mitochondrial mass, a substantial increase in oxidative enzymes, increased

capacity to deliver oxygen to muscle cells during exercise as a result of increased myoglobin content of muscle, increased capillary density per muscle fiber, and increased 2,3-DPG in erythrocytes. Each of these structural or biochemical responses to intense physical conditioning would facilitate more complete oxidation of carbohydrates and fatty acids so as to permit more efficient utilization of energy substrates. Thereby, training facilitates a substantial increase in capacity to produce ATP/quantity of substrate utilized. Otherwise stated, an amount of physical work that would require exhaustive physical effort in the untrained state with its concommitant of severe hyperkalemia and metabolic acidosis can be achieved after training with substantially less hyperkalemia and less acid production. Nevertheless, even supertrained individuals are capable of developing the same degree of metabolic acidosis and hyperkalemia as the untrained individual provided they push themselves to the point of sheer exhaustion. This is illustrated in Figure 1. This figure illustrates serum potassium values before and after exercise in individuals who participated in a 54 mile marathon. Undoubtedly, these individuals were in excellent physical condition. However this probably represents ultimate exertion and accordingly, rather astronomical values for venous potassium concentration. Based upon the observations from Mitchell's laboratory (11), potassium concentration in venous blood from the legs might have been higher.

We should now consider the following question: Does potassium release from the contracting muscle cell have any biologic purpose?

There is considerable evidence to indicate that sudden release of potassium ions into the interstitial fluid of muscle triggers exercise hyperemia (13). It has been shown experimentally that potassium concentration in the interstitial fluid generally rises to about 8.5 mEq/L (but may rise as high as 15 mEq/L) and at this concentration acts as a vasodilator. The resulting increased muscle blood flow during exercise subserves three major functions: (1) to increase delivery of substrates for muscle cell contraction, (2) to deliver heat from the contracting muscle into the systemic circulation and (3) to return certain by-products to the liver, such as alanine or lactic acid so that they may be converted into glucose. Wildenthal and his associates have examined the role that potassium release might play on important hemodynamic and respiratory responses to muscular exercise (14). They showed that infusions of 0.3 to 1 mmole of KCl into the gracilis muscle led to an increase in arterial pressure, heart rate, cardiac output, left ventricular contractility and ventilatory volume. These responses were similar to those observed during electrically stimulated muscle work. They also occurred even when the venous drainage of the muscle was diverted. They found that beta adrenergic blockade with propranolol reduced the heart rate and cardiac output responses and eliminated the inotropic changes but did not block the blood pressure rise. However, cutting the femoral and sciatic nerves abolished

ill these changes. They proposed that potassium release, not necessarily hyperkalemia, mediated several important hemodynamic and respiratory responses to exercise by local stimulation of reflex activity in the contracting skeletal muscle.

Physiological Responses to Hyperkalemia

When acute hyperkalemia occurs consequent to release from cells during exercise or injury, absorption from the gut, or intravenous infusion, there are three principal mechanisms whereby it can be dissipated. These include:

1. Excretion into the urine.
2. Excretion into the bowel lumen.
3. Cellular uptake.

Potassium excretion into the urine is obviously a very important pathway to dissipate hyperkalemia since under conditions of urinary suppression, hyperkalemia due to any circumstance is not only aggravated but more prolonged. Nevertheless, under conditions of exercise, wherein renal blood flow and glomerular filtration rate are essentially nullified, other mechanisms must be dominant. Under ordinary circumstances, excretion of potassium into the bowel lumen does not account for any substantial amount of potassium dissipation. This pathway of potassium excretion is important only in patients with end-stage renal disease. Therefore, cellular uptake of potassium ions must be the most important means by which acute hyperkalemia is dissipated in those circumstances in which urinary excretion is inefficient.

Simple chemical diffusion of potassium ions into cell water does not occur because the intracellular concentration of potassium is approximately 150 mEq/L. Three processes can cause net movement of potassium into cells. These include: alkalosis, active transport and passive diffusion under the influence of an electrical field.

Acute hyperkalemia carries the risk of skeletal muscle paralysis, cardiac arrhythmia or loss of myocardial contractility (15). The latter is compounded in the presence of severe acidosis (16). Because of the extreme dangers of hyperkalemia, there exists a number of well defined, physiological responses that can promote movement of potassium into cells. These include the following:

1. Hyperventilation
2. Beta adrenergic receptor stimulation
3. Insulin release
4. Aldosterone secretion
5. Na, K-ATPase activation

Hyperventilation occurs very rapidly in response to hyperkalemia and apparently serves to induce acute respiratory alkalosis. Respiratory alkalosis in turn promotes movement of potassium (and orthophosphate) ions from extracellular fluid into cell water. (Movement of K in excess of PO_4 in the pesence of alkalosis might be predicted from Figure 2).

Evidence that acute hyperkalemia stimulates beta adrenergic receptors is mostly inferential and based upon studies conducted under conditions of beta adrenergic receptor blockade or by observing effects of catecholamines on potassium transport and distribution. There is evidence that hyperkalemia stimulates release of catecholamines (17). Injection of epinephrine is followed by mild, transient, hyperkalemia associated with (but perhaps not caused by) glycogenolysis (1,18-20). This hyperkalemic response can be inhibited by adrenergic blockers such as phentolamine (18). Hyperkalemia is followed by more prolonged hypokalemia. Availability of pure beta receptor stimulators such as isoproterenol and more recently salbutamol have proven that this hypokalemic phase is due to beta receptor stimulation that causes a shift of potassium into cells. The site of tissue uptake is mainly the liver and skeletal muscle (21). The action of salbutamol has been so potent that this drug has been used successfully to prevent and treat familial hyperkalemic periodic paralysis (22).

Physiological studies by Clausen and his associates (21) have shown that salbutamol stimulates uptake of potassium into intact, isolated skeletal muscle fibers as well as simultaneous efflux of sodium. Since this response can be blocked by ouabain, it is presumed that beta receptor stimulation activates sodium-potassium ATPase. Epinephrine has the same effect. Both compounds cause hyperpolarization of the muscle cell. This implies that B-receptor activation in muscle activates Na,K-ATPase primarily, Na^+ is actively transported from the cell, thus generating increased electronegativity. Thereby potassium ions enter the cell under the influence of an electrical field. These results can be reproduced by aminophylline or dibutyryl cyclic AMP, thus suggesting its effect is mediated by an increase in the concentration of cyclic AMP in the cell. An example of sodium and potassium shifts in response to adrenalin (ADR) is shown in Table I.

