FLUID REPLACEMENT AND HEAT STRESS

Committee on Military Nutrition Research
Food and Nutrition Board
Institute of Medicine

Bernadette M. Marriott, Editor

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Preface

This publication is the third printing of the proceedings of a workshop held in February 1989, on the subject of fluid replacement and military performance. This workshop was organized at the request of the U.S. Army Medical Research and Development Command to explore the question of the potential utility of fluid replacement, including carbohydrate-electrolyte beverages, in enhancing sustained military performance in military operations. Through the Army project officer and the Division of Military Nutrition, U.S. Army Institute of Environmental Medicine (USARIEM), the committee was specifically asked to address twelve questions.

1. Under what conditions, if any, does fluid replacement as water or a fluid replacement product containing electrolytes and a source of carbohydrate enhance performance or endurance with respect to participation in likely military activities?
2. If a fluid replacement beverage is recommended, what is its appropriate composition and how would the composition vary under different military activities and environmental conditions?
3. Under what circumstances is glycogen depletion regarded as a problem, and what types of carbohydrate-containing beverages might be provided to ameliorate such problems? Are there special problems related to maintenance of glycogen stores?
4. If electrolyte-carbohydrate-containing solutions or fluids are recommended, what is appropriate timing for provision of the solutions with

respect to performance of the military task or recovery following performance of the task?

5. What are the rates of gastric emptying, intestinal absorption, and the body's utilization of the components of the solution?
6. What are the important considerations in the preparation of hygienic and palatable solutions with respect to safety, quality, and acceptance?
7. What considerations are important for treatment of diarrheal disease and heat casualties?
8. What replacement regimens are regarded as most appropriate for ensuring field duty following minor heat injuries?
9. What important behavioral aspects should be considered relative to thirst, voluntary hypohydration, work-rest cycles, and other factors?
10. Military missions must be performed under different environmental conditions--how do these environmental conditions influence body fluid replacement?
11. Are there specific effects (e.g., hormonal) related to age or gender that should be considered in the use of replacement solutions?
12. What are the major unanswered questions regarding sound replacement beverage practices for the military?

The first chapter of the report is an Executive Summary followed by the conclusions and recommendations formulated by the Committee on Military Nutrition Research based on the papers presented at the workshop and on committee members' knowledge and experience. The conclusions and recommendations were developed in executive session of the committee and opinions expressed are those of the committee members and not necessarily those of the authors of the papers.

The papers presented at a workshop held in February 1989 make up Part II of the volume. After oral presentation at the workshop, the papers were reviewed by a group of experts other than those on the committee, and authors have been given an opportunity to alter their papers or not in response to reviewers' comments. However, the papers represent the personal opinion of the authors and do not necessarily reflect the committee's views.

Prior to the **Second Printing** in April, 1991, the authors were given the opportunity to review the printed document for typographical errors, spelling and punctuation. Minor changes of this nature were made by the committee staff prior to printing.

The third printing is in response to continuing demand for copies of the report and has been reformatted in the book style of the more recent reports of the CMNR providing a uniform filing and shelving option for the publications. The interest in this report is a tribute to the excellence of the

contributions of the participants in the workshop and the conclusions and recommendations developed by the Committee on Military Nutrition Research. As chairman of the CMNR, I wish to thank all who participated in the workshop and to recognize in particular E.R. Buskirk and Edward S. Horton who helped organize and co-chaired this workshop. Their assistance was invaluable in providing information and insights into the questions posed by the Army. The contributions of former committee members Alan L. Forbes and Daniel Rudman to the program of the Committee on Military Nutrition Research leading up to this workshop are appreciated. The committee is grateful to the anonymous reviewers of this report for their important contribution. The committee also wishes to acknowledge the assistance of its former staff, Susan Berkow and Elsie Sturgis, who helped make the workshop a success through their skilled and expert work. Also, I recognize on behalf of the members of the CMNR the contribution of Bernadette Marriott, Deputy Director of the Food and Nutrition Board and staff person to the CMNR for working through the editorial revision of the second printing in 1991 and the reformatting of the report in this the third printing. The committee is grateful to Donna F. Allen for her care and precision in assisting with all stages in the development of this third version. I also express my appreciation to all of the members of the CMNR--past and present who have conscientiously contributed their expertise in the development of recommendations in response to issues raised by the Army.

Robert Nesheim, *Chairman*
Committee on Military Nutrition Research

Contents

Part I

Executive Summary

PART I IS THE EXECUTIVE SUMMARY OF THE REPORT. The Executive Summary comprises Chapter 1 of the report. It describes the task presented to the Committee on Military Nutrition Research (CMNR) by the Military Nutrition Division, U.S. Army Institute for Environmental Medicine (USARIEM), U.S. Army Medical Research and Development Command; summarizes the relevant background material; and presents the committee's findings. The Executive Summary also includes specific and general recommendations developed by the CMNR.

1

Committee Summary and Recommendations

INTRODUCTION

Advances in our understanding of the value of carbohydrate-electrolyte solutions have come from information derived from two major fields of study--exercise physiology and sports nutrition--and from research on diarrheal diseases. Research in the first area has been concerned with physical performance, primarily of athletes. Research results have demonstrated that even small fluid deficits have adverse effects on performance through elevated heart rates, reduced sweat rates, and elevated body temperature. Glucose-electrolyte solutions have been found useful in rehydration and in preventing dehydration. Carbohydrate is needed to facilitate sodium and water absorption. Other ions may or may not be needed, depending on sweat losses or losses from the gastrointestinal tract. Advances in exercise physiology also have demonstrated the value of carbohydrate solutions in providing energy for muscular activity in endurance events that last at least 60 minutes and involve vigorous exercise.

Diarrhea is a major, perhaps the most important, contributor to death of infants and preschool children in less-developed countries. Death rates are being reduced around the world through the use of oral rehydration therapy (ORT), which involves the use of carbohydrate-electrolyte solutions and is based on the same basic physiologic mechanism as the rehydration solutions given to athletes, i.e., the provision of glucose to promote the absorption of sodium and potassium ions and of water.

Both these established uses for carbohydrate-electrolyte beverages have potential military applications. Military personnel are often called upon to perform heavy physical activity during training or combat conditions in very

hot environments--either dry climates, as in Middle-Eastern deserts, or under humid tropical conditions. The resultant high sweat rates can lead to dehydration. In some cases, the subjects may be acclimated to heat, but in others (for example, in basic training, or in emergency troop deployment to the tropics) they may not, and may thus be vulnerable to extensive electrolyte losses. This problem could be accentuated when personnel have been given garrison or field rations with reduced sodium to meet prudent dietary goals established for the general population in 1989 by the Diet and Health Committee of the Food and Nutrition Board, National Academy of Sciences.

A carbohydrate-electrolyte beverage could be useful in providing glucose to sustain muscular activity in troops involved in heavy physical activity for long periods. Recognizing that the maintenance of an adequate hydration status is dependent on an adequate fluid intake, the military has for a long time instructed troops on ways to maintain a safe supply of drinking water under field conditions. Carbohydrate-electrolyte solutions are useful in rehydration during episodes of diarrhea, especially to counteract acute dehydration that results when diarrhea occurs in conjunction with heavy sweat losses.

FINDINGS FROM THE WORKSHOP PRESENTATIONS

Maintaining an adequate state of hydration is important for the maintenance of high levels of physical performance by soldiers in the field. At a 3% decrease in body weight due to dehydration, there is a substantial decrease in physical working capacity. The maintenance of adequate fluid intake is of primary importance in the prevention of hypohydration that may otherwise occur under such conditions as prolonged air travel, extended working hours, wearing of chemical protective clothing, missed meals, or working in mountainous areas or in hot or extremely cold environments. Increased psychological stress associated with basic or field training exercises or anticipation of combat or actual combat may lead to extreme hypohydration due to decreased voluntary fluid intake. Conscious efforts to increase fluid intake before and during such situations could prevent this condition. Training and the initiation of disciplined programs to increase both voluntary and programmed fluid intake are important preventive actions.

Heavy physical activity, especially in hot environments, and wearing of protective clothing promote sweating and will lead not only to excessive fluid losses but also to associated electrolyte losses. Sodium, potassium, and chloride losses in sweat are affected by temperature, humidity, and state of acclimatization. Febrile conditions or gastrointestinal disturbances, parti

cularly those associated with vomiting and diarrhea, may result in significant fluid and electrolyte losses and require replacement of electrolytes in addition to fluid. Gastrointestinal losses may also include hydrogen ion, bicarbonate, magnesium, and other cations and anions, depending on the cause of the losses and the severity of the disturbance.

Glycogen depletion from muscle and liver may result from prolonged physical exercise--more than 60 or 90 minutes at 60% to 70% of exercise capacity or several hours at lower exercise intensities. Such depletion may be aggravated by poor nutritional intake of carbohydrates, inadequate periods of recovery from previous glycogen-depleting exercise, and sustained negative calorie balance. Under these conditions, soldiers may benefit from consuming fluid replacement beverages containing carbohydrates. This is particularly true if food intake is inadequate, resulting in significant caloric deficit or limited carbohydrate intake. The resultant reduced muscle and liver glycogen content will result in earlier fatigue and slower recovery.

It is evident from the research reported at this workshop that a fluid replacement solution may play an important role in preventing fluid, electrolyte, and glycogen depletion, thereby maintaining or improving a soldier's performance. It is also evident that the composition of the replacement fluid might well vary, depending on the physical demands of the military activity and the environmental conditions under which the activity is undertaken.

Water intake is the primary requirement to ensure adequate hydration during psychological and environmental stress not associated with intense physical activity and during sedentary activity at high altitudes. If a normal meal pattern is established and fluid is consumed, the body's balance is restored.

Palatability of the fluid replacement solution is important to ensure compliance. This may be enhanced by appropriate coloring and flavoring. The solution should also be compatible with halogens to make it possible to use halogen-treated water in the preparation of the solutions.

AREAS FOR FUTURE RESEARCH

The participants whose papers appear in this volume provided an excellent review of the current state of knowledge on fluid replacement and stress. These proceedings will provide investigators and product formulators with important guidance in the development and testing of electrolyte-carbohydrate-containing fluid replacement products for use by the military. Continued research is needed on energy, electrolyte, and fluid requirements in different environmental and operational conditions that require different

types of physical activity. More studies are also needed to provide us with a better understanding of (1) the factors affecting liver and muscle metabolism and injury during heat stress, and (2) the factors that are important in preventing muscle injury during heat stress and in enhancing muscle recovery. The following issues raised at the workshop could lead to a better understanding of the appropriate composition and usage of a fluid replacement beverage:

- What are the effects of food in the small intestine on fluid and electrolyte absorption? How are fluid and electrolyte absorption affected relative to timing of meals?
- What are the effects of hypohydration on the absorption of electrolyte-carbohydrate solutions?
- What factors regulate depletion of muscle and liver glycogen stores during negative caloric balance or prolonged physical activity?
- What is the role of glycogen depletion in the fatigue of different muscle groups? What other factors related to beverage composition determine muscular fatigue?
- What factors determine the rate of glycogen depletion and resynthesis? There is a need to obtain quantitative data on the effects of feeding and the provision of electrolyte-carbohydrate solutions in maintaining glycogen stores and enhancing replenishment of glycogen stores following glycogen-depleting physical activity.
- What are the effects of fluid and electrolyte deficits combined with elevations in body temperature on cognitive and mental function?
- What factors need to be considered in product development and water purification techniques to provide compatible systems for field use under a variety of environmental and operational conditions? Factors such as halogen or other purification requirements and the composition of local water supplies need to be considered in relation to formulation of practical electrolyte-carbohydrate mixtures.
- What effect would result from the provision of an electrolyte-carbohydrate replacement solution on soldiers who previously consumed a low-sodium diet?
- Will the addition of specific amino acids such as glycine be beneficial in enhancing sodium and water absorption?

RECOMMENDATIONS

When used appropriately, electrolyte-carbohydrate-containing beverages appear to have the potential not only for maintaining but also, possibly, for enhancing performance and endurance in a variety of military situations. The specific needs for water, electrolytes, and carbohydrate may vary somewhat depending on the specific circumstances in which the solution is used. The ideal solution would be one that could be diluted in different ways to meet the relative specific needs of the personnel.

The goal of using such a solution should be to maximize fluid intake, replace electrolyte losses, and provide a carbohydrate source for energy and rapid replenishment of muscle and liver glycogen stores during and following physical activity. The use of an electrolyte-carbohydrate-containing beverage may be applicable to a number of circumstances in the military such as the following:

- Maintaining adequate fluid intake prior to military operations during which voluntary dehydration is probable.
- Providing fluid, electrolyte, and carbohydrate replacement during physical work in a variety of environmental conditions, including high temperatures, humidities, or wearing of chemical protective clothing. In such situations, sweat rates are high and account for large fluid and electrolyte losses.
- Providing rapid rehydration following heavy or prolonged physical work, thereby facilitating recovery from heat injury.
- Providing carbohydrate during and following physical activity to maintain plasma glucose concentrations, furnishing carbohydrates for energy, and enhancing replenishment of glycogen stores during postoperational recovery.
- Replacing gastrointestinal losses due to vomiting or diarrheal diseases.

The committee recommends that the Surgeon General of the Army evaluate the use of electrolyte-carbohydrate fluid replacement products as an aid to maintaining proper hydration of soldiers during periods involving psychological and environmental stress and also assess the effectiveness of these products in maintaining or enhancing both physical and cognitive performance during training activities and field operations.

Physical demands and adverse environmental conditions that occur during military training and operations may lead to any one or all the conditions summarized above. In view of this, the committee concludes that there are circumstances in which the performance of military personnel

would be improved by appropriate use of electrolyte-carbohydrate solutions under field conditions.

Below are the committee's recommendations developed following the workshop:

- The solutions should provide approximately 20 to 30 meq of sodium per liter, 2 to 5 meq of potassium per liter, and chloride as the only anion.
- The carbohydrate content should be provided as glucose or sucrose, malto-dextrin, or other complex carbohydrate in a concentration of 5% to 10%.
- The value of additional magnesium, bicarbonate, and phosphate to compensate for gastrointestinal losses due to diarrhea or other gastrointestinal disturbances should be determined.
- The promotion of fluid intake with such palatability and psychogenic aids as flavorings and colorings should be evaluated with respect to the promotion of fluid intake. The components of the solution must be compatible with halogens or other water purifiers.
- A variety of training and field operations should be considered as a means for evaluating the effectiveness of prototype electrolyte-carbohydrate-containing solutions under the following conditions:

  - When soldiers are in significant negative caloric balance.
  - Under conditions of hypohydration.
  - When the solution is the principal beverage available.
  - Under conditions of environmental extremes, especially those conducive to stress. Interventions for prevention and therapy of heat-related disorders should be evaluated.
  - When used by soldiers previously on a low sodium diet (less than 3 g/day) who are suddenly exposed to hot or humid environments and who are performing heavy physical activity.
  - Under field conditions when halogen-treated water is likely to be available. Do any of the components in the prepared solution interfere with purification of the water? Is the resulting beverage sufficiently palatable to ensure an intake adequate to prevent significant hypohydration?

Part II

Invited Papers

IN PART II THE EXPERT PAPERS that formed the basis for the development of the basic science summary and recommendations in Part I are included here in the order they were presented at the workshop. A sub-committee of the CMNR worked with the Army Grant Officer Representative, COL E. Wayne Askew to define the focus for the workshop and the report. Speakers were selected who were active senior investigators and well known for their research in the specific area. Each speaker was asked to carefully review the literature in their own field of expertise in preparation for their presentation. In their presentation and in their chapter, the invited experts were requested to make critical comments on the relevant research and conclude with their personal recommendations. After the workshop, each author was given the opportunity to revise or add to their papers based on committee questions. The final papers were used by the committee in the development of Part I. Although the conclusions of the following chapters focussed on fluid replacement and heat stress in a military setting, these chapters provide a state-of-the art review of fluid and carbohydrate-electrolyte beverage intake during any type of outdoor activity whether heavy work, sports, or recreation.

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2

Use of Electrolytes in Fluid Replacement Solutions: What Have We Learned From Intestinal Absorption Studies?

Carl V. Gisolfi[1]

INTRODUCTION

There is abundant evidence to indicate that fluid replacement during exercise, especially in the heat, is essential to prevent hyperthermia and improve work capacity (Adolph and Associates, 1947). It is also well established that the inclusion of carbohydrates in oral hydration solutions (OHSs) can prolong exercise and improve performance (Christensen and Hansen, 1939; Coyle et al., 1983; Lamb and Brodowicz, 1964; Murray, 1987). It is considerably less clear what role electrolytes play when they are added to these solutions. Are electrolytes lost in sufficient quantities to warrant their replacement in OHSs? If not, is there any other reason to include them

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in such beverages? For example, does their inclusion in OHSs enhance the absorption of water and other solutes? Do they contribute to beverage palatability, osmoregulation, or maintenance of plasma volume?

The purpose of this paper is to review the effects of Na^+on the intestinal absorption of water and carbohydrates during rest and exercise. It begins with a brief review of the methods employed in such studies and is followed by a discussion of the interactions among sodium, water, and glucose absorption. The emphasis will be on in vivo experiments on human subjects.

METHODS

Although there are several different methods of studying absorption (Leiper and Maughan, 1988; Modigliani et al., 1973), the segmental perfusion technique provides the most quantitative assessment of water and solute absorption in humans (Fordtran et al., 1961; Schedl and Clifton, 1963). This technique requires the subject to pass a multilumen catheter into the small intestine under fluoroscopic guidance. A mercury ball enclosed by an inflatable balloon is attached to the distal end to facilitate movement through the intestine. The test solution is infused at a constant rate (usually 8 to 20 ml/min) and contains a water-soluble nonabsorbable marker (usually polyethylene glycol).

When this technique was first introduced, it employed only a double-lumen tube with a mercury bag attached to its distal end. One lumen was used for infusion and the other was used to sample the perfusate at the end of the test segment. The drawbacks of the double-lumen tube are (1) reflux of the perfused solution proximally, and (2) contamination of the perfused solution by proximal endogenous secretions (Modigliani et al., 1973). To eliminate these problems, (1) an occlusive balloon proximal to the infusion port was included to prevent reflux and contamination of intestinal secretions, or (2) a third lumen was added to the catheter. The disadvantage of the occlusive balloon is that it may interfere with intestinal motility.

Most investigators who use the segmental perfusion technique employ a triple-lumen tube. By this technique, the test solution is perfused through the most proximal port and is sampled from the two more distal sites. The distance (10-15 cm) between the perfusion port and the first sampling site is called the mixing segment. It allows the marker to form a homogeneous solution with the intestinal contents before a sample is drawn (1 ml/min) from the proximal sampling site. The fluid then traverses the test segment (usually 20-40 cm) and is collected continuously by siphonage at the distal sampling site. It is not necessary to collect all of the solution, because the

flux calculations depend only on changes in concentration of the marker and the test solution. Accuracy of the technique depends on two assumptions: (1) that the marker is not absorbed appreciably, and (2) that complete mixing has occurred. It is important to realize that the composition of the solution under study is not the composition of the solution perfused, but rather is the composition of the fluid collected from the proximal sampling site before it enters the test segment. It is also important to understand that the results from such studies apply only to the portion of gut represented by the test segment. Different results could be obtained by perfusing a larger segment or a different segment of the intestine.

WATER AND ELECTROLYTE ABSORPTION

Electrolyte and nonelectrolyte absorption involve both active and passive transport along the entire length of the intestine. Water is primarily absorbed in the proximal small intestine (duodenum and jejunum), but it is absorbed more efficiently in the colon (American Gastroenterological Association, 1989); it is a passive process dependent upon net solute absorption (Curran, 1968).

Water transport and fluid homeostasis are highly dependent upon Na^+ absorption. This is a two-step process involving (1) passive Na^+ entry across the brush border membrane via simple diffusion or cotransport with electrolytes or nonelectrolytes, and (2) active Na^+extrusion across the basolateral membrane via the Na^+ - K^+ pump (Powell et al., 1985). Na^+ - sugar coupling stoichiometry across the brush border is 2:1 (Kimmich and Randles, 1984). Na^+ may also move passively across the cell via bulk flow through the intercellular (paracellular) pathway.

Glucose-Stimulated Na+ Absorption

This phenomenon was first observed in the guinea pig small intestine by Riklis and Quastel (1958), and it is now a firmly entrenched biological concept (Powell et al., 1985; Schultz and Curran, 1970). It occurs in the small intestine but not in the colon (Binder and Sandle, 1987) and is attributed to either glucose-Na^+ cotransport (an active process) or to glucose-stimulated Na^+ absorption secondary to solvent drag (a passive process). Fordtran (1975) has presented convincing evidence that up to 85% of the glucose-stimulated Na^+ absorption in the human jejunum is due to passive transport.

The concentration of Na^+ in the jejunal lumen plays a crucial role in determining the rate of sugar enhancement of Na^+ absorption, but not in the ileum. Using the double-lumen technique with a proximal occlusive balloon, Spiller et al. (1987) reported that perfusing solutions with less than 90 meq Na^+ per liter resulted in net Na^+ secretion into the jejunum of normal human subjects. Fordtran (1975) found that when the luminal Na^+ concentration in the human jejunum was 120 meq/liter, Na^+ absorption was virtually doubled compared with a luminal concentration of 80 meq/liter. Water absorption followed net solute absorption and was therefore highly dependent upon Na^+ transport. Olsen and Ingelfinger (1968) perfused different segments of the intestine with isotonic solutions containing various concentrations of glucose and either 0 or 140 meq of Na^+ per liter. When the glucose concentration was between 1 and 3 mmol/liter, and was therefore moving against a concentration gradient, glucose transport was inhibited with Na^+-free perfusions. On the other hand, when the glucose concentration ranged from 6 to 20 mmol/liter in the perfusion solution, glucose transport was not affected by the absence of Na^+ in the perfusion solution. In the human, rat, and dog ileum, Saltzman et al. (1972) were unable to show an important role for intraluminal Na^+ in the active absorption of glucose. Glucose absorption was virtually unaffected when the luminal Na^+ concentration was reduced from 140 to 2.5 meq/liter; however, in the in vivo preparation, Na^+ could be trapped in the negatively charged mucous gel adjacent to the apical membrane, making it impossible to reduce Na^+ to very low levels (Smithson et al., 1981).

Although Na^+ appears to be required to maximize glucose and water absorption in the small intestine, is it necessary to include Na^+ in fluid replacement beverages or will intestinal secretions suffice in supplying the needed electrolytes? In a recent study by Wheeler and Banwell (1986), there was no difference in water absorption from carbohydrate-electrolyte solutions perfused into the jejunum of normal human subjects compared with that when plain water was perfused. They concluded that the limiting factor in rehydration was gastric emptying. In a similar study, Gisolfi et al. (1990) found significantly greater water absorption from a 6% carbohydrate-electrolyte solution than from distilled water. The difference between studies could be attributed to differences in the intestinal segment perfused, the form of carbohydrate used, or the electrolyte concentration of the solutions. Wheeler and Banwell (1986) perfused the jejunum with solutions containing complex carbohydrates and 10 meq of Na^+ per liter, whereas Gisolfi et al. (1990) perfused the duodenojejunum with more simple sugars and 20 meq of Na^+ per liter.

What is the optimal ratio of Na^+ to glucose required to maximize water absorption, and what form of carbohydrate best facilitates net Na^+ and

water transport? Schedl and Clifton (1963) were the first investigators to demonstrate that glucose markedly enhances water absorption from the human small intestine; 56 mmol glucose (1% solution) made isotonic with Ringer's solution increased water absorption fivefold over Ringer's solution alone. Water absorption was the greatest in the duodenojejunum. Jones et al. (1987) found that glucose absorption was significantly faster from maltotriose and a glucose oligomer mixture than from isocaloric 140 mmol glucose. Water and sodium absorption were not measured. Wheeler and Banwell (1986) found that water and mineral absorption from solutions containing glucose polymers and fructose or glucose polymers, fructose, and sucrose were not different from absorption from solutions containing only water. Malawer et al. (1965) systematically varied sodium:glucose ratios of isotonic solutions perfused through the jejunum and concluded that water absorption was directly proportional to net solute movement and was maximal with 140 mmol glucose. The ratio of sodium to glucose absorbed depended upon the ratio of sodium to glucose perfused. Similar in vivo studies by Sladen and Dawson (1969) with isotonic glucose-saline solutions showed that water absorption correlated well with total solute absorption and was maximal with 56-84 mmol glucose. Fordtran (1975) found maximal water absorption when glucose in the test solution was 130 mmol and Na^+ was 80 meq/liter, with Cl^- as the major anion. None of these studies identified the optimal form of carbohydrate or the optimal glucose : sodium molar ratio that maximizes water absorption.