TABLE I.

	EFFECT OF ADRENALINE			
EXPERIMENTAL CONDITIONS	Na CONTENT (μmole/g wet wt.)	P	K CONTENT (μmole/g wet wt.)	P
CONTROL	10.0±2.0 (6)		82.2±0.6 (6)	
ADR PRESENT FOR 15 MIN	5.3±0.7 (6)	<0.05	86.2±0.7 (6)	<0.005
CONTROL	9.9±1.4 (15)		84.2±0.6 (15)	
ADR PRESENT FOR 90 MIN	3.3±1.6 (14)	<0.001	89.2±1.0 (4)	<0.001

Clausen J. Physiol 1977 (21)

Insulin release also occurs in response to even slight degrees of hyperkalemia (23,23a). Insulin thus released acts immediately so as to stimulate movement of potassium into intracellular water. Apparently, insulin also activates sodium, potassium-ATPase, increases intracellular electronegativity and promotes movement of potassium into the cell. This response occurs independently of glucose (24,25).

That aldosterone secretion increases in response to hyperkalemia is also well established. Although this response would not appear to be a true defense mechanism against acute hyperkalemia because of the lag, it is well-known that mineralocorticoid deficiency is clearly associated with potassium intolerance.

Although transport ATPase is apparently activated by beta adrenergic stimulation and insulin, there is little doubt that the enzyme is also directly activated by extracellular elevations of potassium concentration. In fact, even modest elevations of serum potassium can be shown to exert an extremely powerful stimulating effect on activity of this enzyme in vitro. This relationship is nicely demonstrated in Figure 4 reproduced from a review by Skou (26). This figure illustrates that when sodium concentration is 150 mEq/L, similar to that existing in extracellular fluid,

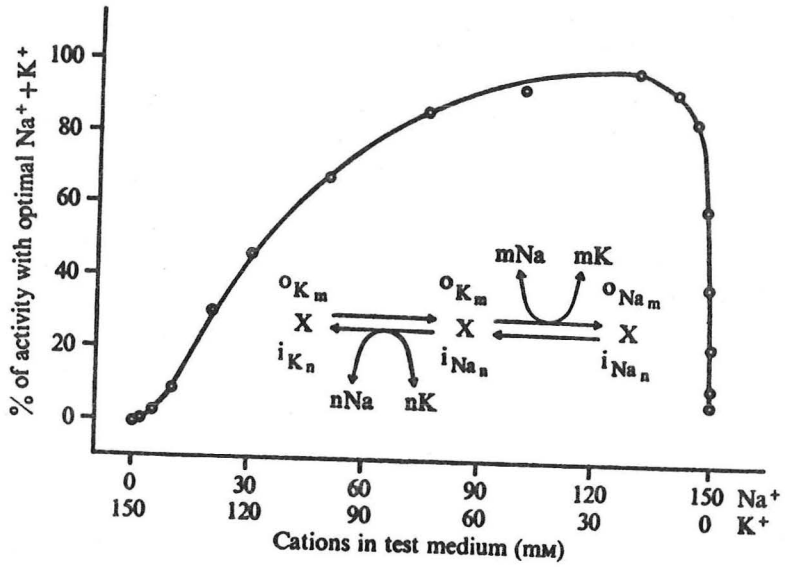

Fig. 4

an increase of potassium concentration from 0 to approximately 10 mEq/L causes nearly a 100% increase in activity of Na, K-ATPase. It has also been shown that this response is dependent upon optimal concentrations of ATP in the cell. Thus when ATP declines to concentrations below 1 mmole, activation of this enzyme by hyperkalemia is sharply blunted (26). Such a relationship may have physiologic relevance in a subject who is performing exhaustive physical exercise who becomes hyperkalemic. Thus, it has been shown that although ATP concentration in muscle remains relatively normal during sustained exercise, it eventually declines as physical exhaustion appears. A similar correlation can be made between exercise hyperkalemia and exhaustion. Namely, hyperkalemia is generally only mild or modest until exhaustion appears at which time it mounts rapidly. Perhaps the decline of ATP reduces activity of the enzyme in response to hyperkalemia, thereby potassium is no longer transported back into cells at a rate sufficient to prevent severe hyperkalemia.

Some of the interrelationships between exercise, hyperkalemia and certain other events are shown in Figure 5. These data were obtained on a healthy young man exercised on a treadmill to the point of sheer exhaustion. In the upper portion of the figure, it is shown that his serum