In the rat duodenojejunum, Saunders and Sillery (1985) found the greatest water absorption when 10 mmol polycose (equivalent to 56 mmol glucose oligosaccharides) was added to 120 mmol NaCl and 20 mmol KCl. Thus, the optimal glucose : sodium molar ratio was approximately 1:2. Using the same animal model, Lifshitz and Wapnir (1984) found that a solution containing 60 mmol Na^+ and 111 mmol glucose (2% solution) optimized both water and Na^+ absorption and concluded that the optimal molar glucose:sodium ratio of an oral hydration solution was 2:1. Interestingly, intestinal fluid absorption is not only enhanced by the presence of glucose in luminal fluid but is also enhanced by elevating the glucose concentration in plasma (Lee, 1987).

The mechanism of this increase in fluid absorption is not clear. It is not due to an increase in luminal glucose concentration and infusing NaCl to produce a similar rise in plasma osmolality reduced fluid absorption. Thus, the increase in fluid absorption during glucose infusion is attributed primarily to an increase in plasma glucose concentration and in part to glucose stimulated vasodilation and to glucose increasing intestinal blood flow (Bohlen, 1980).

Fructose Versus Glucose

The mechanism of intestinal fructose absorption is controversial. In humans, it is slower than glucose absorption and is thought to occur by energy-independent, facilitated diffusion (Holdsworth and Dawson, 1965). The absorption capacity of orally ingested fructose taken alone ranges from approximately 5 to 50 g, but when consumed in equal quantities with glucose or given as sucrose, absorption capacity (based on breath hydrogen analysis) is significantly increased. The latter observation led Rumessen and Gudmand-Hoyer (1986) to suggest that glucose enhances fructose absorption in a dose-dependent fashion. This second mechanism of fructose absorption is thought to occur in addition to the transport of a saturating level of free fructose. Fructose at 1 mmol (0.018%) is almost as efficient as 1 mmol (0.018%) glucose in stimulating water and Na^+ absorption compared with the effects of perfusing mannitol, but glucose causes K^+ secretion, whereas fructose causes K^+ absorption (Fordtran, 1975).

In the rat, fructose is absorbed by an active carrier-mediated mechanism (Gracey et al., 1972; Macrae and Neudoerffer, 1972), but infusing 60 mmol (2%) sucrose with 120 mmol NaCl and 20 mmol KCl did not promote water or Na^+ absorption (Saunders and Sillery, 1985). The inhibitory influence of sucrose on water absorption has been observed in both animal and human studies (Fordtran, 1975; Newton et al., 1985; Patra et al., 1982; Wheeler and Banwell, 1986).

ANION TRANSPORT

The major anion included in the perfusion solution can have a significant effect on water and salt absorption. Fordtran (1975) maintained Na^+ and glucose concentrations constant at 80 meq/liter and 65 mmol/liter, respectively, and varied the anion composition of test solutions. Maximal water and Na^+ absorption was found with Cl^- followed by HCO_3^- and then SO_4^{-2}. Combining Cl^- and HCO_3^- was not as effective as Cl^- alone.

EFFECTS OF EXERCISE

Intestinal absorption during exercise is not well understood. Using an indirect method (3-O-methyl glucose), Williams et al. (1964) found that prolonged (4.5 h) moderate exercise in the heat reduced active sugar transport. Using the direct method of segmental perfusion with a triple-lumen catheter, Fordtran and Saltin (1967) found that a 1-h cycle of exercise at 64%-78% $\dot{V}_{O_2\,max}$ had no consistent effect on jejunal or ileal absorption of water, Na^+, Cl^-, K^+, glucose, L-xylose, urea, or tritiated water. Although

exercise has been shown to markedly reduce splanchnic blood flow (Rowell et al., 1964), Fordtran and Saltin (1967) concluded that severe exercise did not reduce intestinal blood flow enough to reduce the rate of either active or passive absorption. In that study, however, five different solutions were perfused through the intestine and most were perfused in only one or two subjects. Thus, it is difficult to generalize about the effects of exercise on intestinal absorption from that investigation. In a more recent study, Barclay and Turnberg (1988) used the triple-lumen perfusion technique to evaluate the effects of cycle exercise at a pulse rate of 40%-50% above the mean resting heart rate on jejunal absorption of an electrolyte solution (Na^+, 136 mmol; Cl^-, 105 mmol; K^+, 5 mmol; SO_4^{-2}, 18 mmol). During exercise, the heart rate increased from 68 ± 4 beats per minute to 103 ± 7 beats per minute; and the absorption of water, Na^+, K^+, and Cl^- fell significantly. They attributed this reduction in absorption to a parasympathetic effect on mucosal transport, but acknowledged other possible explanations. Among these were (1) a reduction in splanchnic blood flow secondary to increased sympathetic drive, (2) release of some humoral mediator, or (3) changes in intestinal motility and transit. Although increased sympathetic activity can reduce splanchnic blood flow (Rowell et al., 1964), the effect of intestinal blood flow on absorption is controversial (Brunsson et al., 1979; Varro et al., 1965; Williams et al., 1964). Changes in motility and transit are also controversial (Morris and Turnberg, 1980). Cammack et al. (1982) reported that moderate exercise had no effect on small bowel transit of a solid meal, whereas Keeling and Martin (1987) reported a significant decrease in small bowel transit of a liquid meal.

SUMMARY AND NEEDED RESEARCH

The inclusion of electrolytes in fluid replacement beverages is important to offset the losses in sweat and urine during prolonged exercise in the heat; but, perhaps more importantly, electrolytes should be incorporated into these beverages because they play a pivotal role in glucose, water, and salt absorption, which, in turn, is essential for the maintenance of plasma volume and osmoregulation. Glucose-stimulated Na^+ absorption is a well-accepted biological phenomenon in the human intestine. The ratio of carbohydrate to salt and the form of carbohydrate that maximizes water absorption is controversial and warrants further investigation. The effects of exercise, hydration state, and ambient conditions on intestinal absorption have not been studied systematically and require investigation.

RECOMMENDATIONS

The following recommendations are based on current understanding of the interactions between water, electrolyte, and carbohydrate transport. It must also be recognized that the composition of a solution can be altered before it reaches the intestine. Thus, recommendations based solely on intestinal absorption data must be taken with a note of caution. Furthermore, it is possible that the segmental perfusion technique itself could alter the normal absorptive properties of the intestine. Much research is required in this field before we can understand how to formulate a rehydration beverage that maximizes water and carbohydrate absorption. Whether this same beverage can also serve as an oral hydration solution in the treatment of diarrheal disease also requires more research.

- Include Na^+ in the amount of 20-30 meq/liter in the formulation of an oral hydration beverage.
- Include glucose in the beverage in the concentration of at least 50 mmol (0.9%). Maximal water absorption has been observed with values as high as 140 mmol (2.5%). Most drinks provided for use after sports and other activities contain 5%-10% carbohydrate, and these higher concentrations must be evaluated to determine the optimal amount that can be absorbed without reducing water transport.
- Include 5-10 meq of K^+ per liter to offset the potential loss of K^+ in sweat, the K^+-secretory effect of glucose, and the potential loss of K^+ in diarrheal disease.
- The primary (or only) anion should be Cl^-. By comparison, all other anions tend to reduce water absorption.
- Consider the inclusion of a small amount of fructose, because glucose causes K^+ secretion in the jejunum, while fructose causes K^+ absorption.
- Determine the effectiveness of glucose polymers instead of glucose to reduce osmolality and provide for more Na^+ without reducing the glucose concentration below a minimal level.

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3

Formulation of Carbohydrate-Electrolyte Beverages

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INTRODUCTION

The optimal formulation of carbohydrate-electrolyte beverages for the soldier in the field is an important consideration for the health and combat effectiveness of that soldier. This is especially true for soldiers who are exposed to thermal stress that leads to rapid dehydration and for those who are undergoing prolonged physical exertion that leads to both rapid dehydration and exhaustion. The combination of thermal stress and physical exertion makes beverage formulation even more critical. In this paper it is assumed that the role of the beverages in question is to replenish depleted body fluid stores for the purpose of minimizing dehydration and to supply carbohydrates for the purpose of forestalling exhaustion. Furthermore, the emphasis in this paper is on the role played by rates of gastric emptying and intestinal absorption associated with various beverage formulations in determining the efficacy of those formulations.

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EFFECTS OF WITHHOLDING WATER BEFORE OR DURING PROLONGED EXERTION

Early Experiments

In 1944, Pitts et al. reported data from a series of experiments in which men walked on a treadmill for 1 to 4 h at 5.6 km/h up a 2.5% grade with or without fluid replenishment (Table 3-1). The environmental temperatures ranged from 32° to 38°C, the relative humidity was 35% to 83%, and the subjects were allowed to rest for 10 min each hour. When the subjects drank nothing during the walks, their rectal temperatures and pulse rates were usually higher and their sweat rates were lower than

Table 3-1 Mean Heart Rates, Rectal Temperatures, and Sweat Rates after 4 h walking at 38°C and 35% relative humidity (n = 3-7)

Fluid Type	Heart Rate (beat/min)	Rectal Temp. (°C)	Sweat Rate (liter/h)
None	154	38.9	0.76
Water ad libitum	143	38.4	0.74
Water each 15 min at sweat rate	132	38.3	0.08
0.2% NaCl each 15 min at sweat rate	131	38.3	0.81
3.5% Glucose each 15 min at sweat rate	126	38.1	0.71

Source: Pitts et al. (1944).

when water, 2% saline, or 3.5% glucose in volumes equivalent to sweat loss were consumed every 15 min or when water was consumed in quantities that just satisfied thirst. These early experiments demonstrated that progressive dehydration during prolonged exertion in the heat can adversely affect cardiovascular function, as reflected by elevated heart rates, and temperature regulation, as indicated by high rectal temperatures and reduced sweat rates. More recent investigators have confirmed these observations (Candas et al., 1988).

The experiments of Pitts et al. (1944) also suggested that thirst was not an adequate stimulus for the subjects to replace all of the water they lost as sweat. This was confirmed several years later in an experiment reported by Brown (1947), in which military recruits attempted to complete a 34-km hike in a desert environment at temperatures ranging from 30° to 33°C with or without free access to water. Without water, 7 of 13 subjects became

exhausted before completing the hike and lost 7.5% of their body weight. When water was provided, only 1 of 9 subjects became prematurely exhausted, but the subjects still lost 4.5% of their body weight during the hike. More sophisticated contemporary studies have confirmed that during prolonged exertion in hot environments, one must consume more fluid than that which satisfies thirst if progressive dehydration is to be avoided (Hubbard et al., 1984).

Reduced Plasma Volume and Increased Body Fluid Osmolality

Even in the absence of significant dehydration during prolonged exertion, some of the plasma volume usually moves out of the capillaries and into the interstitial or intracellular spaces, but progressive dehydration during the exertion increases the overall loss of plasma. For example, Costill et al. (1981) measured fluid volume shifts in 7 men who cycled for 2 h at 50% of maximal oxygen uptake $\dot{V}_{O_2\,max}$ in a chamber with a temperature of 30°C and a relative humidity of 46%. After only 10 min of cycling, there was a plasma volume loss of 4.4%, and by the end of 2 h, the plasma volume was 9% less than the baseline. Another study showed a plasma volume loss of as much as 16% during prolonged exercise (Costill and Fink, 1974). A plasma volume loss of this magnitude indicates a significant reduction in the volume of circulating blood that is availabel to meet the increasing demands for blood by muscles for producing force and by skin for dissipating heat.

A loss of plasma volume during exercise is often accompanied by a deterioration in the ability of the exerciser to regulate body temperature. However, it is apparent that there is no clear cause-and-effect association between plasma volume losses and failing temperature regulation because experimentally increasing or reducing plasma volume during exercise does not necessarily result in a systematic improvement or deterioration, respectively, in temperature regulation (Fortney et al., 1981, 1984; Nadel et al., 1980). The adverse effects of dehydration on temperature regulation appear to be a complex function of increased body fluid osmolality and decreased plasma volume (Fortney et al., 1984). Thus, even in the absence of a decrease in plasma volume, an increased plasma osmolality caused by dehydration raises the thresholds for initiation of the sweating response and vasodilation in the skin, but a decrease in plasma volume coincident with an increased plasma osmolality additionally reduces the rate of increase in skin blood flow for a given rise in core temperature and reduces the maximal rate of skin blood flow (Fortney et al., 1984; Nadel et al., 1980).

Increased Circulatory Strain

As plasma volume declines with progressively increasing dehydration and as the cutaneous vascular capacity increases because of greater demands for heat dissipation in prolonged exercise, the actively circulating blood volume decreases. This leads to a reduction in ventricular filling pressure, a fall in stroke volume, and a compensatory increase in heart rate (Candas et al., 1986; Francis, 1979; Rowell et al., 1966) that may be inadequate to prevent a reduction in cardiac output (Fortney et al., 1983; Nadel et al., 1980; Rowell et al., 1966). With increasing dehydration, circulation to the skin decreases to shift a greater percentage of the declining blood volume to the working muscles (Fortney et al., 1983). Unfortunately, this shift of fluids away from the skin reduces the ability of the body to dissipate heat and leads to a progressive increase in heat storage.

Decreased Sweating Response

Dehydration-induced decrements in plasma volume and increments in body fluid osmolality result in a decreased threshold for the onset of sweating, and a decrease in the rate of sweating for a given increase in core temperature (Fortney et al., 1984; Harrison et al., 1978). This deterioration in sweating leads to a reduced ability to dissipate heat by evaporation and thus leads to a higher core temperature during prolonged exercise in the dehydrated than in the hydrated condition (Candas et al., 1986, 1988; Costill et al., 1970; Francis, 1979; Sawka et al., 1983).

Altered Electrolyte Distributions

Sodium and chloride are the principal electrolytes lost in sweat, but sweat is hypotonic with respect to blood plasma so that sodium and chloride (and potassium) concentrations in plasma are usually elevated by 1% to 4% during prolonged exercise without fluid replenishment (Costill et al., 1970, 1974, 1976, 1981). Plasma magnesium concentrations either decrease (Costill et al., 1981) or are unchanged from those during rest (Costill et al., 1976). There seem to be no systematic changes with exercise in intracellular concentrations of sodium, chloride, or magnesium in skeletal muscle, perhaps because of variable changes in intracellular water (Costill et al., 1976, 1981). When expressed per unit of wet muscle weight, potassium concentrations in intracellular water typically decrease by 8% to 10% (Costill et al., 1981), but all electrolyte changes in muscle during prolonged

exercise are very minor when expressed per unit of dry weight (Costill et al., 1976, 1981).

EFFECTS OF WATER AND SALINE FEEDINGS DURING PROLONGED EXERCISE

The early experiments of Pitts et al. (1944) on men marching in the desert showed that consumption of water, 0.2% saline, or 3.5% glucose to replace sweat loss resulted in lower heart rates and core temperatures and sometimes greater sweat rates than were noted in a no-fluid condition. Francis (1979) studied eight men under three different hydration treatments during, intermittent exercise consisting of eight 15-min bouts of cycling at 50% $\dot{V}_{O_2\,max}$ interspersed with 5-min recovery intervals. The room air temperature was 32°C, and the relative humidity was 60% to 65%. During the rest intervals, the subjects consumed either water or an electrolyte solution (20 mM sodium, 10 mM potassium, 1.3% glucose) sufficient to replace sweat losses, or no fluid at all. In the no-fluid condition, plasma volume loss after 2 h was 17.7%; when either fluid replacement beverage was consumed, no significant loss occurred. Similarly, compared with the no-fluid condition, heart rate was 15 to 20 beat/min lower, rectal temperature was 1°C lower, and plasma cortisol concentrations were significantly reduced when either fluid was consumed during exercise.

In one experiment, four marathon runners ran on a treadmill for 2 h at 70% $\dot{V}_{O_2\,max}$ under each of three conditions: (1) no fluid, (2) 100 ml of water every 5 min during the first 100 min, or (3) 100 ml of a glucose-electrolyte beverage (20 mM sodium, 15.3 mM chloride, 2.4 mM potassium, 4.4% glucose) every 5 min for the first 100 min (Costill et al., 1970). Compared with the no-fluid treatment, both fluid replacement regimens significantly lowered rectal temperature and reduced the concentrations of sodium and chloride in plasma.

Brandenberger et al. (1986) and Candas et al. (1986) compared the effects of five treatments: (1) no fluid, (2) water, (3) a hypotonic beverage (0.4 mM chloride, 0.04% glucose and fructose), (4) an isotonic drink (23.1 mM sodium, 16.7 mM chloride, 3.2 mM potassium, 2.0 mM calcium, 6.8% sucrose), and (5) a hypertonic sugar solution (7.55% glucose, 7.53% fructose) on temperature regulation and cardiovascular function during 4 h of intermittent cycling at a low intensity (mean = 85 watts) in a hot environment (34°C, 10°C dew point). Fluid was consumed every 10 min after 70 min of exercise in amounts calculated to replace 80% of sweat losses. Relative to the no-fluid condition, all four fluid replenishment regimes decreased rectal temperature, heart rate, plasma protein concentration,

plasma osmolality, and losses of plasma volume, but did not significantly affect sweat rate or skin temperature. Although the hypertonic sugar solution tended to be less effective in minimizing homeostatic disturbances, there were few significant differences attributable to the beverage composition. One exception to this observation was that plasma volume was actually expanded during the isotonic drink treatment, whereas the other beverages only minimized the plasma volume loss found in the no-fluid condition. Hormones in this experiment were determined only for the no-fluid, water, and isotonic beverage treatments; and both water and the isotonic drink negated the rises in plasma concentrations of cortisol and vasopressin and in renin activity; aldosterone increases during exercise were significantly blunted only by the isotonic drink (Brandenberger et al., 1986).

Efficacy of Electrolyte Replacement During Prolonged Exertion

Because substantial quantities of sodium, chloride, and to a lesser extent, potassium are lost in the sweat during prolonged exertion, especially in the heat, many are concerned that this electrolyte loss should be replenished during exercise to maintain the appropriate distribution of electrolytes in the various fluid compartments of the body. However, there is little direct evidence of a beneficial effect of electrolyte replacement for any but a small proportion of endurance athletes. The fact that electrolyte concentrations in plasma usually rise during exercise without fluid replacement (Costill et al., 1970, 1974, 1976, 1981) indicates that electrolyte supplements are not needed. Furthermore, during repeated exposures to prolonged physical exertion, the kidneys very effectively conserve sodium and potassium so that the electrolyte balance is usually maintained when an athlete consumes a normal diet or a diet low in potassium (Costill et al., 1976), or a diet high or low in sodium (Armstrong et al., 1985). However, recent case studies have been reported in which athletes who participated in very prolonged exercise experienced severe hyponatremia, i.e., low plasma sodium concentrations during exercise (Hiller et al., 1985; Noakes et al., 1985) or up to 7 days after competition (Noakes et al., 1985). These athletes usually consumed large quantities of water or beverages low in electrolytes. Conceivably, ingestion of electrolyte beverages for soldiers sensitive to the development of hyponatremia could be effective in obliterating or reducing the severity of hyponatremia. It should also be noted that small amounts of sodium chloride in a beverage enhance palatability. Since palatability determines in large measure how much fluid a person will voluntarily ingest (Hubbard et al., 1984), it may well be that electrolytes in beverages are important to encourage consumption of as much fluid as possible. Finally, recent evidence

suggests that sodium in fluid replacement beverages is important for maintaining the osmotic drive for drinking during recovery from prolonged exertion (Nose et al., 1988).

Summary of Effects of Water and Saline Replacement on Homeostasis During Prolonged Exertion

Fluid replacement during strenuous prolonged exertion is unquestionably beneficial in minimizing the adverse effects of dehydration on cardiovascular function and temperature regulation. Although not all studies have demonstrated significant improvements in all markers of cardiovascular function and temperature regulation, there is overwhelming cumulative evidence that fluid replacement lowers cardiovascular strain and improves thermoregulation when compared with cardiovascular strain and thermoregulation under conditions in which fluid is withheld during prolonged exertion.

The value of electrolytes added to fluids consumed during prolonged exertion has yet to be conclusively demonstrated, but individuals susceptible to hyponatremia with water feedings alone may profit from electrolyte supplements. Also, sodium may be important for optimal rehydration following prolonged exertion. Furthermore, the low concentrations of electrolytes found in most fluid replacement beverages (Table 3-2) are apparently benign and may encourage fluid consumption by enhancing beverage palatability.

Table 3-2 Approximate Composition of Beverages That May Be Consumed During Prolonged Exercise

Beverage Type	Sodium (mM)	Potassium (mM)	Sucrose (%)	Glucose (%)	Polymers (%)	Fructose (%)
Apple juice	2	31.0	2.9	9.0[a]	-	-
Body fuel 450	16	2.0	-	-	4.5	-
Cola drinks	4	0.1	3.7	6.8[a]	-	-
Exceed	10	5.0	-	-	5.0	2.0
Gatorade	20	3.0	4.0	2.0	-	-
Gookinaid ERG	16	10.0	-	5.0	-	-
Isostar	23	5.0	6.8	0.1	0.1	-
Lemonade	1	5.0	2.6	7.0[a]	-	-
Orange juice	1	52.0	7.0	5.0[a]	-	-

[a]variable mixture of glucose and fructose

HOW IMPORTANT IS THE GASTRIC EMPTYING RATE OF A BEVERAGE CONSUMED DURING PROLONGED EXERTION

A comprehensive analysis of the literature on gastric emptying and intestinal absorption related to beverages consumed during exercise has been published recently (Murray, 1987). Only highlights of this issue are addressed here. The first study of gastric emptying and intestinal absorption of beverages consumed during exercise was that of Fordtran and Saltin (1967). They studied the gastric emptying characteristics of water and a glucose-electrolyte solution (13.3% glucose, 0.3% sodium chloride) and the intestinal absorption of six sugar-saline solutions in five subjects at rest and after an hour of treadmill running at 70% $\dot{V}_{O_2\,max}$. They found that gastric emptying rates were slightly reduced during exercise and that the effects of exercise on water absorption in the intestine were highly variable. Furthermore, gastric emptying rates for the 13.3% glucose solution were substantially slower than those for water. Subsequently, Costill and Saltin (1974) systematically varied the intensity of cycling exercise and the glucose content, temperature, and volume of beverages ingested during cycling. They showed that cycling at intensities up to 60% $\dot{V}_{O_2\,max}$ did not significantly reduce gastric emptying rates; intensities greater than 70% $\dot{V}_{O_2\,max}$ did. Having demonstrated that gastric emptying during moderate-intensity exercise was similar to that during rest, Costill and Saltin (1974) tested gastric emptying characteristics of various beverages in resting subjects. One of their findings was that a solution of 2.5% glucose in 34 mM saline had emptied as rapidly after 15 min as did the saline alone, whereas 5%, 10%, and 15% glucose added to the saline progressively slowed gastric emptying. These findings with measurements of gastric emptying 15 to 20 min after beverage ingestion were generally confirmed by others (Brener et al., 1983; Coyle et al., 1978; Foster et al., 1980; Hunt et al., 1985; Neufer et al., 1986).