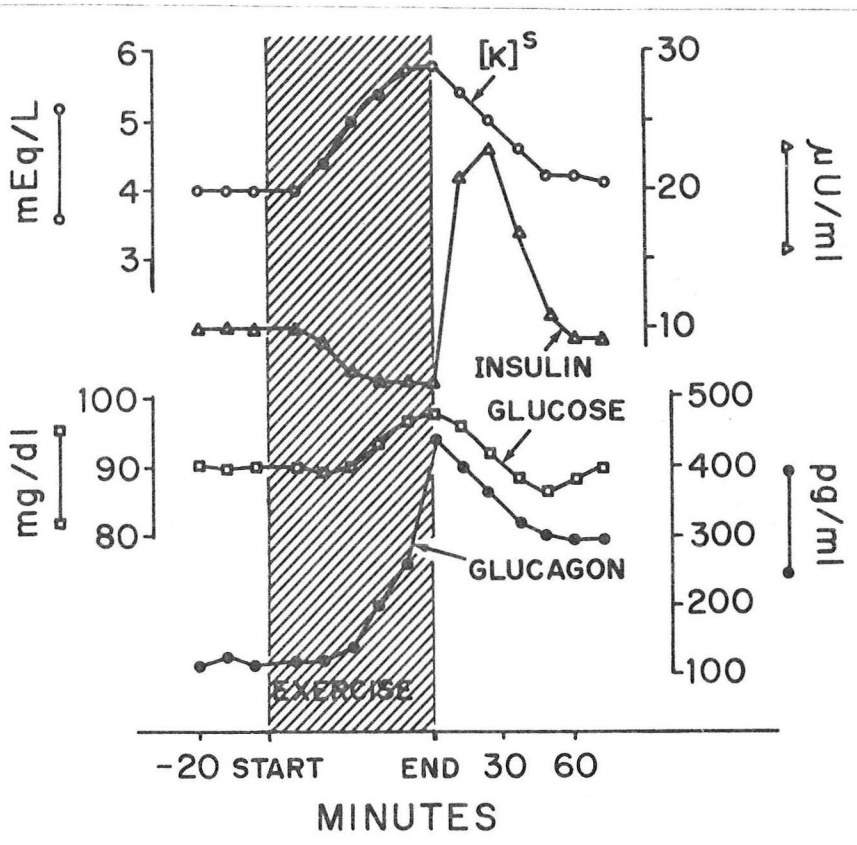

Fig. 5

potassium concentration rose from 4 mEq/L to 5.8 mEq/L at the point of exhaustion. Serum insulin concentration declined from 10 to 4 μU/ml during exercise, a normal response. However, immediately upon cessation of exercise, there was a sharp rise of insulin concentration to 22 μU/ml. It seems possible that the release of insulin upon completion of exercise might have helped to dissipate hyperkalemia. Although not measured, it has been shown by many investigators that a substantial release of catecholamines occurs during such exercise (27). The plasma concentration of prostaglandin also increases during exercise. Infused individually, both prostaglandins and catecholamines block release of insulin from the beta cell. Since catecholamines have a very short half life, it seems possible that their concentration might have fallen rapidly as exercise stopped thereby permitting release of insulin. Although not specifically related to this discussion, the figure shows that glucagon is released in substantial quantities during exercise and is associated with a slight rise of blood glucose concentration despite physical exhaustion (28). It is assumed that glucagon release during exercise helps to maintain an adequate supply of glucose for the brain.

EXERCISE TRAINING AND POTASSIUM TOLERANCE

When a normal man or experimental animal is exposed repeatedly to hyperkalemia, or ingests progressively increasing quantities of potassium, a physiologic state develops that permits administration of potassium loads that otherwise could be fatal. This phenomenon is known as potassium adaptation. In general terms, it is characterized by increased capacity to excrete potassium into the urine, increased capacity for secretion of potassium into the bowel lumen and increased capacity to transport potassium into intracellular water. Table II summarizes some of those events that permit enhanced excretion of potassium into the urine in the adapted animal. First, when serum potassium increases, there is an immediate increase of potassium excretion into the urine. In fact, employing the isolated perfused kidney, Silva has shown that potassium excretion into

TABLE II

RENAL MECHANISMS FOR POTASSIUM EXCRETION

1. NONADAPTIVE
   (a) K EXCRETION INCREASES IN PROPORTION TO SERUM K CONCENTRATION

2. ADAPTIVE
   (a) ENHANCED PERITUBULAR K UPTAKE
   K IN CELL INCREASES
   (b) K INCREASES URINE FLOW
   (c) ELECTRONEGATIVITY OF LUMEN INCREASES
   (d) Na,K-ATPase ACTIVITY INCREASES

the urine increases in linear relationship to the increase in serum potassium concentration (28). This response occurs even in the unadapted animal. On the other hand, at least four distinct processes have been identified that permit increased secretion of potassium by the potassium adapted kidney. These include:

(a) Enhanced peritubular potassium uptake which results in an increased potassium concentration inside the tubular cell.

(b) Potassium excretion is flow dependent. Administration of a potassium load increases urine flow.

(c) The tubular lumen becomes more electronegative. Since potassium ions are positively charged, this increased electronegativity enhances movement of potassium ions into the tubular lumen.

(d) There occurs an increase in the activity of magnesium dependent, sodium, potassium ATPase. This enzyme is located in the basolateral membrane of the distal nephron (the thick ascending limb, the collecting duct and the distal convoluted tubule). By increasing its activity or quantity, any increase in the ambient concentration of potassium ions should enhance potassium transport. Since the pump is electrogenic, the increased electrical potential difference would in turn increase the rate of potassium transport. This increase in sodium potassium ATPase in the kidney is not dependent upon either aldosterone or sodium deprivation *per se* although either of these two factors can produce renal potassium adaptation independently.

The Colon in Potassium Adaptation

Increased potassium secretion occurs into the bowel lumen in the presence of renal insufficiency (29) and experimentally in the potassium adapted animal (30). This process is thought to be aldosterone dependent (31) since it has been illustrated independently that aldosterone increases sodium reabsorption and simultaneously promotes potassium secretion into the colon. Similar to the renal tubule in the potassium adapted animal, the bowel lumen becomes more electronegative with respect to the cell interior after potassium adaptation. This suggests that at least part of the increased capacity to transport potassium into the bowel lumen is mediated electrically. It has also been shown that bowel ATPase undergoes adaptation (32). In contrast to the kidney, this adaptation of ATPase is aldosterone dependent and is abolished by adrenalectomy and probably by spironolactone.

Cellular Uptake of Potassium

Wallace O. Fenn published a classic review on the role of potassium in physiological processes in 1940 (1). He noted, "-after injection of potassium, there is evidence that the liver absorbs more than its proportional share. However, most of the injected potassium must be absorbed by muscles since the rate of disappearance from the blood is apparently not influenced by removal of the kidney, liver or alimentary canal."

It has been shown that potassium loads are dissipated more rapidly in the K-adapted animal even in the anephric state. Unfortunately, it has not been proven that the rate or quantity of tissue uptake is higher in the K-adapted animal. The quantity of potassium that must be transported into intracellular water in order to prevent otherwise fatal hyperkalemia is small. Since muscle potassium content is large, such a small increment would be technically almost impossible to measure. Similarly, increased total tissue content of transport ATPase has not been identified in skeletal muscle in potassium adapted animals. This is probably related to the fact that the fraction of tissue actually involved in potassium transport in skeletal muscle is very small compared to epithelial structures. Consequently, to identify increased transport ATPase would require isolation of sarcolemmal membranes or other structures possessing capacity for sodium and potassium transport.