Gastric emptying of carbohydrate-containing beverages seems to be regulated to provide a fairly constant rate of energy delivery (i.e., 2.0 to 2.5 kcal/min) to the small intestine, regardless of the energy density or osmolality of the ingested beverage (Brener et al., 1983; Hunt et al., 1985). In other words, after a few minutes of unregulated emptying into the intestine, a solution containing 10% glucose should empty approximately half as quickly as a solution of 5% glucose to deliver energy to the intestine at the same rate. The gastric emptying rate for water is approximately 15 ml/min for the first 15 min and that for 5% carbohydrate is about 12 ml/min; solutions containing progressively greater concentrations of carbohydrate empty progressively more slowly (Brener et al., 1983). If the maximal rate of energy delivery from the stomach to the intestine is 2.0 to 2.5 kcal/min (120

to 150 kcal/h), approximately 36.0 to 37.5 g of carbohydrate could be delivered to the intestine per hour.

Thus, if a 6% carbohydrate solution were ingested, 600 to 625 ml would have to be emptied from the stomach each hour to provide maximal rates of energy delivery. At emptying rates of approximately 10 ml/min for such a solution, this maximal rate of energy delivery is clearly possible and practical (e.g., with 150 to 250 ml feedings of a 6% solution every 15 to 20 min).

Theoretically, the difference between delivery of water and a 6% carbohydrate solution from the stomach to the intestine would be approximately 275 to 300 ml/h. If water and the glucose solution were absorbed from the intestine at similar rates, it would appear that fluid replenishment would be improved by 275 to 300 ml/h from the consumption of water compared with that of a 6% carbohydrate solution. However, because glucose stimulates water absorption from the intestine (Sladen and Dawson, 1969), this apparent advantage of water over a moderately concentrated glucose solution for fluid replacement may not exist (Murray, 1987).

It should be noted that the previously cited studies of gastric emptying characteristics of ingested beverages typically did not include measurements of cardiovascular or thermoregulatory function or performance capacity while subjects were consuming the beverages during exercise. Nevertheless, it is widely believed that cardiovascular function, temperature regulation, and physical performance are adversely affected during prolonged exertion if the ingested beverages contain sugar concentrations greater than 2.5%. This belief is unfounded.

EVIDENCE THAT MODERATELY CONCENTRATED CARBOHYDRATE-ELECTROLYTE SOLUTIONS ARE EFFECTIVE IN MAINTAINING HOMEOSTASIS, ARE ADVANTAGEOUS TO THE MAINTENANCE OF CARBOHYDRATE FUEL, AND MAY IMPROVE PERFORMANCE

In a study of champion marathoners, Costill et al. (1970) found similar gastric residues remaining in the stomachs of three of four runners after a 2-h run at 70% $\dot{V}_{O_2\,max}$, regardless of whether they drank 100 ml of water or a glucose-electrolyte beverage (4.4% glucose, 20 mM sodium, 2.4 mM K^+) every 5 min for the first 100 min of the run. More importantly, rectal temperatures, heart rates, ventilation rates, oxygen uptakes, sweat rates, and hemoconcentration values were similar for both drink treatments.

Our group investigated the effects of four beverages differing in their carbohydrate and electrolyte contents on homeostasis and performance in a cycling task to exhaustion (Brodowicz et al., 1984). Cyclists were asked to

ride as long as possible at an intensity equal to 74% of their maximal oxygen uptake under each of the four drink conditions (Table 3-3). Rectal temperature, heart rate, plasma volume change, sweat rate, and ratings of perceived exertion and gastrointestinal distress were similar under all drink conditions. Blood glucose was higher with the carbohydrate beverages; and mean ride times (min) were 68.9, 70.8, 73.1, 75.1 for beverages P, M, L, and S, respectively ($P<0.05$ for P vs. S; Table 3). Glucose polymers provided no advantage over simple sugars in this experiment or in those reported by others (Massicotte et al., 1989; Mitchell et al., 1988; Murray et al., 1987; Owen et al., 1986). Because of the discrepancy between the published data showing slower rates of gastric emptying for beverages containing carbohydrate and electrolytes and the finding that assumed rates of gastric emptying

Table 3-3 Beverages Used in the Study of Brodowicz et al. (1984)

Beverages	Composition
P	Flavored water, 0.1 mM Na^+
L	2.5% Glucose, 10.2 mM Na^+
M	6% Glucose polymers, 10.2 mM Na^+
S	4.6% Sucrose, 2% glucose, 20.4 mM Na^+

had no apparent bearing on homeostasis or performance, we developed a simplified procedure to track the accumulation in plasma of deuterium oxide (D_2O) from D_2O-labeled beverages (Davis et al., 1987). We used this D_2O accumulation as an index of relative rates of fluid entry into the blood after ingestion of various beverages. We found that the technique could easily distinguish between D_2O accumulation rates for drinks with known differences in gastric emptying characteristics. Profiles for D_2O accumulation in plasma of rested subjects were indistinguishable for water and drinks containing carbohydrate concentrations up to 10% (Davis et al., 1990). We also found that D_2O accumulation profiles for water and for beverages containing carbohydrate concentrations of 2.5% and 6% were indistinguishable during prolonged exertion (Davis et al., 1988a). However, D_2O accumulation was significantly retarded by beverages containing 12% carbohydrate (Davis et al., 1988b). The 12% carbohydrate beverage was also closely associated with symptoms of gastrointestinal discomfort and failure to complete the required cycling task.

Owen et al. (1986) compared water, a 10% glucose polymer solution, and a 10% glucose solution ingested in volumes of 200 ml every 30 min during treadmill running at 65% $\dot{V}_{O_2\,max}$ for 2 h in a hot environment; they detected no significant beverage effects on gastric emptying, plasma volume

changes, rectal or mean skin temperatures, or sweat rates. In another comparison of water and beverages containing 5%, 6%, or 7.5% carbohydrate, it was found that all carbohydrate beverages improved performance relative to water in maximal 12-min cycling sprints following seven 12-min sprints at 70% $\dot{V}_{O_2\,max}$ interspersed with 3-min rest intervals (Mitchell et al., 1988). Furthermore, no important beverage-related effects were detected for plasma volume changes, weight loss, oxygen uptake, or gastric emptying. Presumably, the fact that fluid feedings in this experiment were given in relatively small volumes (167 ml) intermittently as opposed to a 400-ml single feeding (Costill and Saltin, 1974) explained the lack of gastric emptying differences among the different beverages.

Coupled with numerous other reports (see Costill, 1988, and Murray, 1987, for reviews) that show benefits to prolonged exercise performance when carbohydrate is consumed during exercise, the studies cited in this section show that any differences in gastric emptying that may exist among water and beverages with moderate (5% to 8%) concentrations of carbohydrate are of little importance in determining the efficacy of a beverage for minimizing disturbances in homeostasis and for maximizing performance. In fact, moderately concentrated carbohydrate-electrolyte solutions improve the supply of carbohydrates to the tissues and are usually associated with improved physical performance. Finally, despite numerous comparisons of alternative formulations, there seems to be no evidence that any of these are superior to those of many of the availabel commercial beverages.

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4

Considerations for Replacement Beverages: Fluid-Electrolyte Balance and Heat Illness

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INTRODUCTION

Two case reports (attached as appendices) have been presented during this workshop. The first case report involved an endurathon staged on a hot, humid day at Fort Bragg, North Carolina. A group of 40 soldiers competed from 9 a.m. to 3 p.m. in the following seven consecutive events: an 8-km run, a 1-h road march while carrying 32 kg of equipment, a 2-h river excursion in a rubber boat, an 8-km run while wearing combat boots and full uniform, an obstacle course, a pistol marksmanship contest, and a 1.6 km team litter carry (68 kg weight). A 10-min rest period was allowed between each event for water consumption; soldiers ate a variety of snacks, but no meals were provided. Eight cases of heat illness (e.g. heat exhaustion, heat cramps, heat prostration) occurred after the fifth event. Prior to the sixth event, a carbohydrate-electrolyte solution was provided for these soldiers and no further heat illness episodes occurred. At 10 p.m., this unit was unexpectedly placed on alert and began several hours of mission preparation.

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Prior to the 15-hour flight to the Mid-East, each soldier received two box lunches and two 1-liter containers of Gatorade. Upon arrival, warm potable water was availabel, but it was not palatable. Gatorade powder was added to water storage containers at two-thirds strength. During the next 36 hours of duty there were no heat casualties.

The second case report involved a Ranger Batallion of approximately 750 soldiers who were involved in a mission designed to rescue U.S. citizens in 1983. One half of these men flew from Fort Lewis, Washington (air temperature of 7°–13°C). Prior to this mission, soldiers were allowed to rest for 4 to 6 h. They remained in full combat gear for 6 h prior to their parachute jump and were not relieved until they had spent 6 h in intermittent combat at a site that was covered with dense plant growth (ambient conditions of 29°–32°C, 85% relative humidity). The load which the average soldier carried weighed 29 to 34 kg, but some men carried gear weighing more than 45 kg. Prior to this operation, Rangers drank 10 to 12 liters of water per day and a forced hydration program was followed during this mission; each man carried 4 liters of pure water. Gatorade also was utilized, by diluting it to one-quarter strength with water. This Ranger unit experienced no heat casualities during this mission despite being relatively unacclimatized.

The purposes of this paper are to comment on the first case report by K. Alitz (Appendix 1) and the second by C. Donovan (Appendix 2) presented during this conference, and to emphasize the specific need (or lack of need) for carbohydrate-electrolyte solutions, which soldiers experience during duty in hot environments. Because this paper focuses on fluids and electrolytes, it is helpful to reiterate the following aspects of their reports: (1) Gatorade was used in dilute form at two-thirds (K. Alitz, Security Operations Training Facility, Fort Bragg, North Carolina, personal communication, 1989) and one-quarter (C. Donovan, Tuttle Army Health Clinic, personal communication, 1989) strength, (2) meals were sacrificed so that the mission could be accomplished, and (3) Donovan stated that a rigorous hydration program virtually eliminated heat illness at a time when other U.S. personnel experienced significant heat casualties. In regard to the third point, the Heat Research Division of the U.S. Army Research Institute of Environmental Medicine (USARIEM), has received a recent communication describing a similar hydration program at Fort McClellan, Alabama (D. Compton, USA MEDDAC, Fort McClelland, Alabama, personal communication, 1988). This program resulted in a decrease in July-August heat casualties from 21 (1987) to 6 (1988), when troops were placed on a regimen of drinking 0.5-1 quart of water per hour.

SALT DEFICITS

If salt and water losses are compared for three continuous foot races--10 km (6.21 ml), 42.1 km (26.2 ml), and 161 km (100 ml)--the total sodium chloride (NaCl) loss on a hot day will be 0.5-6, 2-29, and 54-93 g, respectively. These calculated NaCl losses are based on total sweat losses of 0.5-1.5, 2-6.6, and 18-35 liters, respectively (R. Lind, Medical Director of Western States 100 Mile Race, personal communication, 1988), and sweat salt concentrations of 1-4 g of NaCl per liter. If these losses are compared with the daily NaCl intake in garrison dining facilities (95% confidence limits, 6-24 g of NaCl per day) (Rose et al., 1989), or by eating three meals-ready-to-eat (MRE's) (12.6 g of NaCl per day) (Popper et al., 1987), it is clear that NaCl supplementation may be required in certain physically demanding situations. Although the military relevancy of a 161-km foot race (lasting 17-26 h) can be questioned, it is clear that the stress of the endurathon and subsequent deployment, described in the case study of Alitz, probably lies somewhere between these 42.1-km and 161-km events.

Table 4-1 clarifies this point in more relevant terms. These data (Armstrong et al., 1985) describe the effects of a 6-h simulated desert march on fluid-electrolyte balance. Our measurements (brisk walk, 5% incline, 30 min of exercise per hour, wearing shorts and sneakers) indicated that electrolyte deficits may be encountered (Table 4-1) when these losses are compared with the salt contents of the 24-h garrison meal [95% confidence limits, 101-415 meq of Na^+ per day, 67-144 meq K^+ per day (Rose et al., 1989)] and 24-h MRE [216 meq of Na^+ per day; 71 meq of K^+ per day (Popper et al., 1987)]. While 6-h sodium (Na^+) deficits may be partially reduced via liberal seasoning of meals with table salt, the potassium (K^+) deficits are less likely to be reduced in this manner.

POTENTIAL OVERCONSUMPTION OF SALT

In contrast, it is theoretically possible to consume more NaCl than is physiologically required. The calculated 24-h salt consumption in Alitz's and Donovan's case reports are as follows. Based upon the consumption of 10 liters of diluted Gatorade (0.9 g of NaCl per liter, full-strength) per day from Donovan's report, and three MRE per day [12.6 g of NaCl (Popper et al., 1987)], maximum total salt intakes are calculated, using Alitz's information, as 6 + 13 = 19 g of NaCl per day and, using Donovan's report, as 2 + 13 = 15 g of NaCl per day. If one MRE salt packet (4 g of NaCl) were consumed at each meal, these values would increase to 31 g and 27 g of NaCl per day, based respectively on the reports of Alitz and Donovan.

consumed at each meal, these values would increase to 31 g and 27 g of NaCl per day, based respectively on the reports of Alitz and Donovan.

Table 4-1 Projected Effects of a 6-h Simulated Desert March

EXPERIMENTAL DESIGN
Subjects, 12 healthy males
Air temp, 40.6°C (dry bulb), 25.5°C (wet bulb)
Treadmill walking at 1.34 m/s, 5% grade
Ad libitum water intake
FLUID-ELECTROLYTE LOSS PER 6 h
Sweat loss, 3.5 ± 0.1 liter
Sweat Na^+ concentration, 12.7-46.7 meq/liter
Sweat K^+ concentration, 1.7-4.8 meq/liter
Na^+ loss, 72-244 total meq[a]
K^+ loss, 23-70 total meq[a]
PROJECTED ELECTROLYTE LOSS PER 24 h[b]
Na^+ loss, 193-425 meq/liter
K^+ loss, 62-240 meq/liter

[a]Urine + sweat (measured via whole-body washdown).
[b]Based on 8 liters of sweat loss and constant urinary electrolyte loss per 24 h.

It has been observed that soldiers eat approximately 70% of all MRE contents in a temperate environment and that few soldiers (<4%) use the MRE salt packets; therefore, a realistic estimate of these NaCl intakes then becomes 6 + 9 = 15 g (after Alitz) and 2 + 9 = 11 g (after Donovan) of NaCl per 24 h. Conn's research (1949) demonstrated that heat-acclimatized males adapted to diets containing 6 g of NaCl per day (from 12 g of NaCl per day) after 5-15 days of this diet. It is likely, then, that the military units described in these case reports consumed more NaCl each day than they required. The human kidney readily removes such levels of excess salt as

they are consumed, yet salt supplementation has been recommended (Hubbard et al., 1986; Leighthead and Lind, 1964; Hubbard and Armstrong, 1988) during the initial 3-5 days of heat exposure because the kidneys require 3-5 days (and the sweat glands require 5-10 days) of heat exposure to maximally conserve Na^+ (Hubbard et al., 1986). Symptoms and casualties of heat syncope and heat exhaustion are greatest during this period and decrease notably after day 5 (Hubbard and Armstrong, 1988). This can best be explained by the fact that the primary adaptations during the initial 3-5 days of heat acclimatization are cardiovascular, and emphasizes the need for adequate salt intake to maintain extracellular fluid and plasma volumes.

Dasler et al. (1973) have published the only study that has examined extremely high salt consumption during heat acclimatization. They found that subjects exhibited impaired heat acclimatization responses when they ate high levels of salt (22.5-30 g of NaCl per day). These responses included cardiovascular impairment; decreased optimal work capacity; and increased excretion of K^+, bicarbonate, and other anions. This impaired heat acclimatization response may have been due to inadequate water intake by their subjects, because the water requirement increases approximately 1 liter for each 5 g of NaCl added to the diet (Baker et al., 1963). In addition, Knochel and Vertel (1967) have implicated salt loading as a possible factor in the production of potassium deficiency, rhabdomyolysis, and heat injury. These two reports impact on the evaluation of carbohydrate-electrolyte replacement beverages, because a soldier could theoretically exceed the NaCl intake in the study of Dasler et al. (1973) if he ate three MRE (13 g of NaCl per day), ate three MRE salt packets (12 g of NaCl per day), and drank 10 liters of Gatorade (12 g of NaCl per day, full-strength) in a 24-h period. In Alitz's, and Donovan's units, these theoretical NaCl totals would be 31 g and 27 g, respectively.

CASE REPORT A: TEN HEATSTROKE PATIENTS

During the past 2 years, we evaluated the time course and extent of recovery in prior heatstroke patients. Ten active-duty male soldiers came to our laboratory for 14-day investigations of their thermoregulatory and heat-acclimatization abilities, as well as for evaluations of blood chemistry values and fluid-electrolyte balance. This work has been published elsewhere (Armstrong et al., 1989), showing that it is useful to consider the events of the day on which these men experienced heatstroke. Nearly all of these soldiers experienced heatstroke (verified by rectal temperature of >106°F, elevated serum enzymes, and altered mental status) at Fort Benning, Georgia, which presents a hot, humid environment at mid-day. In most

cases, they were running in formation at a 7.0-8.5 min/mile pace for 21-43 min. However, 8 of 10 of these men collapsed prior to 7:30 a.m., when the ambient dry bulb temperature was 69°-79°F or lower--certainly not the environmental conditions that would be expected to induce heatstroke.

Prior to the initiation of testing, each volunteer was interviewed in regard to the factors that may have predisposed him to heatstroke. Based on daily physical training and environmental conditions, we defined five of these men to be heat acclimatized and five to be nonacclimatized. The climate of their residence (for 4 years prior to the heatstroke) varied from very hot to temperate. Table 4-2 further defines the predisposing factors which these

Table 4-2 Predisposing Factors for Heatstroke Reported by Soldiers from Fort Benning, Georgia

Predisposing Factors[a]	Soldiers Reporting[b]
Sleep loss	7
Fatigue	6
Long exercise bout(s)	5
Long heat exposure	5
Heat wave	4
Reduced sweat secretion	3
Concurrent fever or disease	3
Excessive use of alcohol	1
Excessive use of tobacco	1
Eating a low-salt diet	1
Recent visit to doctor	1
Taking medication for other complaint	1
Dehydration	1

[a]During the 5 days prior to heatstroke.
[b]Out of a total of 10 subjects.

soldiers reported. Four factors were verified by at least 50% of these volunteers: sleep loss, fatigue, lengthy heat exposure, and a long exercise bout or workout within the 5 days prior to heatstroke. Considering all predisposing factors, it is unlikely that carbohydrate-electrolyte replacement drinks per se would have prevented heatstroke in these soldiers, who were not deprived of food or fluids unless they chose to eat only a portion of the meals offered to them. This may occur in some field situations, but the survey of basic trainee eating habits by Rose et al. (1989) indicated that males left on their plates only 2%-3% of the daily Na^+ offered in their three garrison meals, while females did not eat 7%-10% of the daily Na^+ offered

in their three garrison meals. The issue of anorexia on arrival in a hot environment is unresolved.

CASE REPORT B: HEAT EXHAUSTION IN PANAMA

A scenario similar to the one that Donovan described, as part of this workshop, occurred in Panama during 1985. Eleven cases of heat exhaustion occurred during one field training exercise (FTX) at the Gatun drop zone. The ambient temperature and humidity, which are very stable year-round in Panama, evidently had not changed prior to this FTX, but the events which occurred during the 36 h prior to this incident were crucial. This FTX occurred on a clear, sunny day (air dry bulb temperature >80°F). The troops were wearing full combat gear, including rucksack, weapon, parachute, and reserve chute. Most were heat acclimatized, and most were trained to drink and sprinkle water on their bodies. This paratrooper unit had spent 24-36 h prior to the FTX packing gear, organizing, and planning the next day's activities; this led to sleep loss. Although these soldiers carried 1- and 2-quart (0.95- and 1.9-liter) canteens, their busy schedule resulted in inadequate water and meal intakes. Heat exhaustion is usually a fluid depletion problem that is aggravated by exercise in the heat, resulting in circulatory collapse. It appears that a lengthy period of fluid imbalance, coupled with a 2-h wait on the runway in non-air-conditioned aircraft, precipitated these 11 cases of heat exhaustion. Dense foliage [8-10 feet tall (2.4 - 3 m); little or no air movement] at the drop zone was the final contributing factor. As soldiers landed, they were required to move through this dense foliage to a pickup point. It is likely that a carbohydrate-electrolyte replacement fluid, availabel during the 36-h preparation period, would have helped these soldiers maintain performance throughout the FTX and might have helped them avoid heat exhaustion (Armstrong et al., 1988; Hubbard and Armstrong, 1988).

CASE REPORT C: HEAT EXHAUSTION AMONG RESERVISTS IN TEXAS

Members of the Fifth Army Reserve conducted their annual 2-week FTX at Fort Hood, Texas, in June 1988. Our research team evaluated heat-exhaustion patients who were sent to the 44th Evacuation Hospital. Blood chemistry, hematological, and total body water (TBW) measurements were made on four heat-exhaustion patients (three males and one female). Table 4-3 describes the TBW values [deuterium oxide (D_2O)] for these four patients and two control subjects. The percentage of body weight that TBW

Table 4-3 Total Body Water (D2O) Comparison

Subject	Sex	Age (yr)	Wt (kg)	Ht[a] (cm)	TBW[b] (liter)	TBW: Wt(%)	Urine (specific gravity)
Normal subjects							
A	M	29	102.5	183	60	58	1.024
B	F	28	52.8	154	30	57	1.006
Heat-exhaustion patients[c]							
C	M	45	115.7	193	81	70	1.025
D	M	28	107.5	180	99	93	1.005
E	F	24	49.4	157	41	83	1.024
F	M	25	72.6	183	62	86	1.002

[a]Ht = Height
[b]TBW = Total body water
[c]Fort Hood, Texas, June 1988.

represents in normal males has been reported as 55.6% ± 5.0%, as determined in 25 measurements on 11 subjects (Faller et al., 1955a). This agrees well with the values (expressed as TBW:Wt) for normal subjects presented in Table 4-3 (58% and 57%), but not for the four heat-exhaustion patients, who had ratios of 70%, 93%, 83%, and 86%. A plausible hypothesis involves disrupted fluid absorption at the intestine, leading to impaired or delayed D_2O equilibration with TBW. Our experiments indicate that plasma D_2O equilibration occurs in 2-4 h in normal subjects. We believe that minimal D_2O entered the body water space through the intestine, the TBW pool appeared to be larger than it actually was (Table 4-3), and TBW was thereby overestimated. The involvement of impaired intestinal absorption in patients with heat exhaustion (Armstrong et al., 1988; Hubbard and Armstrong, 1988) and other illnesses (Faller et al., 1955b) has been described elsewhere. These results, similar to malnutrition cases (Brown, 1985), may mean that a carbohydrate-electrolyte solution optimizes intestinal water absorption.

SCENARIO-SPECIFIC NEEDS

Recent review articles (Lamb and Brodowicz, 1986; Murray, 1987) have emphasized the fact that the efficacy of consumption of carbohydrate-electrolyte solutions depends on the research protocol employed. There are two situations in which carbohydrate-electrolyte beverages clearly appear to maintain performance: (1) when a deficiency exists in either carbohydrate or electrolyte stores, and (2) when prolonged, continuous exercise of at least 60-min duration (Murray, 1987) is performed.

Coyle and Coggan (1984) described, earlier in this workshop (See Chapter VIII), the importance of timing as a factor determining the efficacy of carbohydrate consumption. Lamb and Brodowicz (1986) also published a review paper which noted that (1) carbohydrate consumption 0-15 min before exercise may positively affect endurance performance, and (2) there is no published report of a positive effect of carbohydrate intake on performance when carbohydrate is fed 15-60 min before exercise. This is probably due to a reduced blood glucose level following a rapid rise in insulin concentration.

Although many stressful military scenarios suggest that carbohydrate-electrolyte supplements would improve performance (i.e., missed meals, lack of heat acclimatization, diarrheal disease, and exercise in impermeable protective clothing), some scenarios contraindicate the consumption of carbohydrate-electrolyte supplements. For example, total dissolved solids may reach 1.0 g/liter in fresh water, 1-20 g/liter in brackish water, and >35 g/liter in saline water (Daniels, 1988). NaCl constitutes 85% of these total dissolved solids by weight. For soldiers drinking 10-18 liters of fresh water per day (see above), this amounts to 9-15 g of NaCl added to an individual's total solute load. This amount of NaCl would be much larger if brackish or saline water were consumed.

The task performed by soldiers also should be considered in determining whether carbohydrate-electrolyte fluids are necessary to maintain performance. Table 4-4 presents the Military Occupational Specialty (MOS) classifications of the U.S. Army, as described by Sharp et al. (1980). Note that these classifications have been categorized by fitness requirements (high, medium, or low) for strength and stamina. It is instructive to note that 47% of all enlisted personnel work in MOS categories that require medium to low strength and stamina. Thus it appears that they seldom are placed in situations that require carbohydrate-electrolyte supplementation. Their normal dietary intake (e.g., garrison meals or MRE) will usually replace all metabolized carbohydrates and lost electrolytes.

Table 4-4 Military Occupational Specialty (MOS) Classifications

Fitness Requirements Strength	Stamina	Branch	Total MOSs	Percent of Enlisted Personnel
High	High	Engineer, Field artillery, Infantry	10	19
High	Medium	Artillery, Field artillery, Medical	39	13
High	Low	Engineer, Munitions, Transportation	63	21
Medium	Low	Intelligence, Signal, Engineer, Quartermaster	53	21
Low	Low	Admin. Engineer, Intelligence, Transportation	184	26

Source: Sharp et al., 1980.

SUMMARY

The above facts have been presented to support the concept that carbohydrate-electrolyte replacement fluids may be necessary in some, but not all, military field situations. The greatest need for carbohydrate-electrolyte replacement fluids is experienced by soldiers who (1) lose more than 8 liters of sweat per day; (2) are not heat acclimatized (e.g., during the initial 8 days of field living); (3) are performing a prolonged, continuous exercise bout (>60 min); (4) skip meals, have meals interrupted, or encounter anorexia because of a hot environment; (5) experience a caloric deficit of >1,000 kcal per day; or (6) are ill with diarrheal disease. The fluid-electrolyte needs of soldiers are specific to the intensity, frequency, and duration of the exercise involved, as well as the environmental stress encountered. This information is not presented to imply that many different solutions are required, but rather that the best use of such fluids can be recognized with proper soldier training (i.e., when to use them) and simple instructions for field implementation. It appears that carbohydrate-electrolyte replacement fluids, like weapons, should be availabel to the soldier for use when needed.

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Appendix 1

A CASE REPORT FROM FORT BRAGG

K. Alitz

This unit is a small, elite Special Forces Group consisting of carefully selected and highly trained non-commissioned officers (NCOs) and officers. The mission is to deploy worldwide on short notice in support of Department of the Army (DA) directed missions. Much of the equipment is nonstandard and mission dependent. Operational techniques are very specialized and vary greatly with the task. The age varies from 24-39 with the average being 31. The soldiers are extremely physical and maintain themselves in excellent condition. All training is as realistic and demanding as possible.

The following case history, which occurred in the recent past, is not untypical of the demands soldiers in this unit face. It explains why carbohydrate-electrolyte replacement beverages are needed by our soldiers:

It was a hot, humid August day at Fort Bragg, North Carolina. Group A, about 40 men, scheduled endurance training that day. Group A's endurathon consisted of a 7 event exercise. The first event started with a 12,500 foot HALO combat equipment jump from a CH-47 helicopter, followed by a 5 mile, 1 hour road march with weapon, 25 lbs load bearing equipment, and a 45 lb rucksack; a 2 hour rubber boat trip down the Cape Fear River; a 5 mile run in boots and fatigues; a difficult obstacle course; a complex shooting drill with the .45 caliber pistol; and culminating with a 1 mile, 150 lb litter carry.

The endurathon occurred between 0900 h and 1500 h, the average temperature was in the upper 90s with humidity in the high 60s. Individuals carried their own water and there was a 10 minute break at each water point between events. They could snack but no meal was provided. No medical problems were encountered until after Event 5—the obstacle course. Of the 40 participants, there was 1 case of mild heat exhaustion (rectal temperature 100.5 degrees), 4 cases of heat cramps, and 3 cases of heat prostration (nl temperature, extreme fatigue). All 8 individuals responded rapidly to 2 liters D5RL intravenously administered IV and were pulled from further training. Of these, only 2 have had any heat injuries before and they relate a 3-6 quart water intake during training. Prior to the 6th event, which was shooting, an electrolyte solution was brought out to the water points and individuals were encouraged to consume at least 1 quart. There were no further incidents, training was completed, and soldiers were released.

Group B started this same August day at 0800 h with 2 hours of range firing and then individual physical training for 1 1/2 hours. After the lunch meal, Group B flew via C-130 Aircraft to Hunter Army Airfield in Georgia to participate in specialized assault training. Temperatures at the airfield approached 100 degrees F; uniform was a Nomex flight suit and assault gun with Kevlar vest--total weight about 20-25 lbs. Training continued into the evening hours; water was readily availabel and a supper meal was provided. Training was demanding, but there were no medical problems; however, several soldiers complained of weakness and fatigue.

At about 2200 hours the unit was alerted to respond to an incident in the Mid-East. Group B returned immediately to Fort Bragg where the entire unit had been mustered. Equipment was packed and loaded and plans were formulated. After several hectic hours, Groups A and B, along with a support package, departed that night from Fort Bragg via Air Force aircraft to the crisis area.

Each individual was issued 2 box lunches and 2 1-quart jars of cold gatorade for the 15-hour, non-stop flight. Water jugs were on the aircraft, but because of space constraints, they were difficult to get to.

Upon arrival in the staging country, the unit was housed in an empty aircraft hangar. The temperature was high, but humidity was low. Potable water was availabel, but it was warm and not very palatable. Gatorade powder was added to the lister bags at 2/3 strength. The unit spent the next 36 hours preparing for a mission. There were no heat casualties.

This case history illustrates several points which are unique to this unit: (1) demanding physical training often under hostile environments and conditions; (2) short, or no-notice worldwide deployments into combat-type situations; (3) the philosophy that the mission has utmost importance and the soldier will adapt to accomplish the mission; (4) that our soldiers operate often under fluid deficits with excessive water loss and potential electrolyte imbalances.

Gatorade supplement and beverages are used to rehydrate, balance electrolytes, and provide some calories. Gatorade has been found, when used in training and missions, to increase fluid intake, increase morale, be convenient, and decrease the incidents of heat related injuries, if used under the supervision of medical personnel. This unit is eager to try other carbohydrate electrolyte replacement supplements and beverages that will assist in accomplishing the mission.

Appendix 2

CASE STUDY FROM GRENADA

W. Donovan

General:

This study is submitted in reference to the ranger participation in operation "Urgent Fury". This was a U.S. Military operation to rescue American nationals caught in the military/political upheaval on the island nation of Grenada in October of 1983.

Purpose:

To discuss the means by which the rangers addressed the problem of preventing heat casualties at a time when their physical and mental limitations were being put to the ultimate test.

Mission:

The mission was operation "Urgent Fury". The rangers were tasked to secure, either by airborne or airland assault, the Point Salinas airfield, and rescue American medical students to forestall a possible Iran-style hostage situation.

Units:

The 1st and 2nd ranger battalions were initially involved in the operation. A ranger battalion is a "Light Infantry" unit that is organized and equipped to conduct both special and conventional combat operations. It consists of a battalion headquarters, a headquarters company, and three ranger rifle companies.

Approximately 750 rangers were involved in the Grenada operation.

Terrain:

The initial ranger area of operation was the 10,000 foot Point Salinas airfield. The airfield was still under construction at the time and offered few prominent terrain features. Consequently, the airfield did offer unobstructed fields of fire. Follow-on missions which took the rangers even a short

distance from the runway found them quickly encountering the typically steep and thickly covered countryside of Grenada.

Temperature:

When the 1st ranger battalion departed from Hunter Army airfield in Georgia the temperature was approximately 70 degrees. The 2nd ranger battalion departed out of Ft. Lewis, Washington where the approximate temperature was 45 to 55 degrees. The average temperature on the ground in grenada was 85 to 90 degrees.

Weather conditions:

The weather in the ranger area of operations was clear and balmy. The temperature at the time of the drop was 80 degrees, mid-day temperature was 85 to 90 degrees. The humidity was 85%.

Combat loads:

The combat load that the average ranger carried weighed between 65 to 75 pounds. Ranger medical and communication personnel carried rucks weighing 90 to 100 pounds. Mortar and anti-tank teams carried rucks weighing in excess of 100 lbs.

Work/Rest cycle:

All rangers involved in the Grenada operation had a mandatory rest period approximately 4 to 6 hours prior to loading the mission aircraft. Unfortunately, the rangers did not rest again until they were relieved in place by follow-on units some 18 hours later.

Rations used:

The rangers involved in the operation were issued C-rations and MRE's.

Water availability:

The majority of the rangers went into the operation carrying 4 quarts of water. Initially, well water located at the medical school was the primary source of water resupply. Some streams were also utilized. Iodine tablets were used throughout the mission.

Unusual physical or operational demands:

There are several areas of interest worth mentioning:

1. This was an actual combat mission.
2. The rangers were carrying heavy combat loads.
3. Flack jackets were utilized.
4. The rangers were rigged in their parachutes for 6 hours prior to a combat jump.
5. The rangers jumped into a "hot" drop zone.
6. Rangers were initially involved in a fire fight lasting approximately 45 minutes, and sporadic fire fights for the next 2 days.
7. Movement to contact operations in the hills and dense growth surrounding the airfield.
8. Additionally, the rangers had to evacuate WIA's and KIA's to the ranger casualty collections point; this also included the wounded civilians, Grenadian Militia and Cubans.

The rangers did utilize a glucose-electrolyte solution (Gatorade) during the operation. Rangers were instructed to dilute the solution at a 1:4 ratio.

After-Action observations:

The rangers experienced no heat casualties during the Grenada Operation despite drastic changes in temperature, while other U.S. forces experienced significant problems with heat casualties.

Reasons:

1. The rangers were in excellent physical condition.
2. Heat casualty prevention was highlighted in the medical annex during the planning phase of the operation.
3. A prehydration program was immediately initiated with rangers drinking 10 to 12 quarts of water per day.
4. A forced hydration program was rigorously adhered to during the operation.
5. Rangers utilized tropical uniforms.
6. Rangers only carried mission essential equipment.
7. There was excellent leader supervision oriented toward preventing heat casualties.

Summary:

In summation, the rangers involved in the Grenada Operation suffered no heat casualties because of a vigorous hydration program and prior operational planning. Throughout numerous deployments to temperate climates like Hondorus, Panama and Jordan, the rangers have suffered few significant heat related injuries.

Fluid Replacement and Heat Stress, 1993
Pp. 55-68. Washington, D.C.
National Academy Press

5

Carbohydrate Supplements During and Immediately Post Exercise

John L. Ivy[1]

INTRODUCTION

Since the early studies of Christensen and Hansen (1939a,b), the importance of dietary carbohydrates has been recognized with respect to endurance during sustained, prolonged exercise. Christensen and Hansen (1939a) demonstrated a high-carbohydrate diet would significantly enhance endurance during prolonged exercise. They also observed that time to exhaustion was accompanied by hypoglycemia and that ingestion of a carbohydrate supplement at the time of exhaustion rapidly returned the blood glucose concentration back to normal and allowed considerable additional exercise to be performed (Christensen and Hansen, 1939b). On the basis of these results, Christensen and Hansen (1939a,b) suggested that fatigue during prolonged aerobic exercise was the result of depletion of the body's carbohydrate stores. Since the time of their classic research, many studies have been conducted to examine the role of dietary carbohydrates and carbohydrate supplements on aerobic endurance. In general, these

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studies have confirmed that aerobic endurance is directly related to the body's carbohydrate supply and that carbohydrate supplementation can enhance endurance performance. The purposes of this paper are to review the latest information on the effectiveness of carbohydrate supplements to improve aerobic endurance and to review the most effective means of rapidly replenishing the body's carbohydrate stores after exercise.

CARBOHYDRATE SUPPLEMENTS DURING EXERCISE

Continuous Exercise

Christensen and Hansen (1939a,b) reported that a high-carbohydrate diet could delay the onset of hypoglycemia and increase the time to exhaustion during prolonged exercise and that a carbohydrate supplement ingested at the time of exhaustion could rapidly alleviate hypoglycemia and substantially prolong the exercise period. Bagby et al. (1978) demonstrated that continuous infusion of rats with glucose during moderate-intensity running reduced the rate of liver and muscle glycogen utilization and delayed the onset of fatigue. The use of carbohydrate food supplements intermittently during exercise has also been shown to improve endurance performance (Coyle et al., 1983, 1986; Fielding et al., 1985; Hargreaves et al., 1984; Ivy et al., 1979, 1983). To study this effect, we encouraged cyclists to maximize work output during 2 h of isokinetic cycling (Ivy et al., 1979). The subjects were fed either a placebo or 0.2 g of glucose polymer per kilogram of body weight every 15 min during the first 90 min of exercise. There was no improvement in total work accomplished between the placebo and glucose polymer trials. However, during the last 30 min of exercise, the work production for the glucose polymer trial exceeded that of the placebo trial by 11% (Figure 5-1). Of even greater interest was the finding that during the last 10 minutes of the glucose polymer trial, work production was increased to a level in excess of that found over the first 10 min of exercise. These findings were interpreted as indicating that glucose feedings may be of benefit during prolonged exercise lasting longer than 90 min (Ivy et al., 1979).

To investigate this possibility, we had subjects walk to exhaustion while consuming a carbohydrate supplement or placebo (Ivy et al., 1983). Subjects walked on a motorized treadmill with the speed and incline set to elicit an exercise intensity of 45% maximal O_2 uptake $\dot{V}_{O_2\,max}$. The carbohydrate

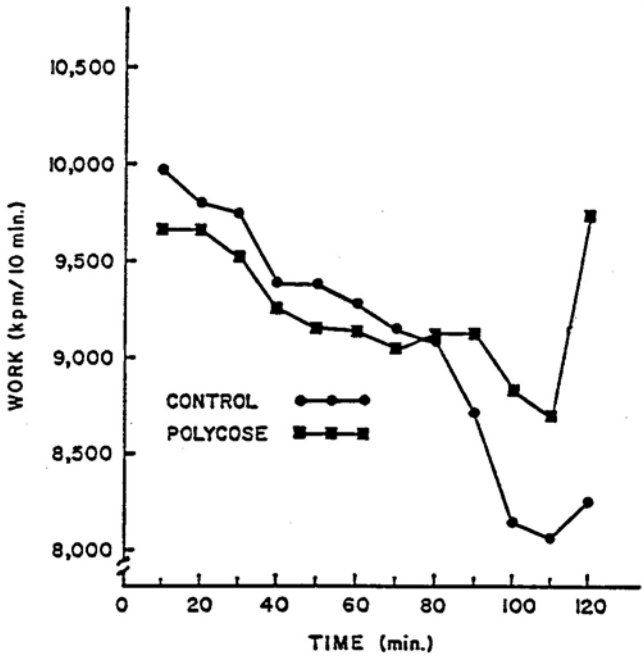

FIGURE 5-1 Work (kilopond meter) performed during isokinetic cycling. Source: Ivy et al. (1979).

supplement was a 20% glucose polymer solution (120 g) that was administered in four equally divided dosages at 60, 90, 120, and 150 min following the start of exercise. It was found that the glucose polymer supplement prevented a decline in plasma glucose and significantly increased the time to exhaustion by 11.5%. At about this same time Coyle et al. (1983) conducted a study in which thev had trained cyclists exercise to fatigue. The initial work rate was 74% $\dot{V}_{O_2\,max}$, and the point of fatigue was defined as the time the subjects could not maintain an exercise intensity of 64% $\dot{V}_{O_2\,max}$. The subjects were fed either a placebo or glucose polymer solution during exercise. During the glucose polymer trial, the subjects were fed a 50% solution containing 1.0 g of glucose polymer per kilogram of body weight 20 min after the start of exercise; after 60, 90, and 120 min they were fed a 6% solution containing 0.25 g of glucose polymer per kilogram of body weight. It was found that the glucose polymer supplement was beneficial only for those subjects who became hypoglycemic in the placebo trial. Time to fatigue for these subjects was 126 min during the placebo trial and 156 min during the glucose polymer trial.

To determine the mechanism by which carbohydrate supplements enhance aerobic endurance, Coyle et al. (1986) had trained cyclists exercise at 70% $\dot{V}_{O_2\,max}$ to fatigue while ingesting a placebo in one trial or a glucose polymer solution (i.e., 2.0 g per kilogram of body weight at 20 min and 0.4 g per kilogram every 20 min thereafter) during another trial. Muscle biopsies were taken from the vastus lateralis to determine the rate of muscle glycogen utilization. During the placebo trial, fatigue occurred after 3 h of exercise as the plasma glucose declined to 2.5 mM and the respiratory exchange ratio declined from 0.85 to 0.80. When the subjects were fed the glucose polymer supplement, plasma glucose and carbohydrate oxidation were prevented from declining and exercise was tolerated for an additional hour. The pattern of muscle glycogen utilization, however, was not different during the first 3 h of exercise with the placebo or the carbohydrate feedings. The additional hour of exercise performed when carbohydrate was fed was accomplished with little reliance on muscle glycogen and without compromising carbohydrate oxidation. It was concluded that carbohydrate supplements used at a relatively high rate could provide the carbohydrate needed to sustain activity during the latter stages of prolonged exercise, when the muscle and liver glycogen stores have been severely reduced.

Intermittent Exercise

The effect of carbohydrate supplementation on endurance during intermittent work has been investigated by Hargreaves et al. (1984) and Fielding et al. (1985). In the study by Hargreaves et al. (1984), 10 trained cyclists exercised for 4 h, during which time they performed repeated 20-min bouts of cycling at 50% $\dot{V}_{O_2\,max}$ followed by 10 min of intense intermittent exercise (30 s at 100% $\dot{V}_{O_2\,max}$ followed by 2 min of rest). During the last sprint bout the subjects were timed to exhaustion. The subjects received a placebo or a sucrose supplement before and at various intervals during exercise. It was found that the sucrose feeding prevented blood glucose from declining and increased the final sprint performance by 45%. A similar exercise protocol was used by Fielding et al. (1985), but subjects were fed every hour or every half-hour. When subjects were fed sucrose every hour, blood glucose declined late in exercise and sprint performance was not different from that which occurred during the placebo treatment. However, when the subjects were fed at half-hour intervals, their blood glucose was prevented from declining and their sprint performance was significantly improved.

Summary

There is overwhelming evidence that carbohydrate supplements can improve endurance during prolonged physical activity of a continuous or intermittent nature. For the supplement to be effective, it must be taken in sufficient amounts to prevent a significant decline in blood glucose. This would require a carbohydrate intake of about 1 g/min, consumed at 15- to 30-min intervals and starting at least 30 min before blood glucose starts to decline.

CARBOHYDRATE SUPPLEMENTS IMMEDIATELY AFTER EXERCISE

Because of the paramount importance of muscle glycogen during intense, prolonged exercise (Ahlborg et al., 1967; Bergstrom et al., 1967; Hermansen et al., 1967) as well as exercise of an anaerobic nature (Jacobs, 1981; Klausen and Sjogaard, 1980), methods for increasing its concentration above normal (supercompensation) and replenishing the glycogen stores on a day-to-day basis have been studied extensively. Bergstrom and Hultman (1967a) observed that glycogen synthesis occurred most rapidly in muscle depleted of its glycogen stores. They also found that consumption of a high-carbohydrate diet for 3 days would elevate the glycogen concentration of muscle above normal, and that this phenomenon was restricted to muscle in which glycogen was previously depleted by exercise (Bergstrom et al., 1967). Subsequent studies by Costill et al. (1981) found that muscle glycogen could be resynthesized to normal pre-exercise concentrations within 24 hours, provided there had not been prior glycogen supercompensation and sufficient carbohydrate was made availabel. Costill et al. (1981) reported that the consumption of 150 to 600 g of carbohydrate per day resulted in proportionately greater muscle glycogen restoration during the 24-h period after exercise and that consumption of more than 600 g of carbohydrate per day was of no additional benefit. It was also demonstrated by Costill et al. (1971) that when the carbohydrate concentration of the diet was inadequate, successive days of intense, prolonged exercise resulted in gradual reduction in the muscle glycogen stores and a deterioration in performance (Figure 5-2). Although means of increasing muscle glycogen to above-normal levels in preparation for competition and maintaining normal glycogen levels on a day-to-day basis have been defined, there has been little research on how to maximize glycogen storage during the hours immediately following exercise. It should also be pointed out that the maximum amount of muscle glycogen stored when the subject eats a high-carbohydrate diet during the

24 h immediately after exercise is approximately 80 μmol/g. Thus, it is possible that intensive exercise training could result in deficient muscle glycogen stores even when one is consuming a high-carbohydrate diet.

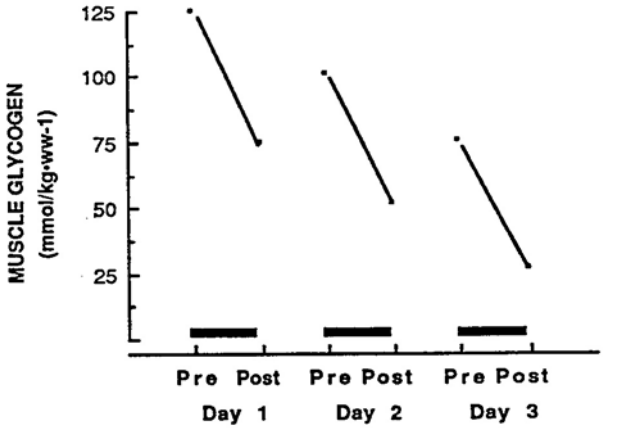

FIGURE 5-2 Effect of low-carbohydrate diet (45% of the calories) on muscle glycogen during 3 consecutive days of repeated 2-h running sessions at 70% $\dot{V}_{O_2\,max}$. Source: Costill et al. (1971).

Glycogen Storage Immediately After Exercise

When a carbohydrate supplement is provided immediately after exercise, the rate of glycogen storage has generally been reported to be between 5 and 8 μmol/g (wet weight) per hour (Keizer et al., 1986; Maehlum et al., 1977, 1978). Maehlum et al. (1978) found that ingestion of 100 g (1.44 g per kilogram of body weight) of glucose 15 min after an exhaustive bicycle exercise resulted in a 7.1 μmol/g (wet weight) per hour glycogen storage rate in the quadriceps during the subsequent 135 min. Maehlum et al. (1977) also found a similar rate of glycogen storage following exercise when a carbohydrate-rich diet was consumed. Keizer et al. (1986) reported that providing approximately 300 g of carbohydrate either in liquid or solid form after exercise resulted in a glycogen storage rate of approximately 5 μmol/g (wet weight) per hour over the first 5 h of recovery.

Time of Postexercise Carbohydrate Consumption

In agreement with previous research findings, we have observed rates of glycogen storage between 5 and 8 μmol/g (wet weight) per hour during the hours immediately after exercise when a carbohydrate supplement was provided (Ivy et al., 1988a,b; Reed et al., 1989). In the first of three studies, we investigated the effect of the time of administration of the carbohydrate supplement on muscle glycogen recovery after exercise. Two grams of glucose polymer per kilogram of body weight was administered in a 25% solution either immediately after exercise (P-EX) or 2 h after exercise (2P-EX) (Ivy et al., 1988a).