Hypokalemia in the Highly Trained Man

There have been at least two reports (2,12) showing that serum potassium concentration may decline or even become abnormally low in healthy individuals who have undergone extensive physical conditioning, especially training for long distance running. Figure 6 shows observations made by Rose (12) on more than 100 young men in the untrained state in the lower part of the panel and after training for long distance running in the upper part of the panel. The average serum potassium concentration before training was 4.1±0.3 mEq/L, after training it was 3.8±0.3 mEq/L. It is to be noted that 21 of these individuals had serum potassium values of 3.5 mEq/L or less after training. As illustrated earlier in the discussion of the intensity of hyperkalemia associated with exhaustive exercise, some of those individuals trained to run the 54 mile marathon had serum potassium values at rest of 2.8 mEq/L. (Fig. 1) Although hypokalemia in the trained state has been interpreted to reflect potassium deficiency (12), it is very clear that hypokalemia can exist under such conditions even when such individuals have trained in very cool climates and have had no exposure to factors conceivably responsible for potassium deficiency (33). Thus hypokalemia in the trained state suggests redistribution of potassium between serum and cells. In support of this notion, Table III shows data on serum potassium, total body potassium and potassium expressed as a function of lean body mass in young men before and after military training in cool weather (33). Untrained, average serum potassium was 4.2 mEq/L and after

TABLE III

PHYSICAL TRAINING AND BODY COMPOSITION
(n=16)

	K (mEq/L)	Total K (mEq)	K (mEq/Kg LBM)
UNTRAINED	4.2 ±0.08	3348 ±40	54.1 ±0.6
TRAINED	3.8 ±0.03	3606 ±50	55.1 ±0.7
P	<0.001	<0.001	<0.001

$$\text{Membrane Potential (Em)} = -61.5 \log \frac{\text{Intracellular [K]}}{\text{Extracellular [K]}}$$

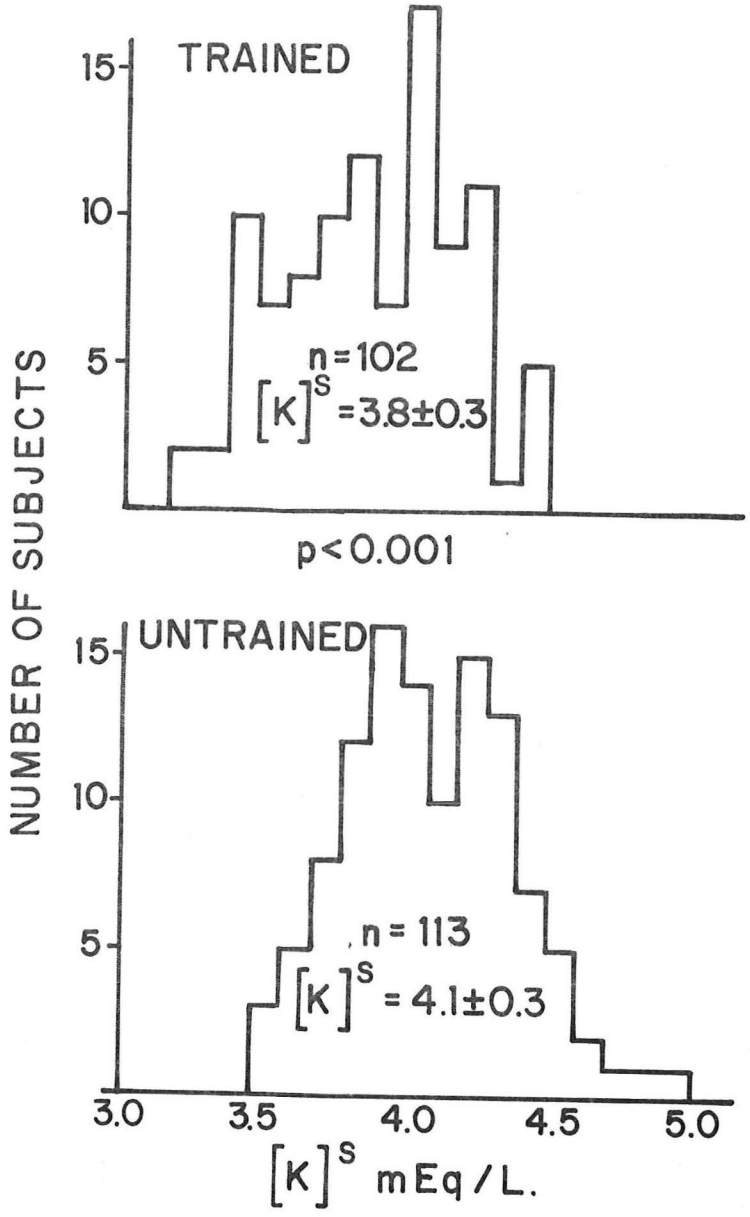

Fig. 6

training the average value fell significantly to 3.8 mEq/L. In the same men, total body potassium, measured by exchangeable ^{42}K, increased from 3,348 mEq to 3,606 mEq. Although the difference was small, they did show a significant increase of potassium/kg lean body mass. This latter value suggests that muscle potassium concentration rose after training. This, in the face of a lowered serum potassium value suggests that muscle membrane potential as calculated by the Nernst equation, became higher as a result of physical training. Since others have reported that exercise hyperkalemia is less intense after conditioning (4,6), it seemed possible that if

electronegativity increased inside the muscle cell as a result of training, that this electrical force might be another biological adaptation to forestall dangerous hyperkalemia during exercise. We examined this possibility on 11 dogs before and after training on the treadmill. Figure 7