During the first 2 h after exercise, the rate of muscle glycogen storage was 7.7 μmol/g (wet weight) per hour for the P-EX treatment, but only 2.5 μmol/g (wet weight) per hour for the 2P-EX treatment. During the second 2 h of recovery, the rate of glycogen storage slowed to 4.3 μmol/g (wet weight) per hour during treatment P-EX, but increased to 4.1 μmol/g (wet weight) per hour during treatment 2P-EX (Figure 5-3). However, even with the increase, the rate of storage during the 2P-EX treatment was still 45% slower than that for the P-EX treatment during the first 2 h of recovery. The

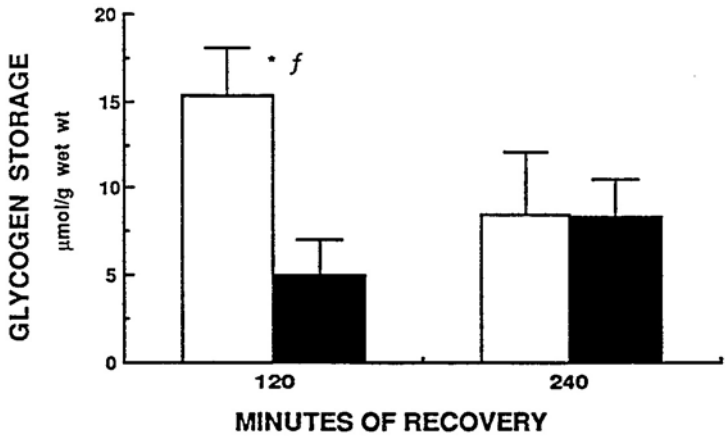

FIGURE 5-3 Muscle glycogen storage during the first 2 h and second 2 h of recovery for the P-EX treatment (open bars) and the 2P-EX treatment (closed bars). The asterisk means the value is significantly different from the basal rate of storage, which is represented by the glycogen storage rate during the first 2 h after exercise of treatment (2P-EX). P-EX, ingestion of the supplement immediately after exercise; 2P-EX, ingestion of the supplement 2 h after exercise. *f* means significantly different than treatment 2P-EX during the second 2 h of recovery ($p<0.05$). Source: Ivy et al. (1988a).

results suggested that delaying the ingestion of a postexercise carbohydrate supplement reduces the rate of muscle glycogen storage. It was also noted that the fall in the glycogen storage rate during the P-EX treatment was accompanied by a decline in the blood glucose and insulin levels. We therefore investigated the possibility that the initial rate of glycogen storage following a postexercise carbohydrate supplement could be sustained by maintaining elevated blood glucose and insulin concentrations with multiple supplements. We also investigated whether the rate of muscle glycogen storage could be enhanced during the initial 4-h period after exercise by substantially increasing the amount of the carbohydrate consumed (Ivy et al., 1988b).

The Effect of Multiple Supplements and Different Amounts of Glucose Polymer

Subjects cycled for 2 h on three separate occasions to deplete their muscle glycogen stores. Immediately after and 2 h after exercise, they consumed 0 g (placebo, P), 1.5 g (low, L), or 3.0 g (high, H) of glucose polymer per kilogram of body weight from a 50% glucose polymer solution. Blood glucose and insulin declined significantly during exercise in each of the three treatments. They remained below the preexercise concentrations during recovery during the P treatment, but increased significantly above the preexercise concentrations during the L and H treatments. By the end of the 4-h recovery period, blood glucose and insulin were still significantly above the preexercise concentrations in both treatments. Consequently, the rate of muscle glycogen storage over the second 2 h of recovery remained similar to that which occurred during the first 2 h of recovery (Ivy et al., 1988a). This is in agreement with the recent finding of Blom et al. (1987) that providing a carbohydrate supplement at 2-h intervals resulted in a consistent rate of muscle glycogen storage during the first 6 h after exercise. Although there was a substantial difference in the amount of glucose consumed for the L (225 g) and H (450 g) treatments, there were no differences in the rates of muscle glycogen storage for these treatments (Figure 5-4). Supporting these results are previous studies demonstrating that a consistent rate of muscle glycogen storage occurs the first few hours following prolonged exhaustive exercise if the amount of carbohydrate consumed is above a threshold level (Blom et al., 1987; Keizer et al., 1986; Maehlum et al., 1977). For example, Blom et al. (1987) found that during the 6 h immediately following exhaustive exercise, the average glycogen storage rate was 5.7 μmol/g (wet

weight) per hour whether 0.7 or 1.4 g of glucose per kilogram of body weight was consumed at 2-h intervals. When the carbohydrate supplement was reduced to 0.35 g per kilogram, however, the rate of storage was reduced by approximately 50%.

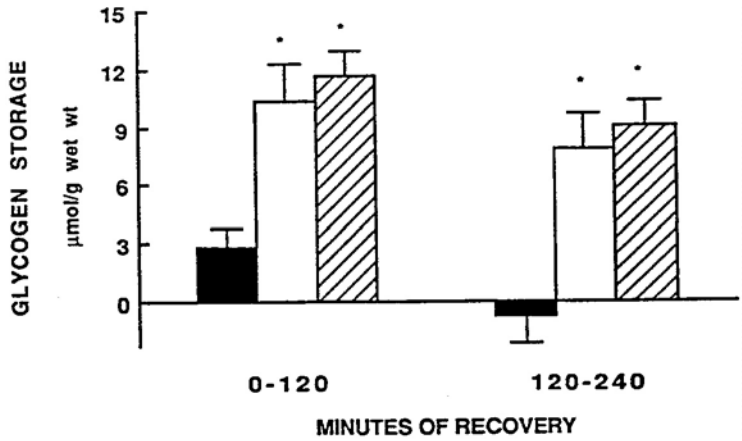

FIGURE 5-4 Muscle glycogen storage during the first 2 h and second 2 h of recovery for the placebo (P, solid bar), low (L, open bar), and high (H, cross-hatched bar) treatments. The asterisk indicates a significant difference from the placebo treatment. Source: Ivy et al. (1988b).

Effect of Glucose Infusion

To determine the role of gastric emptying in muscle glycogen restoration after exercise, we compared the rates of glycogen storage after administering an oral glucose supplement and after bypassing gastric emptying by intravenous infusion of glucose (Reed et al., 1989). Following exercise bouts that resulted in depleted muscle glycogen stores, subjects received 3 g of glucose per kilogram of body weight in a liquid form (50% glucose polymers) or intravenously (20% sterile glucose). The liquid supplement was divided into two equal doses and was administered immediately after and 120 min after exercise. During the infusion treatment, glucose was administered continuously during the first 235 min of the 240-min recovery period. Providing the glucose by infusion as opposed to

providing it orally resulted in a significantly greater rise in blood glucose, suggesting that gastric emptying had restricted the amount of glucose availabel to the muscle for storage (Figure 5-5). However, the rates of glycogen storage were not significantly different between the liquid and infusion treatments (Figure 5-6). These results indicate that the rate of glycogen storage after exercise is not limited by the gastric emptying rate of the supplement if the supplement contains sufficient carbohydrate.

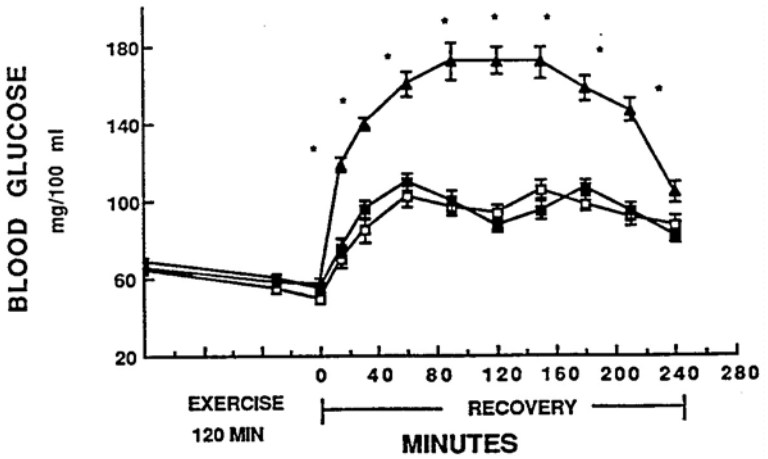

FIGURE 5-5 Blood glucose concentrations during exercise and recovery. Values are expressed as means ± standard errors of the mean in mg per 100 ml at each time point. Significant differences ($p<0.05$) between treatments are denoted by asterisks. Open squares, liquid treatment; closed squares, solid treatment; closed triangles, infusion treatment. Source: Reed et al. (1989).

Differences in the Simple Carbohydrates

Fructose, sucrose, and glucose are common dietary carbohydrates that are consumed during postexercise recovery for the purpose of restoring the

body's glycogen stores. However, the blood glucose and insulin concentrations following their consumption differ considerably. For example, the rise

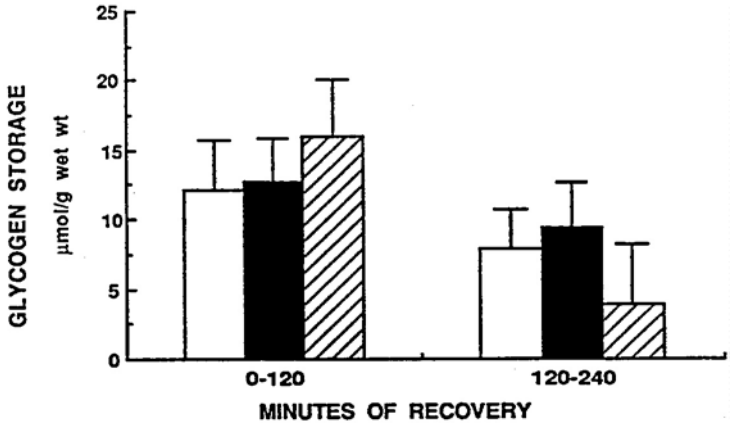

FIGURE 5-6 Glycogen storage rates during recovery. Values are expressed as ± standard errors of the mean in μmol/g during each 120-min period. Open bar, liquid treatment; closed bar, solid treatment; hatched bar, infusion treatment. Source: Reed et al. (1989).

in blood glucose and insulin following the ingestion of fructose is significantly lower than that following the ingestion of glucose (Blom et al., 1987). Because the ingestion of fructose, sucrose and glucose have different effects on blood glucose and insulin, several studies have been conducted to investigate their impact on glycogen restoration after exercise. Blom et al. (1987) found that ingestion of glucose and sucrose were twice as effective as the ingestion of fructose for the restoration of muscle glycogen. Blom et al. (1987) suggested that the differences between the glucose and fructose supplements were due to the ways the body handles these sugars. Fructose metabolism takes place predominantly in the liver (Zakin et al., 1969), whereas most glucose appears to bypass the liver to be stored or oxidized by muscle (Bergstrom and Hultman, 1967a). When infused, fructose gives rise to four times as much liver glycogen storage as glucose (Nilsson and Hultman, 1974). On the other hand, a considerably higher storage of muscle glycogen has been demonstrated in skeletal muscle after glucose infusion than after fructose infusion (Bergstrom and Hultman, 1967b).

The similar rates of glycogen storage for the sucrose and glucose supplements could not be accounted for by Blom et al. (1987). Sucrose contains equimolar amounts of glucose and fructose. If muscle glycogen storage was chiefly dependent upon the glucose moiety of the disaccharide,

one should expect a lower rate of glycogen storage from sucrose than from a similar amount of glucose. One possible explanation provided by Blom et al. (1987) was that fructose by virtue of its rapid metabolism in the liver compared with that of glucose (Zakin et al., 1969), inhibits postexercise hepatic glucose uptake, thereby rendering a larger proportion of absorbed glucose availabel for muscle glycogen synthesis.

Summary

The results suggest that the rate of muscle glycogen storage for the 2h immediately after exercise range between 5 and 8 μmol/g (wet weight) per hour, provided that a glucose supplement in excess of 1.0 g per kilogram of body weight is ingested. This rate of storage can be maintained up to 6 h after exercise if the blood glucose and insulin concentrations are sustained by providing supplements at 2-h intervals. Increasing the amount of carbohydrate consumption above 1.0 g/kg of body weight appears to have little affect on the rate of muscle glycogen storage. Additionally, it appears that carbohydrate supplements composed of glucose or glucose polymers would be more effective for the restoration of muscle glycogen after exercise than would supplements composed predominately of fructose. On the other hand, fructose appears to be a more effective carbohydrate for the replenishment of liver glycogen. Finally, it is suggested that gastric emptying does not limit the rate of muscle glycogen storage after exercise if sufficient carbohydrate is provided.

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6

Gastric Emptying During Exercise: Influence of Carbohydrate Concentration, Carbohydrate Source, and Exercise Intensity

Carl Foster[1]

INTRODUCTION

Physiologists commonly recommend the consumption of fluid (with or without electrolytes) and carbohydrate (CHO) during prolonged exercise, particularly prolonged exercise in heat. This recommendation is based on data showing improved thermoregulation and enhanced endurance secondary to fluid and CHO consumption, respectively. The rate at which solutions empty from the stomach is generally thought to be the primary limiting step in the process of fluid-energy replacement (Fordtran and Saltin, 1967). A number of factors have been identified that influence the rate of gastric emptying (Brouns et al., 1987), including: CHO concentration (osmolality), CHO source (osmolality), exercise intensity, meal volume, meal temperature, fat and protein in the ingestate, particle size, and dietary fiber. This review

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focuses on the first four of these factors in their relation to gastric emptying, with some thought to their application to the needs of the military.

CARBOHYDRATE CONCENTRATION

Early studies of gastric emptying conducted by J. N. Hunt and coworkers (Elias et al., 1968) demonstrated that the presence of mono- and disaccharides slowed the rate of gastric emptying. The magnitude of slowing was generally proportional to the CHO concentration in the test meal. Glucose was shown to be more effective, per osmole, in slowing gastric emptying than galactose. Fructose was shown to be relatively ineffective in slowing gastric emptying. The hypothesized mechanism for the delay of gastric emptying by ingestion of CHO was stimulation of duodenal osmoreceptors. This hypothesis has been supported by studies in which the infusion of glucose into the duodenum produced a profound and long-lasting suppression of gastric emptying (Brener et al., 1983). In a paper that defined the paradigm for exercise-gastric emptying work in the United States, Costill and Saltin (1974) noted a progressive decrease in the rate of gastric emptying with increases in the glucose concentration of the test meal. Their results are summarized in Figure 6-1. Coyle et al. (1978) compared the rate of gastric emptying for three commercially availabel drinks, all glucose/sucrose based, and for water. They noted a decrease in the rate of gastric emptying at CHO concentrations greater than 2.5 g per 100 ml. As with the data of Costill and Saltin (1974), the emptying characteristics of the drinks tested by Coyle et al. (1978) seemed to follow osmotic lines (Figure 6-1). Similar data were presented by Foster et al. (1980) with glucose concentrations as great as 40 g per 100 ml (Figure 6-1).

More recent studies with glucose polymers have likewise suggested a reduction in the rate of gastric emptying somewhat proportional to the total CHO concentration. Although these differences are usually presented in the context of the purported advantage of glucose polymers over that of simple CHO relative to gastric emptying, it appears that the same basic response to increasing CHO concentration is followed. This is well illustrated in Figure 6-2, which compares the gastric emptying of various concentrations of glucose and glucose polymers. There has been less systematic work with glucose polymers; however, these early data (Foster et al., 1980) are generally supported in the literature. Seiple et al. (1983) reported no difference between 5% and 7% glucose polymer-fructose drinks. However, Seiple et al. (1983) used 30- and 60-min emptying periods. Examination of

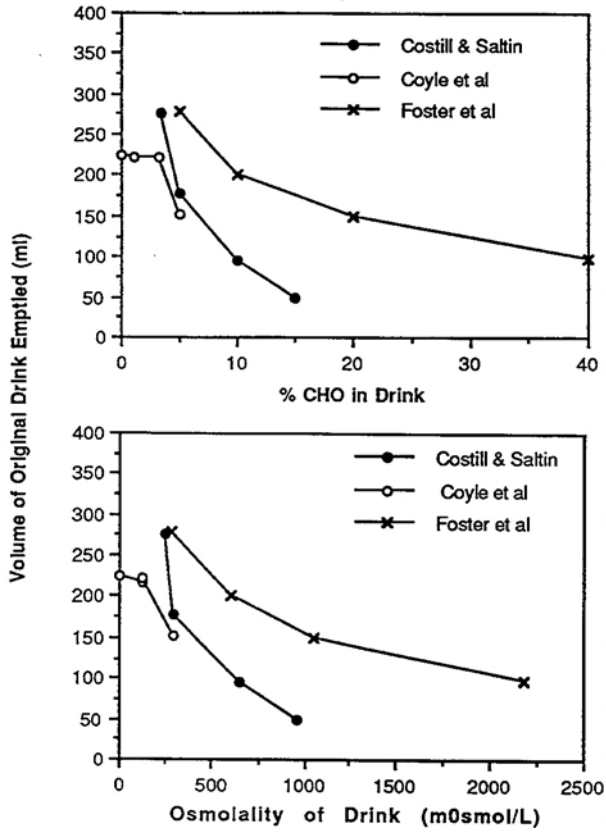

FIGURE 6-1 Relationship of CHO concentration and osmolality of 400 ml of a test drink to the volume of a test drink emptied in 15-30 minutes. Data are adapted from Costill and Saltin (1974), Coyle et al. (1978), and Foster et al. (1980). In general, lower concentrations of simple CHO in the test drink result in a greater volume of the original drink emptied. The CHO concentration appears to exert its effect primarily through the hypothesized duodenal osmoreceptors.

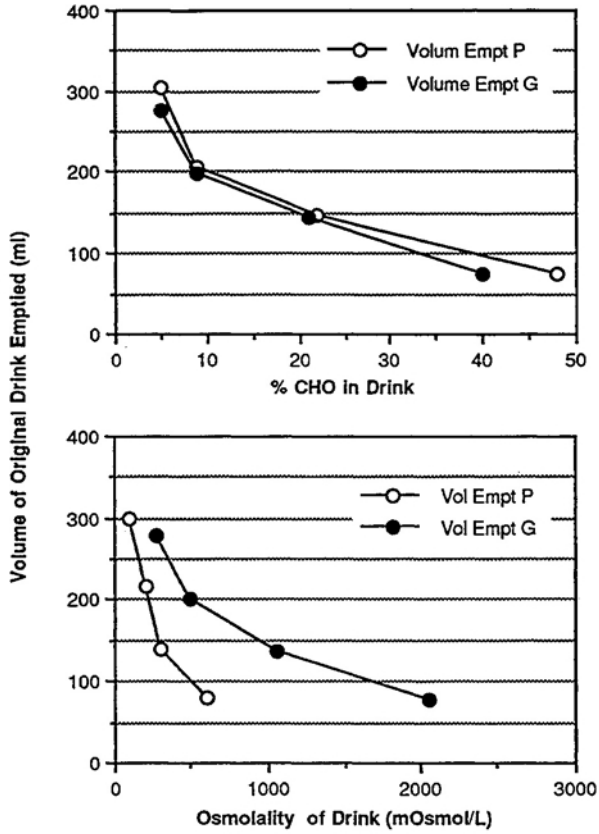

FIGURE 6-2 Comparison of emptying curves for isocaloric test drinks based on glucose (G) or glucose polymers (P). At 5% CHO, the glucose polymer-based drink emptied significantly faster than glucose. At all other CHO concentrations, there were no differences in the amount of the drink emptied. The data on osmolality versus the amount emptied suggest considerable hydrolysis of the glucose polymer proximal to the duodenal osmoreceptors. Adapted from Foster et al. (1980).

their data (Figure 6-3) indicates that at 30 min several of the subjects had already completely emptied their stomachs. The serial recovery method used in this study depends upon the ability to recover some of the original drink. Otherwise, there is no way to determine when the subjects stomach was empty, and thus make an estimate of gastric emptying rate. Thus, the data of Seiple et al. (1983) must be viewed very conservatively. Rehrer et al. (1989), using a different technique, the double sampling method, also demonstrated a reduction in the rate of emptying proportional to the concentration with maltodextrin (glucose polymer)-based drinks. Previously unpublished data from my laboratory (Figure 6-4) suggest that the gastric emptying rates of both glucose and glucose polymers decline with increasing CHO concentration. Even very low concentrations (<2 g per 100 ml) of simple CHO decrease the rate of emptying to less than that of water. Glucose polymers may allow gastric emptying in the range of water up to about 5 g per 100 ml. Our recent experience confirms our earlier data (Foster et al., 1980), suggesting that beyond 5 g per 100 ml the gastric emptying rates of glucose and glucose polymers are very similar.

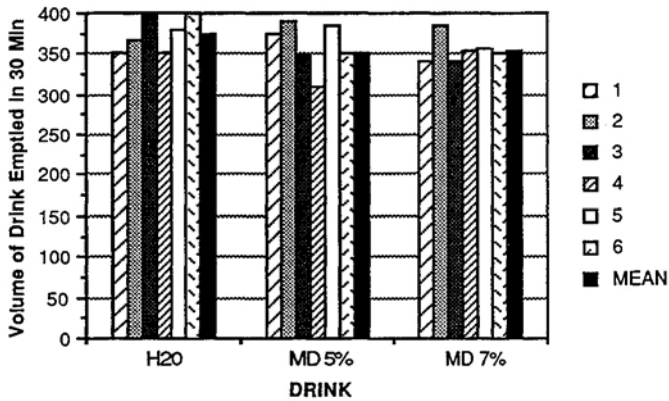

FIGURE 6-3 Individual and mean data for the emptying of 5% and 7% maltodextrin (MD) based drinks. Neither drink was significantly different from water. However, the prolonged emptying period (30 min) allowed complete emptying for some subjects and may invalidate the results. Adapted from Seiple et al. (1983).

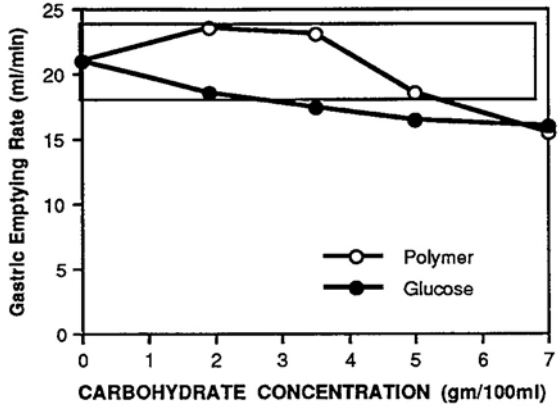

FIGURE 6-4 Average emptying rates of various concentrations of glucose- and glucose polymer-based drinks in subjects performing mild exercise. The boxed area represents the 95% confidence interval (mean ± 2 standard errors) for water. Beyond about 3% CHO the average emptying rate for simple CHO-based drinks is less than that of water. Beyond about 5% CHO, the average emptying rate for glucose polymer-based drinks is less than that of water.

CARBOHYDRATE SOURCE

Early studies by Hunt and Spurrell (1951) demonstrated that test meals containing starch left the stomach more rapidly than did meals containing glucose. This advantage was apparently related more to an initial more rapid emptying rate of starch. Foster et al. (1980) demonstrated that a 5% glucose polymer solution left the stomach more rapidly than isocaloric glucose did. More concentrated solutions of glucose and and glucose polymer left the stomach at similar rates (Figure 6-2). Neufer et al. (1986) showed that the addition of glucose to a polymer-glucose mixture slowed gastric emptying at total CHO concentrations within the range of 5 to 7.5 g per 100 ml. Supportive data for the advantage of polymer-based drinks over glucose-based drinks was provided by Rehrer et al. (1989), who demonstrated that a polymer-fructose (18% CHO)-based drink emptied faster than a less concentrated (15.2% CHO) glucose solution did. Previously unpublished data from my laboratory demonstrate that a 5% polymer-fructose-based drink empties at about the same rate as a 3% to 4% sucrose-based drink (Figure 6-4).

EXERCISE INTENSITY

Early studies by Campbell et al. (1928) and Hellebrandt and Teper (1934) suggested a slightly inhibitory effect of exercise on the gastric emptying rate. Subsequently, Fordtran and Saltin (1967) demonstrated that while the rate of emptying of water was slightly delayed at an exercise intensity of 71% of maximal O_2 uptake ($\dot{V}_{O_2\,max}$), there was no exercise-induced delay in the slower emptying rate of a 13% glucose solution. Costill and Saltin (1974) demonstrated essentially no effect of exercise in the rate of gastric emptying up to about 65%-70% $\dot{V}_{O_2\,max}$. Neufer et al. (1986) demonstrated an enhanced rate of gastric emptying during mild exercise (50%-70% $\dot{V}_{O_2\,max}$) (Figure 6-5). Rehrer et al. (1989) indicated that CHO-containing drinks empty more slowly, at least initially, during exercise. The gastric emptying rate of water was unaffected, at least up to 70% of W_{max}.