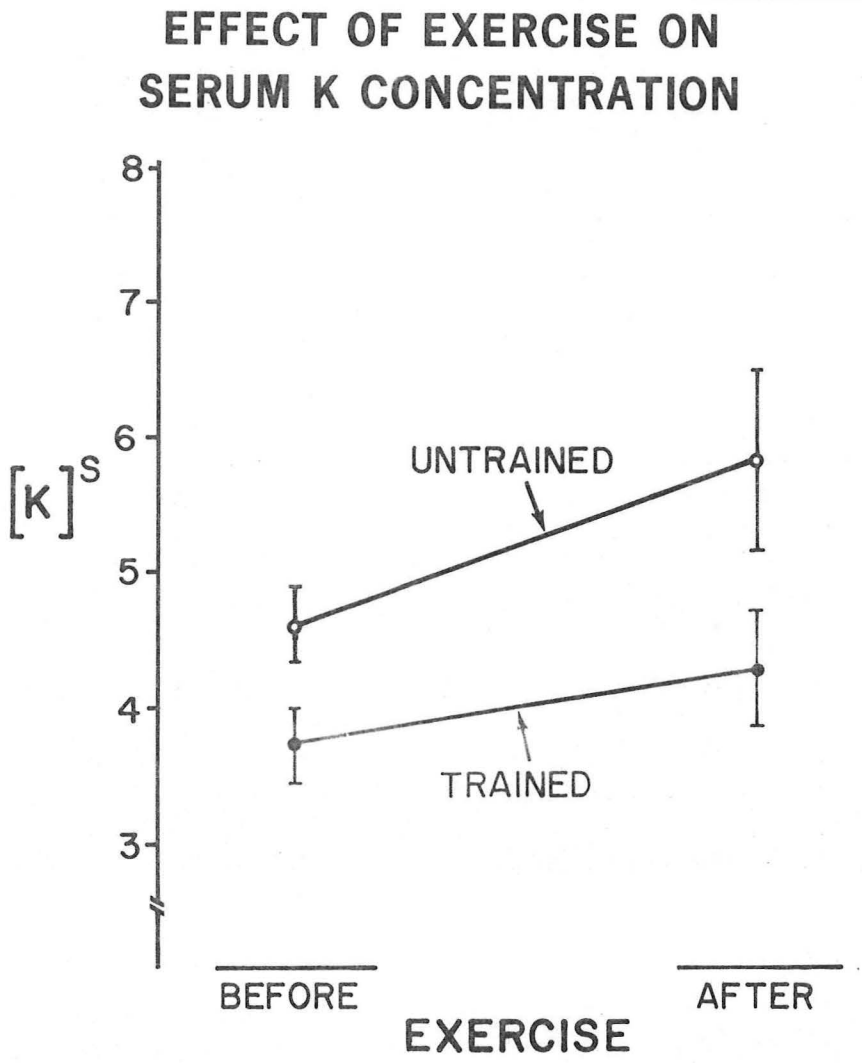

Fig. 7

shows average values for serum potassium before and at the completion of an exhaustive run on the treadmill. The upper line shows that the average serum potassium value in these dogs before training was 4.5 mEq/L and after completion of an exhaustive run was 5.8 mEq/L. After training, the average serum potassium value in these dogs was lower, viz, 3.8 mEq/L and at the point of exhaustion, rose to 4.2 mEq/L. These differences were statistically significant. Measurement of resting muscle cell membrane potential

in these dogs before and after training indicated that cellular hyperpolarization did occur (Fig. 8). The average membrane potential in these dogs before training was 91±1.4 mV. After training the average potential rose to 101±2.5 mV. These values were determined on muscle fibers of the leg. We also examined membrane potentials of intact, isolated intercostal muscles in order to indirectly assess activity of sodium potassium ATPase by measuring the changes of membrane potential in response to inhibiting

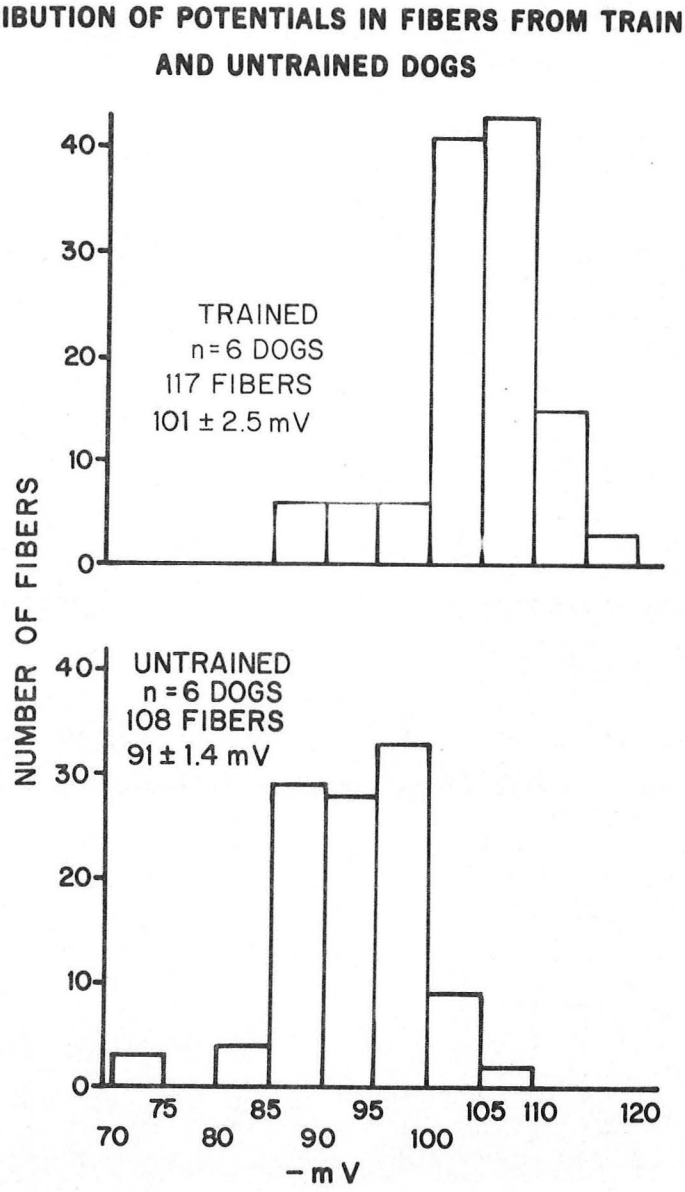

Fig. 8

pump ATPase with ouabain. Figure 9 shows these results before and after training. Untrained, Em of isolated muscle fibers was -88 mV. Following exposure to 10^{-3m} ouabain, there was a decline in membrane potential to