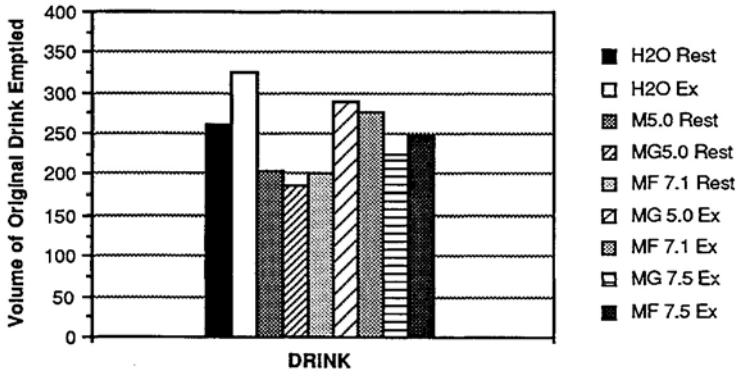

FIGURE 6-5 Data from Neufer et al. (1986) demonstrating the increase in gastric emptying with mild exercise for both water- and CHO drinks containing malto-dextrin (M), glucose (G), and fructose (F). The slower emptying attributable to the presence of glucose in test drinks is also apparent in these data.

Thompson and Foster (1988) demonstrated a slightly enhanced rate of gastric emptying during mild exercise for both water and a concentrated (23% CHO) polymer-based drink. Previously unpublished data from my laboratory suggest that beyond 60% $\dot{V}_{O_2\,max}$ there is a progressive slowing of gastric emptying and that at high exercise intensities (90% $\dot{V}_{O_2\,max}$) even water empties very slowly (Figure 6-6). Commercially availabel drinks based on sucrose (5.9% CHO) and polymers-fructose (7.1% CHO) emptied signifi

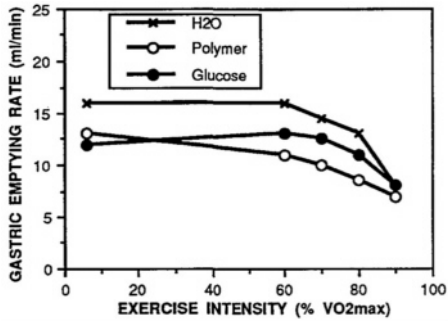

FIGURE 6-6 Average gastric emptying rates with two commercially availabel drinks in relation to exercise intensity. At rest and at moderate exercise intensities, water empties significantly more rapidly than either CHO-containing drink does. At high exercise intensities, everything empties slowly.

cantly more slowly than water up through 70% $\dot{V}_{O_2\,max}$. At higher exercise intensities, the gastric emptying rate of water slowed down to those of the two CHO-containing drinks. The similar emptying rates of the two CHO-containing drinks is consistent with established effects attributable to the CHO source (Figure 6-4). The data on exercise intensity generally follow with increases in exercise intensity (Rowell et al., 1964). The frequency of abdominal complaints and symptoms during high-intensity or competitive exercise (Brouns et al., 1987) suggests that attempting to feed while the gastric emptying rate is suppressed by high-intensity exercise may be inherently futile.

INDIVIDUALITY OF GASTRIC EMPTYING RATES

Much of the data regarding gastric emptying has, properly, focused on the characteristics of the ingestate or the circumstances of the subject. Less appreciated are the differences between subjects in gastric emptying characteristics. In Figure 6-7 are presented previously unpublished data regarding the effect of exercise intensity on the gastric emptying rates of water and two commercially availabel CHO-containing drinks. The data presented in Figure 6-7 represent raw data for the averages presented in

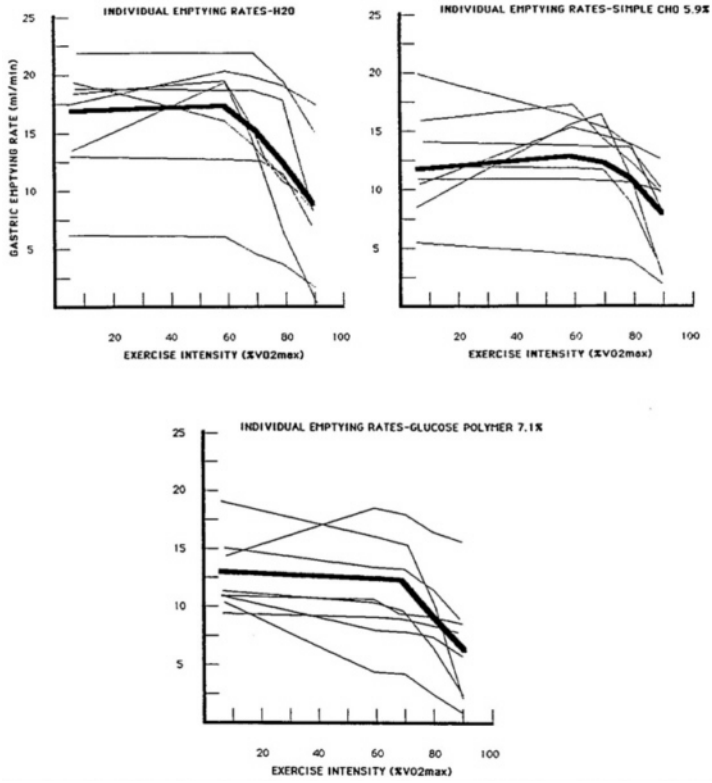

FIGURE 6-7 Individual (thin lines) and mean (heavy line) gastric emptying rates of water and two commercially availabel CHO-containing drinks in relation to exercise intensity. Note the wide variation in individual emptying rates.

Figure 6-5. Note the nearly fourfold difference in the individual emptying rates of all three drinks. Also note that at rest and during mild exercise, some individuals empty CHO-containing drinks faster than the group average for water at rest. Similar data have been observed in subjects at rest by using different concentrations of glucose and glucose polymers (Figure 6-8).

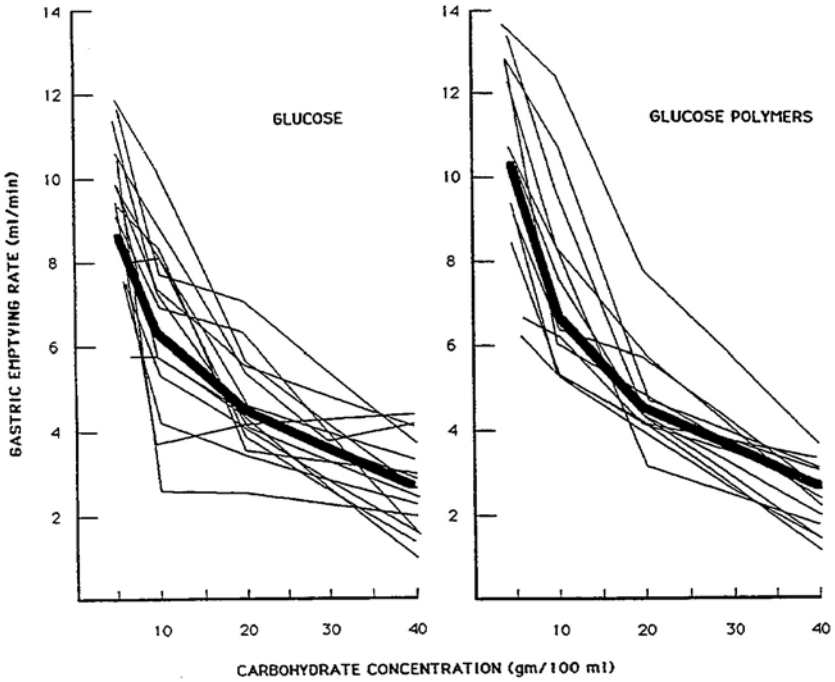

FIGURE 6-8 Individual (thin lines) and mean (heavy line) gastric emptying rates of glucose and glucose polymers in relation to CHO concentration. Note the variations in individual emptying rates. Adapted from Foster et al. (1980).

EFFECTS OF GASTRIC EMPTYING METHODOLOGY

Until the past 5 years the dominant method for studying gastric emptying was the serial recovery method. This method was introduced by J. N. Hunt in the 1950s (Hunt and Spurrell, 1951). Results by this method suggested that CHO concentrations of greater than about 5% produced significant delays in gastric emptying and that glucose polymers had some small advantage over simple sugars as the source of CHO for drinks designed for sports participants. More recent reports from several laboratories (Mitchell et al., 1988; Owen et al., 1986; Ryan et al., 1989) in which the serial feeding method was used, have suggested that much higher concentrations of CHO can be emptied fairly completely during exercise. Owen et al. (1986) showed that with the serial feeding of 200 ml of water, 10% glucose polymer or 10% glucose every 20 min, as much as 40%-60% of the drink is emptied after 2 h of exercise in the heat. The expected differences attributable to CHO source were evident, and the emptying of water was delayed in a hot environment, presumably secondary to the reduction in splanchnic blood flow attributable to prolonged exercise in the heat (Figure 6-9). Mitchell et al. (1988) demonstrated that as much as 90% of several drinks,

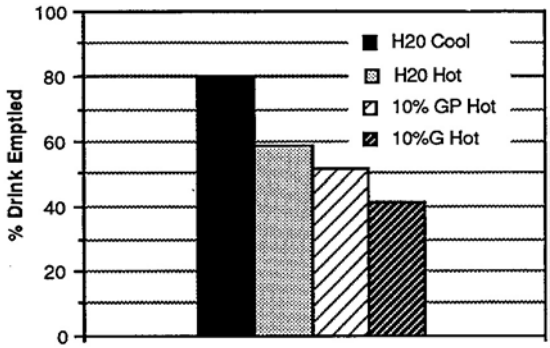

FIGURE 6-9 Relative emptying of different drinks during 2 h of exercise in the heat. These data were adapted from Owen et al. (1986) who used the serial feeding method and demonstrated surprisingly favorable emptying of relatively concentrated glucose and glucose polymer (GP) drinks. Note the general suppression of gastric emptying secondary to thermal stress.

water and several glucose-sucrose-polymer variants in the range of 5%-7.5% CHO, emptied during 2 h of interval exercise when 8.5 ml of the test drink per kilogram of body weight per hour was consumed during the interval. This represented an average of about 165 ml every 15 min. Ryan et al. (1989) demonstrated that as much as 90% of several drinks, water (5% glucose, 5% glucose polymer, or 5% glucose polymer-fructose) could be emptied during 3 h of exercise (60% $\dot{V}_{O_2\,max}$) in the heat when 350 ml was given every 20 min. This represents the greatest effective rate of emptying that has yet been demonstrated during exercise, particularly with fairly concentrated CHO-containing solutions.

The mechanism that allows this rate of emptying has been apparent, but largely ignored, for many years. Hunt and Spurrell (1951) demonstrated nearly 40 years ago that the rate of gastric emptying increased with increasing volumes of ingestate. Similar data were presented by Costill and Saltin (1974), at least up to ingestate volumes of 600 ml, which is 1.5 times the standard 400 ml used in many studies using the serial recovery method (Costill and Saltin, 1974; Coyle et al., 1978; Foster et al., 1980; Neufer et al., 1986; Seiple et al., 1983; Thompson and Foster, 1988). Contemporary data from Hunt et al. (1985) support the notion of accelerated gastric emptying with larger meal volumes. Recent data from Rehrer et al. (1989), using the double sampling method, demonstrate that the emptying rate of CHO-containing drinks relative to that of water declines as the stomach becomes progressively less filled. This seems to be more important during exercise (Figure 6-10) than at rest (Figure 6-11). Thus, recent methodological variations lead to the conclusion that maintenance of a high gastric volume may override some of the inhibitory effects on gastric emptying attributable to the presence of CHO in the ingestate.

MILITARY APPLICATIONS

Just as military needs vary greatly with mission characteristics, the need for fluid and CHO replacement varies with the requirements of the individuals who are required to perform defined functions. During high-intensity exercise, gastric emptying is very slow secondary to the low splanchnic blood flow. If high-intensity exercise is required, then drinking during rest intervals becomes the only logical alternative. During more prolonged exercise, frequent (every 15-20 min) consumption of moderate (150 ml) to large (350 ml) volumes of drink are possible with favorable results. Some individuals may be particularly intolerant to forced drinking, however. Whether the ability to tolerate high intragastric volumes can be improved with training remains to be determined. However, it seems that the

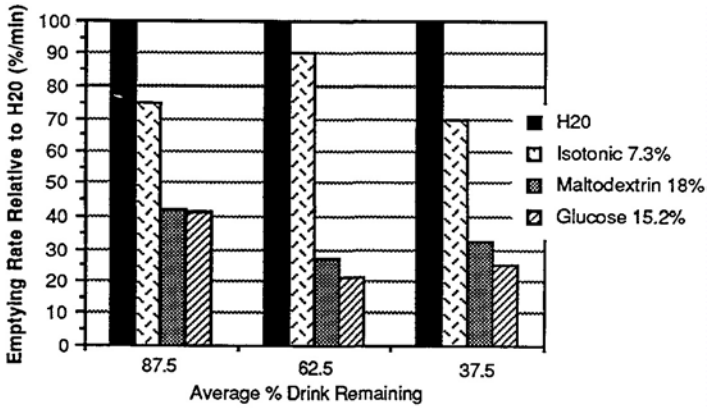

FIGURE 6-10 Normalized rate of emptying of various drinks in relation to the relative fullness of the stomach during moderate to heavy exercise. Note that CHO-containing beverages empty relatively more slowly as the overall emptying rate slows down as the stomach becomes relatively less full. These data support the hypothesis that high gastric volumes can accelerate gastric emptying and override the suppression of emptying attributable to the presence of CHO. This suppression becomes important at lower gastric volumes. Adapted from Rehrer et al. (1989).

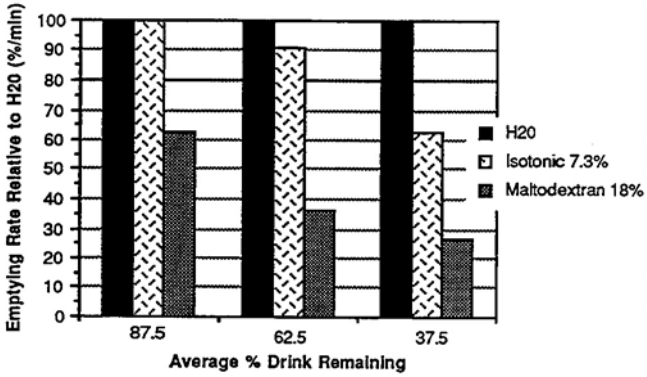

FIGURE 6-11 Normalized rate of gastric emptying of various drinks in relation to the relative fullness of the stomach at rest. Note the minimal effect of CHO at high gastric volumes (similar to that in Figure 6-10) and the less overall importance of CHO during rest compared with the slower emptying rates in Figure 6-10. Adapted from Rehrer at al. (1989).

frequent complaints of gastrointestinal symptoms by athletes during competition are as much a function of the unfamiliarity of exercising with a full stomach as of delays in gastric emptying solely attributable to the CHO source or exercise intensity. Under most circumstances it appears that glucose polymer-based drinks have some advantage over simple CHO-based drinks, particularly at the higher end of the emptying rate spectrum.

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7

Interaction of Water Bioavailability, Thermoregulation, and Exercise Performance

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INTRODUCTION

During muscular exercise, the magnitude of core temperature elevation is proportional to the metabolic rate and somewhat independent of the environmental condition (Nielsen, 1938). The elevation of the core temperature represents the storage of metabolic heat, which is a by-product of skeletal muscle contraction. At the initiation of exercise, the metabolic rate increases immediately; however, the thermoregulatory effector responses respond more slowly. The thermoregulatory effector responses, which enable dry and evaporative heat loss to occur, increase in proportion to the rate of heat production (Nielsen, 1966). Eventually, these heat loss mechanisms increase sufficiently to balance metabolic heat production, allowing a steady-state core temperature to be achieved.

An individual's aerobic fitness (Armstrong and Pandolf, 1988), acclimatization state (Wenger, 1988), and hydration level (Sawka, 1988) have

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been known to be the primary factors modifying the core temperature and thermoregulatory responses to muscular exercise. Aerobically fit people who are heat acclimated and fully hydrated optimize their ability to limit body heat storage and maintain performance during exercise-heat stress. Hydration level is particularly important because a body fluid deficit incurred before or during exercise in the heat neutralizes the thermoregulatory advantages conferred by high aerobic fitness (Cadarette et al., 1984) and heat acclimatization (Buskirk et al., 1958; Sawka et al., 1983).

BODY WATER LOSS

In hot environments, body fluid is lost primarily through eccrine sweat gland secretion, which results in evaporative cooling of the body. For a given person, the sweating rate is dependent on environmental conditions (ambient temperature, dew point temperature, radiant load, and air velocity), clothing (insulation and moisture permeability), and physical activity level (Adolph and Associates, 1947; Shapiro et al., 1982). Adolph and Associates (1947) reported that for 91 men studied during diverse military activities in the desert, the average sweating rate was 4.1 liters every 24 h, but values ranged from 1 to 11 liters every 24 h. During more intense physical exercise, much higher sweating rates can occur, and sweating rates of 1 liter/h are very common (Shapiro et al., 1982).

During physical exercise in the heat, the principal problem is that of precisely matching the volume of fluid intake to the volume of sweat output. This is a difficult problem to solve since thirst does not provide a good index of body water requirements (Adolph and Associates, 1947; Engell et al., 1987). Numerous investigators (Adolph and Associates, 1947; Bar-Or et al., 1980; Phillips et al., 1984) report that ad libitum water intake results in incomplete water replacement or voluntary dehydration during exercise and heat exposure. It is not uncommon for individuals to voluntarily dehydrate 2%-8% of their body weight during exercise-heat stress, despite the availability of adequate amounts of fluid for rehydration (Adolph and Associates, 1947; Buskirk and Beetham, 1960; Greenleaf et al., 1983).

Thirst is probably not perceived until an individual has incurred a water deficit of approximately 2% of body weight (Adolph and Associates, 1947). As a result, it is likely that unless forced hydration is practiced, some level of dehydration will occur during exercise in the heat. Neufer et al. (1988) recently found that hypohydration reduces the gastric emptying rate of ingested fluids during exercise in the heat. They found an approximate 20% reduction in gastric emptying rate during three successive 15-min bouts of exercise in a warm environment (35°C, 20% relative humidity) when

subjects were hypohydrated as compared when they were euhydrated. The volume of ingested fluid emptied into the intestines was inversely correlated (Figure 7-1) with the subjects' core temperature (Neufer et al., 1988). In this paper it is shown that hypohydration mediates an increased core temperature during exercise. Therefore, forced hydration during the early stages of exercise-heat stress is important, not only to avoid voluntary dehydration but also to maximize the bioavailability of the ingested fluids.

Sweat loss results in a reduction of total body water if an adequate amount of fluid is not consumed. The question arises as to how water loss is partitioned among the body fluid compartments. As a consequence of free fluid exchange, hypohydration affects each fluid compartment (Costill et al., 1976; Durkot et al., 1986; Nose et al., 1983). When body water loss is minimal, the water deficit comes primarily from the extracellular space. As more body water is lost, a proportionately greater percentage of the water deficit comes from the intracellular space (Costill et al., 1976; Durkot et al., 1986).

The plasma volume responses for heat-acclimated subjects when they were euhydrated and hypohydrated by 3%, 5%, and 7% of their body weight are presented on the bottom of Figure 7-2 (Sawka et al., 1985). Note that plasma volumes were generally smaller with increased hypohydration levels,

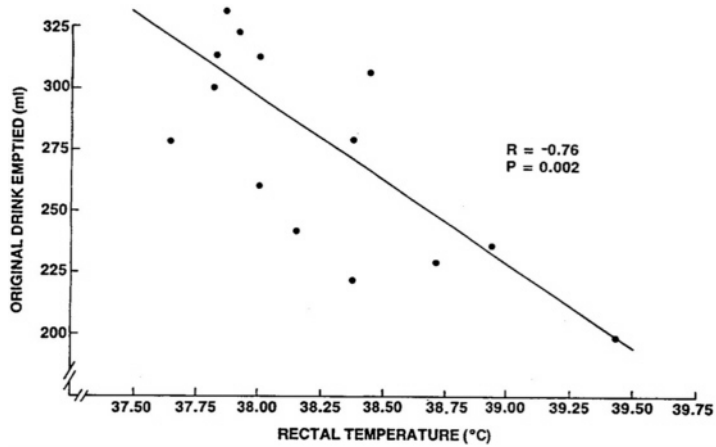

FIGURE 7-1 Correlation of final rectal temperatures (°C) and the corresponding volume (ml) of original drink emptied during exercise (50% $\dot{V}_{O_2\,max}$) when euhydrated and hypohydrated by 5% of body weight. Source: Neufer et al. (1988).

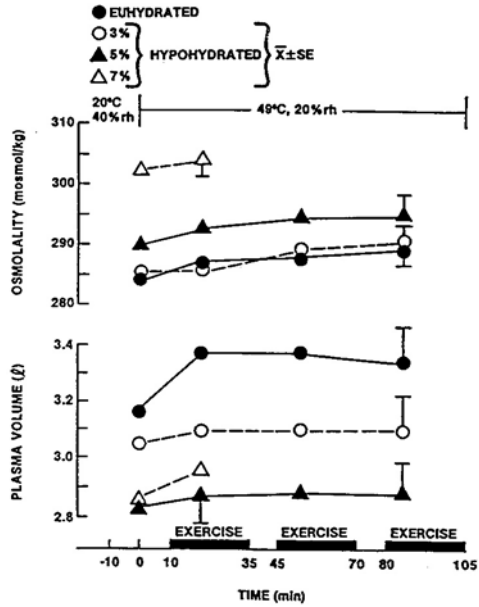

FIGURE 7-2 Plasma osmolality and plasma volume at rest and exercise when euhydrated and hypohydrated by 3%, 5%, and 7% of body weight. Source: Sawka et al. (1985).

although there was some evidence of a plasma volume defense during the 7% hypohydration experiment. The most important point from Figure 7-2 is the observation that the hypohydration-mediated plasma volume reduction that occurred at rest continued throughout the subsequent moderate-intensity exercise. In fact, the differences between the euhydration and hypohydration plasma volumes were greater during exercise than during rest because of the small exercise-induced hemodilution that occurred when subjects were euhydrated but not hypohydrated (Sawka et al., 1984a, 1985).

It is known that exercise or heat-induced hypohydration increases the osmotic pressure in the plasma. Eccrine sweat is ordinarily hypotonic relative to plasma (Sawka, 1988); therefore, the plasma becomes hyperosmotic when hypohydration is induced primarily by sweat output (Sawka et al., 1985; Senay, 1979). For resting subjects, plasma osmolality increases from about 283 mosmol/kg when they are euhydrated to levels exceeding 300 mosmol/kg when hypohydrated (Figure 7-2). Sodium, potassium, and their anions (chloride) are primarily responsible for the elevated plasma osmolality during hypohydration (Senay, 1979).

EXERCISE PERFORMANCE AND PHYSIOLOGICAL RESPONSES

Several investigations have examined the effects of hypohydration on maximal aerobic power and physical work capacity. In the absence of heat stress, a relatively large water deficit (6%-7%) has a minimal effect on maximal aerobic power, but reduces physical work capacity by approximately 20% (Sawka et al., 1984b). In a hot environment, Craig and Cummings (1966) demonstrated that small (2%) to moderate (4%) water deficits reduce maximal aerobic power (10%-27%) and physical work capacity (22%-48%). In addition, these decrements increase dramatically with the magnitude of water deficit. Consistent with these findings, hypohydration combined with hyperthermia in a moderate environment reduces maximal aerobic power by 6% and exercise time by 12% from euhydration levels (Sawka et al., 1979b). These investigations demonstrate that maximal exercise performance is reduced when hypohydration is combined with thermal strain. Likewise, submaximal endurance exercise is also reduced by dehydration acting through the thermoregulatory and cardiovascular systems (Sawka et al., 1979a, 1980).