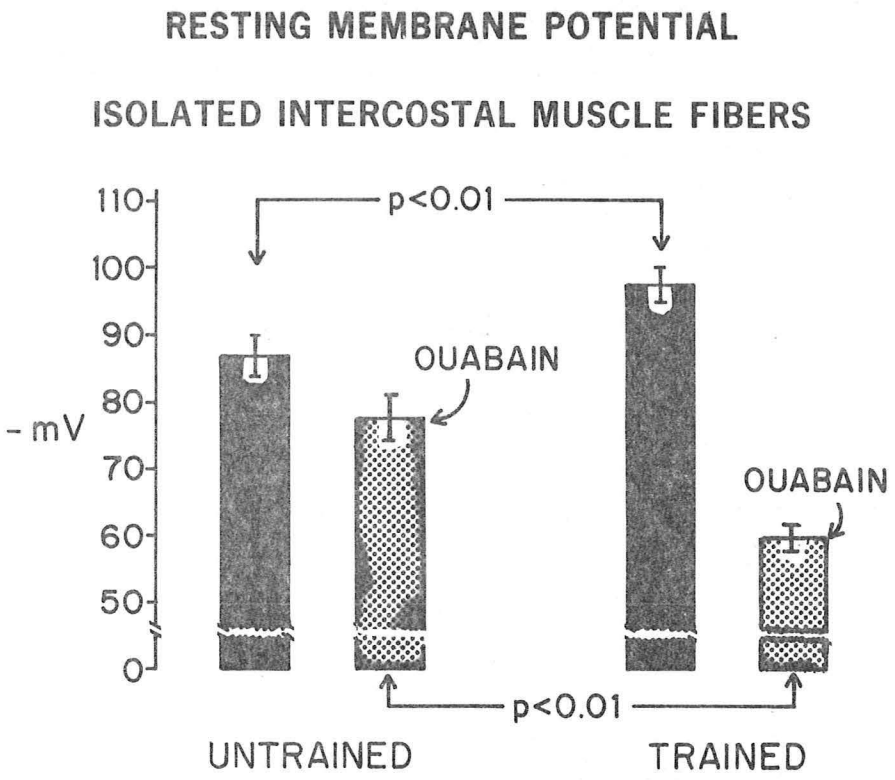

Fig. 9

-78±4mV. After training, average resting potential of the intercostal fibers rose to -98mV. Following exposure to ouabain, the average potential difference declined to an average value of 58±3mV. These findings at least inferentially suggest that ATPase activity of skeletal muscle increased as a result of exercised training. Although the tissue content of potassium did not change (untrained 39.8 vs trained 39.7 mEq/dg fat free dry weight), the calculated muscle cell potassium concentration rose respectively from 149 to 159 mEq/L of intracellular water ($p<0.01$).

We further assessed the possibility that increased intracellular electronegativity as a result of training would enhance dissipation of hyperkalemia. Employing the same dog before and after training, we infused potassium chloride at a rate of 2.8 mEq/min until "cardiotoxicity" was reached. Cardiotoxicity was defined electrocardiographically as atrioventricular dissociation, ventricular tachycardia or a broad sine wave. The next table (Table IV) shows those results. In the untrained state, the dogs could tolerate potassium infusion for 3.6 minutes which represented a total potassium dose of 9.9 mEq. After training, the time to cardiotoxicity rose to an average value of 11 minutes representing a dosage of 30.9 mEq of potassium chloride. We also attempted to examine certain other factors that might have induced potassium adaptation in these dogs.

First we examined the possibility that insulin release might have been exaggerated after potassium adaptation and thus accounted for more rapid transport of

TABLE IV
EFFECTS OF TRAINING ON TOLERANCE TO INTRAVENOUS KCl AT 2.8 mEq/MIN

	Time to Cardiotoxicity (min)	Total K Infused (mEq)
UNTRAINED	3.6 ±1.1	9.9 ±3.1
TRAINED	11.0 ±3.6	30.9 ±10.0
P	<0.5	< 0.05

potassium into cells. Average baseline values for insulin before potassium infusion showed a slight rise from 7.0 to 9.9 μU/ml after training. The peak level of insulin in venous blood at the point of cardiotoxicity was also higher after training. However since KCl was infused longer and more potassium could be tolerated when the animals were trained, it seems possible that higher insulin levels might have resulted from more prolonged stimulus to release. Thus, insulin levels per se may have nothing to do with the phenomenon of increased potassium tolerance in the conditioned dog. To assess this possibility, trained dogs were infused with somatostatin in sufficient quantities to suppress insulin release during potassium infusion and during exhaustive exercise. In neither situation was potassium tolerance or the hyperkalemic response to exercise changed from that of the untreated, adapted animal. We concluded therefore that insulin release during K infusion was not the single factor underlying the animal's capacity to dissipate hyperkalemia.

Others have shown that prolonged volume contraction or feeding a low sodium diet will result in potassium adaptation in dogs or rats. Since such observations suggest that aldosterone may play a role in potassium adaptation, we examined the effects of large doses of spironolactone on tolerance to intravenous potassium chloride. Six of the trained dogs that had demonstrated potassium tolerance were given 1.0 gm of spironolactone 12 hours before and 1.0 gm 2 hours before potassium chloride infusion. This presumed blockade of aldosterone action exerted no effect on potassium tolerance. Finally, since beta receptor stimulation could play a role in potassium adaptation, we administered blocking doses of propranolol before potassium infusion. Assuming that relative bradycardia reflected beta blockade, potassium chloride was infused according to our normal protocol. Despite propranolol, there was no apparent effect on potassium tolerance.

We would conclude from the foregoing that the most likely mechanism responsible for development of potassium adaptation induced by exercise training is increased ATPase activity in skeletal muscle. One report (34) has shown that a single period of electrically stimulated muscle contractions for 15 minutes caused a 18-28% increase in sarcolemmal ATPase activity in the rat. We anticipate that conditioned dogs and highly trained endurance runners will demonstrate the same findings.

Disturbances of Serum Potassium Regulation

The syndrome of hyporeninemic hypoaldosteronism is usually recognized because of persistent mild to moderate hyperkalemia (35). Many of these patients also display hyperchloremic metabolic acidosis. They often show inadequate renin release in response to extracellular volume depletion or erect posture, and for unexplained reasons, decreased production of aldosterone that does not respond to hyperkalemia. Of interest, about 1/3 to 1/2 of these patients have diabetes mellitus. The syndrome of hyporeninemic hypoaldosteronism occurs more commonly in the aged whose renin-aldosterone responsiveness is blunted in comparison to younger subjects. Most patients show mild to moderate renal insufficiency, often but not always the result of diseases affecting the renal medulla.

Patients with the syndrome of hyporeninemic hypoaldosteronism usually show defects in two or more of those systems that play an important role in potassium adaptation. Individually, they would demonstrate disruption of (a) the potassium-insulin response, (b) the kaliuretic effect of hyperkalemia, (c) kaliogenic aldosterone secretion and (d) volume contraction-mediated renin release and aldosterone production. At this time I suspect but have no information to prove possible interference with (e) transport ATP-ase adaptation or (f) possible interference with operation of B-adrenergic receptors. While it appears that a single defect in the K-adaptation system would not ordinarily cause hyperkalemia, if certain drugs are taken the susceptible patient may become hyperkalemic. For example, it has been shown that hyperkalemia is much more likely to occur during therapy with spironolactone or triamterene in a patient with diabetes mellitus. Perhaps hyperkalemia would occur in a normal subject medicated with both spironolactone and propranolol. A list of drugs reported to cause hyperkalemia is as follows:

TABLE V

COMMONLY USED DRUGS THAT CAN CAUSE HYPERKALEMIA

1. PROPRANOLOL (INDERAL)
2. IBUPROFEN (MOTRIN)
3. INDOMETHACIN (INDOCIN)
4. NAPROXEN (NAPROSYN)
5. SPIRONOLACTONE (ALDACTONE)
6. TRIAMTERENE (DYRENIUM)

Hyperkalemia During β-Adrenergic Receptor Blockade

Propranolol used in low dosage for treatment of essential hypertension generally results in slight elevation of serum potassium concentration. It has also been shown to exaggerate exercise hyperkalemia. Propranolol has been shown to impair cellular uptake of potassium in dogs with ligated ureters (36). The following evidence suggests that significant hyperkalemia may result during beta blockade with propranolol.

A 49 year old former alcoholic man, with untreated diabetes mellitus, was admitted to the hospital with a recurrent bout of pancreatitis. He had known chronic calcific pancreatitis which was presumably the cause of his insulin deficiency. He had undergone a coronary artery by-pass graft and because of persistent angina, was taking propranolol 40 mg every 8 hours.

Physical examination showed a blood pressure of 190/110 mm Hg and slight epigastric tenderness.

Laboratory findings: BUN 28 mg/dL, creatinine 2.0 mg/dL, serum glucose 170 mg/dL. Electrolyte concentrations: Na^+ 139 mEq/L, Cl^- 114 mEq/L, K^+ 7.1 mEq/L and total CO_2 12 mmoles/L. The patient had no ketonuria. Blood pH 7.44. Electrolytes measured two days following discontinuation of propranolol: Na^+ 134, K^+ 4.5, Cl^- 102 and total CO_2 25 mmole/L respectively.

That patients receiving propranolol may develop moderate degrees of hyperkalemia is becoming more widely recognized. Bethune and McKay (37) observed a patient after cardiopulmonary by-pass who was on propranolol whose serum potassium rose to 7.0 mEq/L. The patient responded to glucose, insulin and calcium infusions. Because of this observation, they reviewed 45 consecutive patients who had undergone cardiopulmonary by-pass. Sixteen of these patients had received beta blockers until the evening of surgery, twelve propranolol and four oxprenolol. During cardiopulmonary by-pass, serum potassium rose an average of .92 mEq/L in these patients. In 18 patients who had received digitalis and diuretics but no beta blockers, serum potassium fell an average of 0.5 mEq/L during surgery. Finally, 11 patients had not been on drugs before surgery and their serum potassium value fell an average of 0.2 mEq/L. The difference between those patients receiving beta blockers and those not receiving beta blockers was highly significant. The authors pointed out that hyperkalemia as result of beta blockade could well be responsible for difficulties in re-establishing the circulation following cardiopulmonary by-pass. Of interest, they also noted that hyperkalemia has not been observed in patients receiving metoprolol.

Elevations of serum potassium concentration averaging 0.3 to 0.5 mEq/L have been observed in large number of patients taking 80 mg of propranolol daily or 964mg of alprenolol (38) daily. In these patients, plasma renin activity and aldosterone declined coincident with an elevation of serum potassium concentration.

Although such slight elevation of serum potassium concentration during beta blocker therapy is probably of little importance in patients with uncomplicated essential hypertension, it could conceivably become important in those who have diabetes mellitus, adrenal insufficiency or impaired renal function (39). It might also be important in patients who perform significant exertion. One study on normal subjects showed that the average rise of serum potassium during exercise was significantly higher during propranolol therapy. This response is shown in Figure 10 (40).