In comparison with euhydration, hypohydration increases core temperature during exercise in comfortable (Grande et al., 1959; Neufer et al., 1988; Sawka et al., 1980) as well as hot (Claremont et al., 1976; Pearcy et al., 1956; Pitts et al., 1944) environments. A water deficit of only 1% of body weight significantly elevates core temperature during exercise (Ekblom et al., 1970). It is believed that as the severity of hypohydration increases, there is a concomitant gradation in the elevation of core temperature during exercise. Two studies examined core temperature responses to exercise while hypohydration levels were varied during independent tests in the same subjects. Strydom and Holdsworth (1968) studied two miners at two hypohydration levels [low (3%-5%) and high (5%-8%) weight loss] and found higher core temperatures at the high hypohydration level. Sawka et al. (1985) reported that hypohydration linearly increased the core temperature response during exercise in the heat (0.15°C) for each percent decrease in body weight. Figure 7-3 provides an example of an individual's core temperature response to exercise in the heat while he was euhydrated and while he was at three separate hypohydration levels (Sawka et al., 1985). Clearly, the greater the water deficit, the greater the steady-state core temperature response during exercise.

The hypohydration-mediated increase in heat storage is the result of either an increase in metabolic heat production or a decrease in heat loss. Hypohydration does not influence the rate of aerobic or anaerobic metabolism during exercise (Greenleaf and Castle, 1971; Saltin, 1964; Sawka

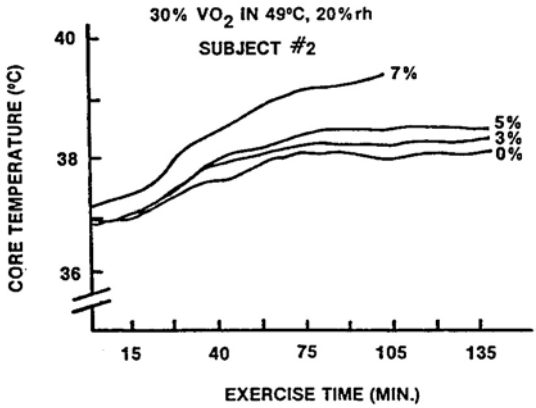

FIGURE 7-3 Core temperature responses during exercise-heat stress when an individual was euhydrated and hypohydrated by 3%, 5%, and 7% of body weight. Source: Sawka et al. (1985).

et al., 1979a, 1980, 1983, 1984a, 1985) and, as a result, does not cause greater metabolic heat production. Therefore, decreased heat dissipation must be responsible for the hypohydration-mediated heat storage during exercise. The relative contribution of evaporative and dry heat exchange during exercise depends on the specific environmental conditions, but both avenues of heat loss are adversely affected by hypohydration (Fortney et al., 1981a,b; Sawka et al., 1984b).

Hypohydration is associated with reduced or unchanged sweating rates at a given metabolic rate during exercise in the heat (Sawka et al., 1984b). Those investigators who report no change in sweating rate usually still observed an elevated core temperature. Therefore, during hypohydration the sweating rate is lower for a given core temperature, and the potential for heat dissipation through sweat evaporation is reduced. Figure 7-4 presents data (Sawka et al., 1989) showing that three hypohydrated subjects had an increased threshold temperature for thermoregulatory sweating during exercise. Since core temperature provides 90% of the drive for thermoregulatory sweating, Figure 7-4 indicates that the sweating rate is reduced for a given thermal drive. Likewise, a recent study has demonstrated a systematically reduced sweating rate with increased hypohydration levels during exercise in the heat (Sawka et al., 1985).

The physiological mechanisms mediating the reduced sweating rate response during hypohydration are not clearly defined. Both the singular and combined effects of plasma hyperosmolality (Candas et al., 1986; Fortney et al., 1984; Harrison et al., 1978; Sawka et al., 1985) and plasma hypovolemia (Fortney et al., 1981b; Hertzman and Ferguson, 1960; Sawka et.al., 1985) have

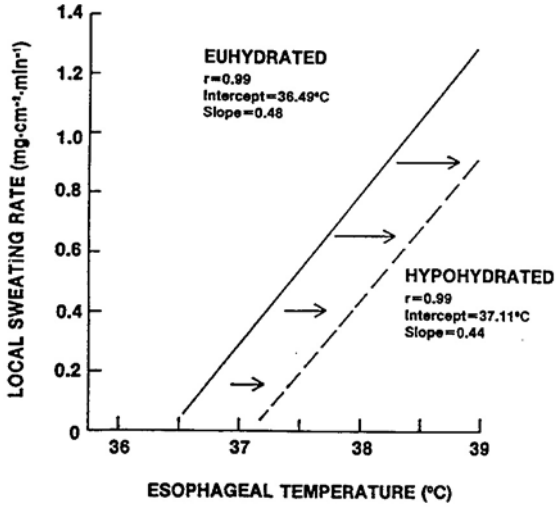

FIGURE 7-4 The local sweating rate (dew-point hygrometry) for a given core temperature during exercise-heat stress for three subjects when euhydrated and hypohydrated by 5% of body weight. Source: Sawka et al. (1989)

have been suggested as mediating this reduced sweating response. Plasma hyperosmolality maintains a strong ($r = -0.76$) and consistent relationship with the reduced sweating rates during hypohydration. Consistent with these findings, Senay (1979) reported an inverse relationship between plasma osmolality and sweating rate ($r = -0.62$) when hypohydration occurs. Also, several investigators (Harrison et al., 1978; Nielsen, 1974; Nielsen et al., 1971) have reported that plasma hyperosmolality elevates core temperature responses during exercise-heat stress, despite the maintenance of euhydration. Hyperosmolality can decrease sweating by a direct central nervous system effect on the hypothalamic thermoregulatory centers (Doris, 1983; Senay, 1979; Silva and Boulant, 1984) or by a peripheral effect at the eccrine sweat gland (Greenleaf and Castle, 1971; Nielsen et al., 1971).

Hypovolemia can also mediate a decreased sweating rate during exercise in the heat (Fortney et al., 1981b; Sawka et al., 1985). The thermoregulatory disadvantages of hypohydration can also be partially reversed by the reestablishment of the normal blood volume during exercise in the heat (Stephenson et al., 1983). Fortney et al. (1981b) have provided strong evidence that an isosmotic hypovolemia causes a reduced sweating rate and elevated core temperature response during exercise. They theorized that hypovolemia may alter the activity of atrial baroreceptors that have afferent input to the hypothalamus. Therefore, a reduced atrial filling

pressure might modify neural information to the hypothalamic thermoregulatory centers that control the sweating rate.

The effects of hypohydration on cardiovascular responses to submaximal exercise have been investigated (Allen et al., 1977; Nadel et al., 1981; Saltin, 1964; Sawka et al., 1979a; Sproles et al., 1976). During the submaximal exercise with little thermal strain, hypohydration elicits an increase in heart rate and a decrease in stroke volume, with no change in cardiac output relative to euhydration levels (Allen et al., 1977; Saltin, 1964; Sproles et al., 1976). During hypohydration, a decreased blood volume apparently reduces the end-diastolic ventricular volume and stroke volume, requiring a compensatory increase in heart rate to maintain cardiac output. During submaximal exercise with moderate (Nadel et al., 1981) or severe (Sawka et al., 1979a) thermal strain, hypohydration (3%-4%) increases heart rate, decreases stroke volume, and decreases cardiac output relative to euhydration levels. Likewise, Sproles et al. (1976) demonstrated that a severe water deficit (7% of body weight) in the absence of thermal strain, can also reduce cardiac output during submaximal exercise.

The combination of exercise and heat strain results in competition between the central and peripheral circulations for a limited blood volume (Rowell, 1983). As the body temperature increases during exercise, cutaneous vasodilation occurs, thus decreasing venous resistance and pressure. As a result of decreased blood volume and increased blood displacement to cutaneous vascular beds, venous return and thus cardiac output are decreased below euhydration levels (Nadel et al., 1981; Sawka et al., 1979a). Nadel et al. (1981) report that these conditions also reduce cutaneous blood flow for a given core temperature and therefore the potential for sensible heat exchange. Likewise, hyperosmolality, in the absence of hypovolemia, can also reduce the cutaneous blood flow response during exercise-heat stress (Fortney et al., 1984).

Another physiological mechanism by which hypohydration might limit submaximal endurance exercise is by altering skeletal muscle metabolism. In preliminary work (Neufer et al., 1989b), we found higher plasma glucose, lactate, and glycerol responses during 1 h of cycling exercise (50% $\dot{V}_{O_2\,max}$ 18° C, 30% relative humidity) when subjects were hypohydrated (−5% body weight) than when they were euhydrated (Figure 7-5). However, no significant differences were observed in the respiratory exchange ratio, muscle glycogen use, or plasma free fatty acid concentrations between experiments. In the absence of any apparent differences in lipolysis and muscle substrate use, we interpreted these findings as probably indicating a reduced hepatic blood flow, as evidenced by the higher plasma glucose, lactate, and glycerol levels observed during the hypohydration experiment. Since 3 to 4 g of water is bound to each 1 g of glycogen, we hypothesized that hypohydration might

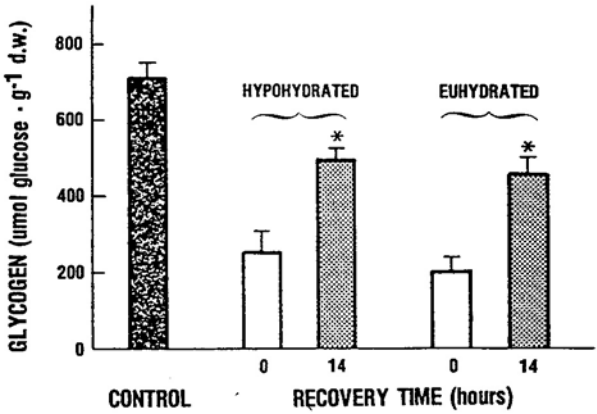

FIGURE 7-5 Skeletal muscle glycogen resynthesis after exercise when euhydrated and when hypohydrated by 5% of body weight (d.w. indicates dry weight). The asterisks indicate values significantly different ($P < 0.05$) from those at zero. Source: Neufer et al. (1989b)

also reduce glycogen resynthesis, despite the intake of an adequate carbohydrate diet. Preliminary findings (Neufer et al., 1989a) indicate that despite reduced muscle and body water availability muscle glycogen resynthesis is not altered by hypohydration during the first 15 h after heavy exercise.

In summary, it is of optimal importance that individuals rapidly replace their sweat losses while performing exercise. The fluid replacement is necessary to minimize plasma hyperosmolality and to restore the blood volume in hypohydrated individuals. The plasma hyperosmolality and hypovolemia, which result from body water loss, act singularly and together to reduce the efficiency of the thermoregulatory system.

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8

Timing of Carbohydrate Supplementation During Prolonged Strenuous Exercise

Edward F. Coyle[1] *and Andrew R. Coggan*

INTRODUCTION

Both muscle glycogen and plasma glucose are oxidized by skeletal muscle to supply energy during prolonged exercise (Ahlborg and Felig, 1982; Ahlborg et al., 1974; Bergstrom and Hultman, 1966, 1967; Gollnick et al., 1981; Hermansen et al., 1967; Ivy et al., 1983; Pallikarakis et al., 1986; Pirnay et al., 1982; Wahren, 1970). Although the underlying mechanisms are uncertain, there appears to be a gradual shift from intramuscular glycogen toward blood-borne glucose as the predominant carbohydrate energy source as exercise proceeds and as muscle glycogen is depleted (Coggan and Coyle, 1987; Coyle et al., 1986; Gollnick et al., 1981; Ivy et al., 1983; Wahren, 1970). The contribution of glucose to oxidative metabolism may be limited, however, by a decline in the plasma glucose concentration late in exercise as liver glycogen stores diminish. Therefore, it may be necessary to ingest carbohydrate to maintain or elevate the blood glucose concentration. We

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have previously demonstrated that feeding carbohydrate throughout exercise at 70%-74% of maximal O_2 uptake (i.e., $\dot{V}_{O_2\,max}$) can delay fatigue by 30 to 60 min (e.g., from 3 h to 4 h) (Coyle et al., 1983, 1986). A major finding was that carbohydrate feedings did not spare muscle glycogen utilization and that trained cyclists were able to exercise for the additional hour when fed carbohydrate without relying upon muscle glycogen for a fuel (Coyle et al., 1986). Instead, it appears that when the blood glucose concentration is maintained at 5 mM by carbohydrate feeding, highly trained cyclists are capable of relying upon blood glucose for almost all of their carbohydrate energy during the later stages of prolonged strenuous exercise. When exercising without feedings, the blood glucose concentration declines progressively after the first hour and reaches hypoglycemic levels (i.e., <2.5 mM) after 3 h of exercise (Coyle et al., 1983, 1986). Figure 8-1 describes our theory that the source of carbohydrate energy shifts from muscle glycogen to blood glucose as the duration of exercise progresses. Thus, blood glucose appears to be the most important source of energy after 3 h of strenuous cycling. It is therefore important that people have adequate glucose in their blood during the later stages of exercise in order to delay fatigue.

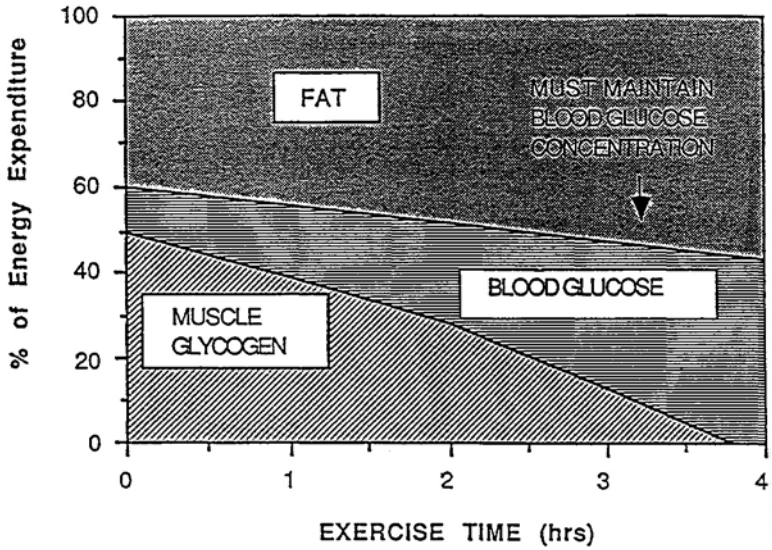

FIGURE 8-1 Theoretical representation of the sources of energy during prolonged cycling at 70% of maximal oxygen uptake. Source: Redrawn from Coyle et al. (1986).

This paper addresses the question of whether there is a critical time when carbohydrate must be administered during exercise in order to delay fatigue. Two recent studies from our laboratory are summarized in an attempt to answer this question (Coggan and Coyle, 1987; 1989).

REVERSAL OF FATIGUE BY CARBOHYDRATE INFUSION OR INGESTION

We first determined whether it is possible to reverse fatigue late in exercise through carbohydrate supplementation (Figure 8-2) (Coggan and Coyle, 1987). Instead of providing carbohydrate feedings throughout exercise, the cyclists received only water and exercised at 70% of $\dot{V}_{O_2\,max}$ until fatigued (i.e., exercise bout 1). After they were fatigued, they rested for 20 min and received one of the following treatments:

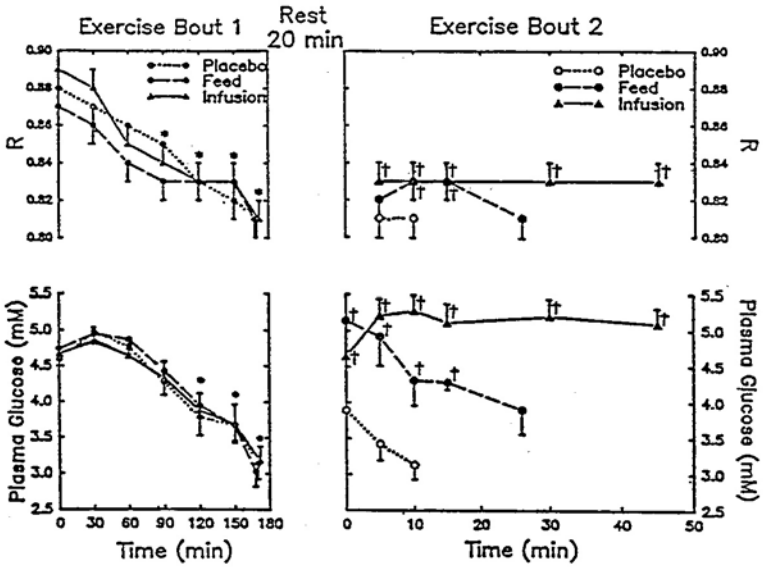

FIGURE 8-2 Respiratory exchange ratio (R) and plasma glucose responses during exercise bouts 1 and 2. The asterisks denote a significant (P<0.05) decline during bout 1; the daggers denote values during exercise bout 2 that were significantly higher (P<0.05) than at the point of fatigue during bout 1. Source: Coggan and Coyle (1987).

1. Intravenous glucose infusion at a rate that elevated and maintained blood glucose concentrations at normally high levels (5.0-5.5 mM; euglycemic clamp procedure).
2. Oral ingestion of 200 g of a carbohydrate solution at the beginning of the rest period [400 ml of 50% (w/v) solution of glucose polymers with sucrose (Exceed, Ross Laboratories)].
3. Oral ingestion of a placebo solution (i.e., aspartame sweetened, colored, and flavored) that contained no energy. The placebo was used to determine the extent to which the 20-min rest period alone restored work tolerance.

After receiving one of these treatments, the cyclists then attempted to continue exercising at the original work rate (i.e., exercise bout 2). It should be noted that the exercise tests were conducted in the laboratory by using a stationary cycle ergometer (Quinton model 845). Exercise bout 1 was begun after an overnight fast.

Exercise Bout 1

Figure 8-2 summarizes the results. As we have shown previously (Coyle et al., 1983, 1986), the cyclists exercised for 168 to 172 min before fatiguing during exercise bout 1. The purpose of exercise bout 1 was to produce fatigue. As was shown previously, fatigue during exercise bout 1 was preceded by a decline in the subjects' respiratory exchange ratio (R), which reflected a proportional decline in the rate at which carbohydrate was used for energy. During the second hour of exercise, the plasma glucose concentration began to decline, and it continued to decline to relatively low values at the point of fatigue (i.e., 3.0-3.2 mM), which occurred after 168 to 172 min. No experimental treatment was provided during exercise bout 1, and each of the three trials elicited identical responses.

Exercise Bout 2

After a 20-min rest period and application of one of the experimental treatments (i.e., placebo, intravenous glucose infusion, or carbohydrate ingestion), the cyclists attempted to continue exercise at the original work rate (i.e., 70% $\dot{V}_{O_2\,max}$) as long as possible (exercise bout 2).

Placebo Ingestion. Plasma glucose increased from 3.1 ± 0.2 to 3.8 ± 0.3 mM because of the 20-min rest period during the placebo trial. As shown in Figure 8-2, however, the plasma glucose concentration declined rapidly to

3.1 mM during exercise bout 2. The subjects were able to tolerate only an average of 10 ± 1 min of exercise before they became fatigued (range, 6-12 min). The cyclists' ability to oxidize carbohydrate did not increase above fatigued levels, as reflected by the R value (Figure 8-2).

These findings during the placebo trial agreed with the concept that carbohydrate depletion (e.g., muscle glycogen depletion and low blood glucose concentration) caused fatigue. The 20-min rest period allowed blood glucose to increase slightly, but it quickly declined and fatigue resulted after only an additional 10 min of exercise.

Glucose Infusion. To ensure that the blood glucose concentration was restored to normally high levels and that it was maintained during exercise bout 2, glucose was infused intravenously using a Harvard syringe pump. Infusion of a priming dose (4.1 ± 0.8 g) elevated plasma glucose to 4.6 ± 0.4 mM at the start of exercise bout 2. Blood samples were obtained every 5 min during exercise, and the rate of glucose infusion was adjusted in order to maintain blood glucose in the range of 4.5-5.5 mM. In this way it was possible to ensure that the supply of glucose presented to the exercising musculature was adequate. Another important aspect of this infusion trial was that it provided an accurate estimate of the rate at which the exercising musculature was relying upon blood glucose for energy. The rates of glucose removal from blood and oxidation are approximately equal to the rate of glucose infusion when the glucose concentration in the blood remains stable, as shown in Figure 8-2. Stated another way, when glucose infusion does not change the blood glucose concentration, this indicates that the rate of entry equals the rate of removal. Almost all of the infused glucose was probably taken up and oxidized by the exercising musculature because insulin concentrations remained low (9-11 μU/ml) and the muscle glycogen concentration in the vastus lateralis remained low (40-47 mmol of glycosyl units per kilogram of muscle) during exercise bout 2.

In order to maintain the plasma glucose concentration at 4.5-5.5 mM, glucose had to be infused at an average rate of 1.08 ± 0.06 g/min during exercise bout 2. This suggests that the infused glucose was being taken up and oxidized by the exercising musculature and other tissues at a similar rate. During this period, the rate of total carbohydrate oxidation was 1.6 g/min. It appears that approximately 70% (i.e., 1.1/1.6) of the carbohydrate energy was provided by the infused glucose. It should be realized that endogenous glucose, from gluconeogenesis and liver glycogenolysis, was probably oxidized in addition to the infused glucose and therefore it is possible that even more than 70% of the carbohydrate energy was provided by total glucose oxidation.

As shown in Figure 8-2, glucose infusion increased the rate of carbohydrate oxidation, as reflected by R, above the levels associated with fatigue (i.e., R of 0.81). Fatigue was also reversed with glucose infusion. The cyclists exercised for an additional 43 ± 5 min (range 27-60 min; $P < 0.05$ versus placebo) during exercise bout 2 before they again became fatigued. Fatigue during exercise bout 1 therefore appears to be due primarily to an inadequate supply of carbohydrate for the exercising musculature, which can be reversed for 43 min with a high rate of glucose infusion (Coggan and Coyle, 1987).

Although it is not practical to infuse glucose intravenously in field situations, these data are important because they indicate that the exercising musculature relies heavily upon blood glucose for fuel during the later stages of prolonged exercise. Therefore, it is not critical that glucose supplementation occur throughout exercise, since it does not spare muscle glycogen utilization and liver glycogen can adequately maintain blood glucose during the early stages of exercise. It is the availability of blood glucose late in exercise that is critical, as demonstrated by the fact that exercise could be maintained for an additional 43 min after fatiguing when glucose was readily availabel through infusion. More importantly, for fatigue to be delayed and for the blood glucose concentration to be maintained, glucose must enter the blood at the rate of more than 1 g/min in trained cyclists. Therefore, feeding schedules and drink composition (e.g., carbohydrate concentration) should be designed with the aim of providing the exercising musculature with 1 g of glucose per min late in exercise. As shown below, in order to provide the exercising musculature with glucose at these high rates late in exercise, carbohydrate ingestion must begin a given length of time before fatigue.

Carbohydrate Ingestion. Ingestion of approximately 200 g of carbohydrate [50% solution containing glucose polymers, sucrose (Exceed, Ross Laboratories)] during the 20-min rest period restored the blood glucose concentration to 5.1 ± 0.4 mM at the beginning of exercise bout 2 (Figure 8-1). Carbohydrate oxidation was also restored during the first 10 to 15 min of exercise. However, the plasma glucose oxidation declined progressively to 3.9 ± 0.3 mM during exercise bout 2. Fatigue occurred after an average of 26 ± 4 min of further exercise (range, 11-44 min). This was significantly ($P < 0.05$) longer than that when the placebo solution was ingested (10 ± 1 min) but significantly less than that when glucose was infused (43 ± 5 min). Fatigue was preceded not only by declining blood glucose but also by a reduction in the rate of carbohydrate oxidation or R (Figure 8-2).