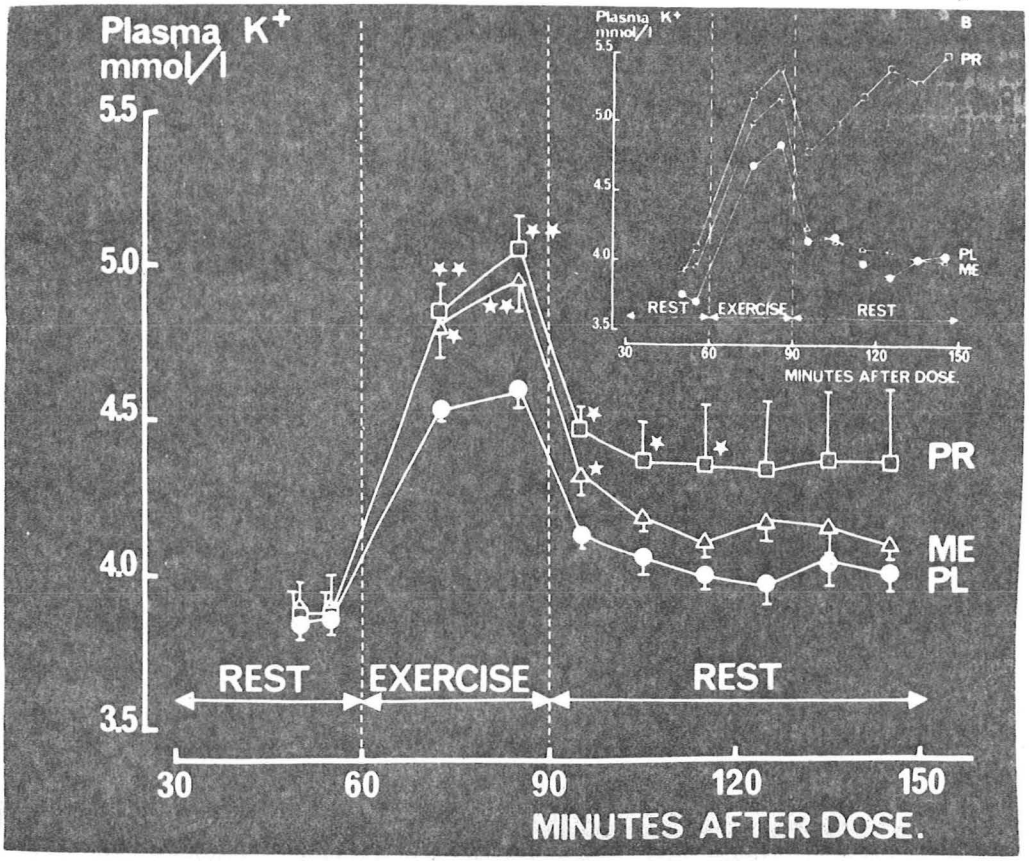

Fig. 10

Hyperkalemia with Prostaglandin Synthetase Inhibition

Based upon earlier studies from Kaplan's laboratory (41) showing that prostaglandins E1 and E2 significantly stimulate synthesis of aldosterone, current theories hold (42) that renal prostaglandins are critical for full expression of the renin-aldosterone response. Tan and his associates have reported that indomethacin therapy may result in the syndrome of hyporeninemic hypoaldosteronism in moderately advanced renal disease (43). Another case of hyperkalemia has been reported as a result of indomethacin therapy in a patient with chronic renal failure by MacCarthy and his associates (44).

Kimberly and his co-workers (45) observed a decline of renal function in patients with systemic lupus erythematosus following treatment with either ibuprofen (Motrin), naproxen or fenoprofen. The patient receiving ibuprofen had no pre-existing evidence of renal disease. However,

following 3 days of ibuprofen 2.4g/day, body weight fell 2Kg, BUN rose from 16 to 43 mg/dL, creatinine from 0.9 to 3.0 mg/dL and potassium from 4.7 to 6.1 mEq/L. Serum sodium concentration also fell from 142 to 130 mEq/L. In this patient there were substantial declines of prostaglandin E excretion into the urine. Despite weight loss, plasma renin activity fell from a baseline of 2.34 to 0.12 ng/ml/hr and urinary aldosterone excretion decreased from 4.7 to 1.1 mg/day. Recovery followed discontinuation of the drug. Those patients receiving naproxen and fenoprofen also showed declines in renal function and an elevation of serum potassium of 0.5mEq/L. However, neither of the latter two patients became frankly hyperkalemic.

Tan and Mulrow (42) examined the effect of indomethacin on the response of plasma renin activity to volume contraction induced by furosemide and the effect of the upright posture. Inhibition of renal prostaglandin production with indomethacin substantially blocks these normal stimulae to renin release.

Decreased prostaglandin E production by the kidney and the associated decreased release of renin could nicely explain a variety of the findings in the patients with the syndrome of hyoreninemic hypoaldosteronism. Such a case has been reported. Norton and his associates (46) studied a 57 year old woman with hypertension, moderate renal insufficiency and hyperkalemic, hyperchloremic metabolic acidosis. This patient showed impaired ability to conserve sodium while receiving a low sodium intake. The associated weight loss was not associated with appropriate elevations of either plasma renin activity or urinary aldosterone excretion. Repeated measurements of immunoreactive prostaglandin E and immunoreactive prostaglandin F into the urine in this patient were compared to values measured in nine normal women. While the patient was receiving 150 mmoles of sodium and 60 mmoles potassium per day, urinary excretion of PGE and PGF were 100±25 and 200±40 mg/day respectively. These values were significantly less than the normal range. Prostaglandin A1 was then infused at a rate of 0.16 to 0.8 mg/kg/min. The patient was supersensitive to the vasodepressor effects of prostanglandin A1. Her plasma aldosterone level rose from 4.3 to 23.4 ng/dL. There was a corresponding increase of aldosterone excretion. However, despite the prostaglandin infusion and sharp fall of blood pressure, there was no response in plasma renin activity. Urinary potassium excretion increased during prostaglandin A1 infusion. The authors proposed that a defect in renal prostaglandin synthesis may play an important role in the pathogenesis of hyporeninemic hypoaldosteronism.

One study since the report by Norby and his associates has failed to confirm evidence for impaired PGE production in hyporeninemic hypoaldosteronism (47). Five women and three men with classic hyporeninemic hypoaldosteronism showed an average serum potassium concentration of 6.7 mEq/L, serum creatinine averaging 2.9 mg/dL and persistently supressed plasma renin activity and plasma aldosterone concentration. Average urinary prostaglandin excretion was 586±201 ng/day. This exceeded their normal values of 400±50 ng/day. Presumably, these measurements were made by the same methods used by Norby and his associates (46). At the present

time therefore, no conclusion can be made concerning a specific role for depressed prostaglandin production in all patients with the syndrome of hyporeninemic hypoaldosteronism. Nevertheless, in view of the isolated observations that prostaglandin synthesis inhibitors such as indomethacin or ibuprofen may result in either hyperkalemia or the frank syndrome of hyporeninemic hypoaldosteronism would seem to suggest that prostaglandins may be implicated in certain cases. Some evidence suggests that hypokalemia and/or potassium deficiency results in increased prostaglandin production and increased plasma renin activity. The best example of this is Bartter's syndrome. Galvez and his associates (48) have shown that prostaglandin production is markedly enhanced in potassium deficient dogs. Recent in vitro studies from Lee's laboratory (49) on slices of rabbit renal medulla, papilla and human medullary tissue show that low extracellular concentrations of potassium stimulate and elevated potassium levels suppress production of immunoreactive PGE2. Any possible effect of potassium-mediated-changes in prostaglandins and their relationship to renin remains unsettled.

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