The progressive reduction in blood glucose during exercise following carbohydrate ingestion and earlier fatigue compared with that after infusion

with glucose suggests that ingested carbohydrate cannot enter the blood quickly enough to maintain the blood glucose concentration and meet the energy requirements of exercise. Therefore, a person generally should not wait until he or she is fatigued to ingest carbohydrate. This agrees with the empirical observation of competitive cyclists that one should feed before becoming hungry.

Interpretation. These findings indicate that people should not wait until they are fatigued before they ingest carbohydrate, because it is likely that the rate of entry of glucose into the blood is too slow to match the rate of removal. We directly demonstrated through glucose infusion that the rate of glucose removal from blood can be well in excess of 1 g/min. These findings were somewhat anticipated based upon the experience of cyclists in competition. We therefore thought it practically important to determine also how long before the point of fatigue a cyclist should begin ingesting carbohydrate in order to restore and maintain blood glucose throughout exercise while improving performance ability.

FEED BEFORE FATIGUE

During a fourth trial the cyclists ingested approximately 200 g of carbohydrate (i.e., 3 g/kg of body weight) in a 50% solution (Exceed, Ross Laboratories) prior to the point of fatigue. The feeding was given after 135 min of exercise, which was on average approximately 35 min prior to the point of fatigue when a placebo solution was ingested. Based upon previous gastric emptying experiments (Foster et al., 1980), we reasoned that 35 min might be long enough to allow a sufficient amount of glucose to enter the blood.

Performance

Figure 8-3 compares the responses to exercise with placebo as opposed to the responses when carbohydrate was ingested after 135 min. Fatigue occurred after 170 ± 10 min when placebo was ingested and was delayed 21% and occurred after 205 ± 14 min when carbohydrate was ingested ($P < 0.05$). All subjects but one demonstrated an improvement in performance, with fatigue delayed by 25 to 58 min. The one individual who did not improve when fed before he became fatigued appeared to become depleted of carbohydrate prematurely during this trial in comparison with his other

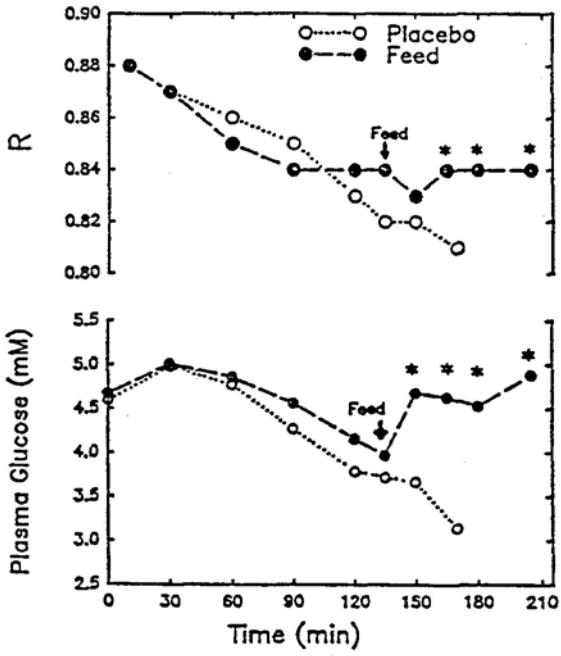

FIGURE 8-3 Respiratory exchange ratio (R) and plasma glucose responses to exercise bout 1 when a placebo was ingested compared with that when a glucose polymer solution (Feed) was ingested 35 min prior to the estimated point of fatigue. The asterisks indicate that Feed was significantly higher than Placebo ($p<0.05$). Source: Coggan and Coyle, 1989.

trials, with declines in R and in plasma glucose after 105 min of exercise to values similar to those observed at fatigue (145-167 min) in his other trials. Because fatigue seemed imminent, the carbohydrate drink was provided at 105 min. As a result, plasma glucose and R increased, and he was able to continue exercising for an additional 45 min.

Plasma Glucose Response

As shown in Figure 8-3, carbohydrate feeding after 135 min reversed the decline in plasma glucose and successfully restored and maintained euglycemia throughout the remainder of exercise. The decline in R was also halted. These findings indicate that fatigue can be effectively delayed by 35 min in cyclists when carbohydrate feeding is not begun until 35 min prior to

the time that fatigue would occur without feeding. The 35-min delay of fatigue when subjects were fed prior to fatigue was of similar magnitude to the 43 min of further exercise that was permitted by intravenous glucose infusion.

Interpretation

These findings suggest that ingested carbohydrate can provide energy at sufficient rates during the later stages of prolonged exercise when it is given at least 35 min prior to the point at which blood glucose supplementation becomes critical. As discussed previously, a person should not wait until he or she is fatigued before ingesting carbohydrate. We expect that the effectiveness of carbohydrate feeding in delaying fatigue, when first provided at a time less than 30 min prior to anticipated fatigue, varies among individuals. Large differences in individual response were observed when individuals were fed at fatigue, as previously discussed. We therefore recommend that carbohydrate feeding should begin, at the latest, 30 min prior to the anticipated fatigue, unless there is reason to believe that given individual can wait longer but still fully benefit from the feeding (i.e., get it into the blood at high rates).

It should be emphasized that the present study was designed to determine how long a cyclist can wait before beginning to feed during prolonged exercise. Although we have determined that he or she can, if need be, wait until approximately 30 min prior to fatigue before beginning to feed, we are not suggesting that this is the ideal feeding schedule. It only indicates that if a person must wait this long before feeding, for whatever reason, the potential for performance enhancement by carbohydrate feeding is not appreciably compromised.

Carbohydrate feedings appear to be an important energy source late in exercise. An obvious question is whether there is any advantage to ingesting carbohydrate throughout exercise or whether an individual should wait until the later stages of exercise before beginning to feed. In separate studies we have shown that fatigue can be delayed 30-60 min both when feedings are taken throughout exercise (Coyle et al., 1983, 1986) and when they are initiated 35 min prior to the point of fatigue when fasted (this study; Coggan and Coyle, 1989). Therefore, we have no reason to recommend that one feeding schedule is superior to the other. The important aspect is that the ingested carbohydrate be capable of supplementing blood glucose stores at a rate of over 1 g/min late in exercise (Coggan and Coyle, 1987).

Carbohydrate will be availabel to supplement blood glucose late in exercise if feedings are taken throughout exercise. In our previous studies (Coyle et al., 1983, 1986), cyclists began feedings after 20 min of exercise (approximately 70 g) and continued feeding every 20 min thereafter (20-28 g). A person should determine whether this type of regimented feeding schedule is possible and tolerable during prolonged activity. If it is not possible to ingest carbohydrate throughout prolonged intense exercise, a feeding schedule should be adopted that allows the ingested glucose to enter the blood at a rate of approximately 1 g/min late in exercise. It should be realized that these recommendations are specific to intense exercise (i.e., cycling at 70%-75% $\dot{V}_{O_2\,max}$) performed for prolonged periods (i.e., 3-4 h).

METABOLIC AND PERFORMANCE EFFECTS OF CARBOHYDRATE FEEDING DURING MILD- TO MODERATE-INTENSITY EXERCISE

Although the benefits of carbohydrate feeding during prolonged exercise at approximately 70% $\dot{V}_{O_2\,max}$ are clear, it has not been firmly established that carbohydrate feeding delays fatigue during exercise of mild to moderate intensities (i.e., 30%-50% $\dot{V}_{O_2\,max}$). The energy for mild exercise is derived largely from the oxidation of blood-borne substrates such as glucose and fatty acids with less reliance upon muscle glycogen (Ahlborg and Felig, 1982; Ahlborg et al., 1974; Gollnick et al., 1981; Pallikarakis et al., 1986: Pirnay et al., 1982). Carbohydrate feeding during exercise at 30%-50% $\dot{V}_{O_2\,max}$ results in an increase in carbohydrate oxidation and a sparing of endogenous carbohydrate stores (Ahlborg and Felig, 1982; Ahlborg et al., 1974; Ivy et al., 1983; Pallikarakis et al., 1986; Pirnay et al., 1982). It appears that the exogenous ingested glucose is oxidized in place of endogenous glucose (i.e., liver glycogen) and free fatty acids. It is not clear whether carbohydrate feeding during prolonged mild-intensity exercise alters muscle glycogen degradation or whether it stimulates muscle glycogen resynthesis in humans (see the paper by J. L. Ivy, this volume).

It does appear that carbohydrate feeding has the potential to delav fatigue during some types of exercise that elicit low percentages of $\dot{V}_{O_2\,max}$. For example, Ivy et al. (1983) observed that carbohydrate feeding during prolonged uphill walking allowed subjects to exercise 31 min longer than when they received a placebo (4 h 59 min versus 4 h 28 min; $P < 0.05$). Although the exercise intensity was only 45% $\dot{V}_{O_2\,max}$, subjects relied heavily upon carbohydrate for energy and fatigued during the fifth hour, primarily because of localized fatigue in the lower leg.

Our concept is that carbohydrate feedings have the potential to delay fatigue because they maintain the blood glucose concentration late in exercise and become an important source of carbohydrate energy without which exercise cannot be tolerated. The salient point is that exercise should be of sufficiently high intensity to demand a prerequisite rate of carbohydrate oxidation. Exercise intensity cannot simply be judged according to the percentage of whole-body maximal oxygen uptake that is elicited. It is possible that exercise performed with a relatively small muscle mass may not elicit a large percentage of $\dot{V}_{O_2\,max}$ but that it can be relatively stressful for a particular muscle group, thus stimulating reliance upon carbohydrate in certain muscle groups or fibers. Stated another way, exercise that is mild regarding the percentage of $\dot{V}_{O_2\,max}$ can be strenuous enough to cause localized fatigue if a relatively small amount of muscle performs a disproportionate amount of work. It is quite likely that field soldiers who performed repetitive motions of lifting, climbing, or walking uphill experience localized muscle fatigue resulting from carbohydrate depletion, and it is possible that they would benefit from carbohydrate feeding. To our knowledge, however, this has yet to be carefully investigated.

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9

Acute Diarrheal Diseases

Robert Whang[1]

INTRODUCTION

Diarrheal diseases represent an enormous health problem worldwide. The annual economic impact of these diseases represents significant losses that can be measured in the billion of dollars of lost productivity and the loss of health resources necessary to treat diarrheal diseases. Mortality in the young and the loss of economic potential from these premature deaths are inestimable when one factors in the morbidity, pain, and suffering resulting from these diseases. Diarrhea can be defined as two to three times the usual number of bowel movements having a liquid consistency, or diarrheal stool can be defined as one that assumes the shape of the container (Samadi et al., 1983). On a worldwide basis it is estimated that 750 million to 1 billion cases occur annually among children under 5 years of age, accounting for between 3 million and 6 million deaths. Diarrheal diseases are second only to respiratory disease in frequency and prevalence in underdeveloped countries (Gorbach and Hoskins, 1980). The success or failure of military campaigns from antiquity to modern times has been influenced by the presence or absence of diarrheal diseases. In recent times, for the years 1966 to 1968, the U.S. Army in Vietnam had peak months with an annualized rate of 70 cases per 1,000 (Ognibene and Barrett, 1982).

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The etiology of acute diarrheal diseases can be divided into three categories: viral, bacterial, and parasitic. In developed nations, such as the United States, rotaviruses and Norwalk-like viruses (10%-27%) are frequent causes of diarrhea (Guerrant et al., 1985). In contrast, in the tropics enterotoxigenic *Escherichia coli* (*E. coli*) (21%-23%), *Shigella,* (8%-11%), and *Campylobacter* (7%-14%) predominate as causative agents of acute diarrhea. Similarly, enterotoxigenic *E. coli* (47%), *Shigella* (1%-22%), and *Salmonella* (4%-7%) are the principal causative agents in travelers' diarrhea. It is anticipated that troops rapidly deployed from the continental United States to tropical areas will be at risk for travelers' diarrhea. Enteric infections can be divided into three types: luminal, mucosal, and systemic (Guerrant et al., 1985). Luminal enteric infections are caused by organisms such as *E. coli, Vibrio cholera,* (*V. cholera*) *Staphylococcus,* and *Giardia.* Diarrhea is caused by enterotoxins that interfere with absorption in the small bowel. In luminal enteric infections, diarrheal stools are watery and there are no fecal white blood cells. Mucosal enteric infections can be caused by *Shigella, Campylobacter jejuni, Salmonella,* and *Clostridium difficile.* There is colonic mucosal invasion by bacteria, causing an inflammatory dysentery with the presence of fecal polymorphonuclear leukocytes. In systemic enteric infections the ileum is involved with the potential invasion of the blood stream and enteric fever. Examples of causative agents are *Salmonella typhi, Yersinia,* and *Campylobacter fetus.*

What is the distribution of diarrheal diseases worldwide? Travelers' diarrhea is found in Mexico, Central and South America, the Caribbean, Africa, the littoral Mediterranean, and Asia (Steffen, 1986). The incidence of travelers' diarrhea ranges as high as 50% in these regions. The incidence of dysentery (diarrhea with fever or blood in stools) among travelers to Mexico, Central and South America, Africa, and Asia ranges upwards of 9%-11%.

Signs and symptoms of travelers' diarrhea include gas (79%), fatigue (74%), cramps (68%), nausea (61%), fever (56%), abdominal pain (55%), anorexia (53%), headaches (39%), chills (30%), and vomiting (29%) (Gorbach and Hoskins, 1980). In small bowel diarrhea caused by *E. coli, Giardia, V. cholera,* or reovirus, the location of pain is in the midabdomen, with large volumes of watery diarrhea causing dehydration (Gorbach and Hoskins, 1980). Proctoscopy is normal. With large bowel diarrhea caused by *Shigella,* invasive *E. coli,* or amebiasis, the pain is in the lower abdomen and in the rectum. The stool volume is usually small and may be mucoid (dysenteric). Blood and leukocytes are very common in the stool. Proctoscopic findings include a friable and hemorrhagic mucosa and mucosal ulcers. What is the efficacy of prophylactic treatment of acute diarrheal diseases? For Peace Corps volunteers, doxycycline, 100 mg twice weekly,

provided protection in 27% of individuals (Santosham et al., 1981). However, doxycycline at 100 mg once daily provided protection in 81% of U.S. military personnel in Mexico (Freeman et al., 1983). In a multidrug study in Mexico, bactrim provided 71% protection during a 21-day study, and 95% protection for a 14-day study, bicozamycin provided 100% protection, and 88% of subjects taking norfloxacin were protected from travelers' diarrhea (Dupont et al., 1986). Bismuth subsalicylate in liquid form (60 ml four times a day) and tablets (600 mg four times a day) provided 77% and 87% protection, respectively (Steffen et al., 1986). Thus, both antibiotic and nonantibiotic prophylaxis provided excellent short-term protection ranging from 14 to 21 days.

Guerrant et al. (1985) state that the appropriate treatment for the vast majority of cases (of acute diarrhea) is simple and effective: oral glucose-and electrolyte- containing rehydration solution. Effective repletion of extracellular and total body water is accomplished by enhancement of small bowel reabsorption of sodium and water by glucose (solvent drag) (Field, 1977). A second generation of oral rehydration solutions (ORSs), the so-called super ORSs, are currently under study (Edelman, 1985). In these super ORS formulations, glycine as well as rice powder augment the effect of glucose in enhancing sodium and water reabsorption by the gut. For example, compared with glucose and electrolyte ORSs, glycerine, glucose, and electrolyte ORSs reduced the volume of stool output from 253 to 126 ml/kg as well as the duration of acute diarrhea from 43 to 30 h (Edelman, 1985).

The ideal ORS for the U.S. Army would serve multiple clinical uses: (1) alleviate fasting and prevent heat injury in encapsulated troops - Military Operational Protective Posture-A (MOPPA), (2) prevent heat injury, (3) treat heat casualties except for heat stroke, and (4) treat acute diarrhea. A powder formulation (Armyde) containing Na, 22.8 meq; Cl, 25.5 meq; K, 9.5 meq; Mg, 5.2 meq; PO_4, 3.2 mg; and glucose, 25 g per packet, was studied under moderate field heat conditions in June 1988 at Fort Hood, Texas. These studies were carried out jointly by the Military Nutrition and Heat Research Division, U.S. Army Research Institute of Environmental Medicine, and the 44th Evacuation Hospital (an Army Reserve Unit) and the results detailed in a technical report (Rose et al., 1989). It is designed such that one packet of this glucose electrolyte powder diluted in one canteen of potable water would be used for heat injury and heat casualty treatments (Na, 22.8 meq/liter; Cl, 25.5 meq/liter; K, 9.5 meq/liter; HCO_3, 10 meq/liter; Mg, 5.2 meq/liter; PO_4, 3.2 meq/liter, and glucose, 25 g, whereas two packets per canteen (Na, 45.6 meq/liter; Cl, 51 meq/liter; K, 19 meq/liter; HCO_3, 20 meq/liter; Mg, 10.4 meq/liter; PO_4, 6.3 meq/liter; and glucose, 50 g/liter) would be used in the treatment of acute diarrhea. In this

initial study no clinical symptoms were noted among the subjects who drank Armyade. Biochemical assessment (serum creatinine, chloride, total protein, albumin, glucose, sodium, potassium, magnesium, blood urea nitrogens, cholesterol, triglyceride) of subjects following 8 days of drinking Armyade did not demonstrate any abnormal changes. While the safety of Armyade appears to have been confirmed, the efficacy under rigorous field conditions in the heat remains to be demonstrated in future studies.

With respect to the potential of acute diarrheal disease and heat injuries in troops rapidly deployed from the continental United States to the tropics, I propose consideration of the following future operational approach: (1) diarrhea prophylaxis (e.g., antibiotic or bismuth subsalicylate tablets), (2) oral rehydration solution (e.g., Armyade at two packets per canteen), and (3) heat injury prophylaxis (e.g., Armyade at one packet per canteen). The purpose of this approach is to conserve and maximize fighting strength in troops who are rapidly deployed to those areas where travelers' diarrhea is a significant problem, such as Central and South America, Africa, or Asia.

CONCLUSIONS

1. Diarrheal diseases are a major health problem in developing countries (Asia, Africa, and Latin America) with an incidence of approximately 750 million to 1 billion cases per year in children under 5 years of age.
2. Diarrheal diseases have afflicted armies from antiquity to modern times.
3. World-wide, glucose-electrolyte rehydration solutions represent a significant contribution to the treatment of diarrhea and have demonstrable efficacy.
4. Oral rehydration solutions are still undergoing modification, including the addition of glycine to the glucose electrolyte solution or rice powder in place of glucose (super ORSs).
5. To ensure maximum fighting efficiency for infantry units deployed at the front or behind enemy lines, consideration should be given to providing diarrhea prophylaxis (e.g., doxycycline) and glucose-electrolyte packets for treatment of diarrhea while these units are in action.
6. There appears to be merit in considering a multipurpose (heat injury prevention, treatment, and replacement of diarrheal losses) glucose-electrolyte packet for use by field troops.

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10

Potassium Deficiency as the Result of Training in Hot Weather

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INTRODUCTION

It has been established by a number of investigators that potentially serious potassium deficiencies can occur in soldiers under conditions of intense, prolonged training in hot weather. Studies conducted during or after World War II (Conn, 1949; Streeten et al., 1960), and confirmed by others since that time (Gordon and Andrews, 1966; Knochel, 1977a; Knochel et al., 1972; Malhotra et al., 1976; Toor et al., 1967), have shown that men working in the heat for 8 to 12 hours on successive days can secrete up to 12 liters of sweat per day. Although measurements of the potassium concentration in sweat have shown values ranging between 2.5 and 21 mEq/liter (Robinson and Robinson, 1954), the majority of investigators have found that sweat produced under conditions of hard work generally ranges between 8 to 10 mEq/liter (Beller et al., 1975; Cage et al., 1970; Dobson and Abele, 1962; Drinkwater et al., 1982; Emrich et al., 1970; Furman and Beer, 1963; Grand et al., 1967; McConahay et al., 1964; Mor et al., 1985; Nose et al., 1988; Verde et al., 1982). This implies that sweat losses alone could explain the development of potassium deficiency during training in the heat.

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Potassium deficiency under the conditions described above could also occur as a result of diffuse skeletal muscle injury secondary to intense exertion, especially when conducted during hot weather. Thus, realizing that muscle cell injury or rhabdomyolysis, as reflected by elevated muscle enzyme activity in the blood, invariably occurs when an untrained individual is subjected to severe muscular exercise in the heat (Demos et al., 1974), it would seem logical to assume that injured muscle cells could not retain sufficient ion transport activity or membrane integrity to maintain the normal distribution of sodium and potassium ions between the muscle cell and the plasma (Bilbrey et al., 1973). If this were so, potassium would leak from muscle cells and be excreted into the urine.

A study was designed to examine these possibilities (Knochel et al., 1972). Healthy young Army recruits who were in good physical condition but untrained and poorly acclimatized to heat were studied during the summer and another group was studied during the winter. The two groups were studied while they were undergoing basic training conducted at Fort Sam Houston, Texas. Training activities were identical to those performed by recruits in basic training at other basic training facilities, with the exception that weapons training was replaced by field training for medical corpsmen activities. Training activities on many of these days were of 12 to 14 hours in duration. The caloric expenditure under such conditions probably exceeds that associated with weapons training. Each day the men consumed a constant diet containing 4,135 kcal that included 100 mEq of potassium, 149 g of protein, 158 g of fat, and 556 g of carbohydrate. Sodium chloride intake was 150 mEq/day in one group and 350 mEq/day in another. The men consumed their diets under the direct observation of a trained dietitian each day throughout the study. Total body potassium content was estimated by weekly determination of exchangeable ^{42}K, which was then indexed as a function of lean body mass. Lean body mass was estimated from body density and from total body water. Each Thursday morning of the study body density was estimated by weighing the men underwater and measuring the total body volume after subtracting measured lung capacity. On the same morning, total body water was estimated by tritium dilution. Tritiated water was given by mouth. Tritiated aldosterone and $NaS_{35}O_4$, which were used to measure aldosterone secretory and excretory rates and extracellular fluid volume, were administered intravenously. Sampling for these determinations was conducted at appropriate intervals after measurement of total body volume. On the same day, a 24-h urine collection was obtained for measurements of creatine, creatinine, urea, calcium, phosphorus, electrolytes, and osmolality. Blood was obtained for measurements of the same biochemical parameters, and in addition, creatine kinase activity was measured as an index of muscle

damage. Plasma renin activity was measured in the men before they arose in the morning and again before the noon meal.

Table 10-1 shows average values for total body K^+, urine K^+, and K^+ from clothing eluates for the subjects studied in both hot and cool weather. In the six subjects studied during training in hot weather, the potassium deficit measured on day 4 averaged 348 mEq, and on day 11 it averaged 463 mEq (Knochel, 1977a; Knochel et al., 1972). The maximum deficits ranged between 370 and 572 mEq. In two men, the maximum deficit appeared on day 4, and in one man it appeared on day 18; in the remainder of the men it occurred on day 11. The average maximum deficit was 510 mEq. Total body potassium as a function of lean body mass fell from 52.2 to 42.5 mEq/kg, thus suggesting a reduction of intracellular muscle potassium content. Thereafter, total body potassium rose during successive weeks, so

Table 10-1 Potassium as Measured in Hot and Cool Weather

	Hot Weather				Cool Weather[a]
	Total Body (mEq/d)	Urine K (mEq)	Clothing K Eluate (mEq)	Total Body K (mEq)	Urine K (mEq/d)
Control	3252	66	29	3330	77
4	2904	57	38	3395	58
11	2789	61	19	3383	82
18	2995	77	24	-	68
25	3235	79	25	3586	62
32	3495[b]	49	14	3716	64

[a] In cool weather, ^{42}K was not availabel for the 18 day study.
[b] Average of 5 subjects only.

that by week 5 the amount of potassium restored was about 200 mEq. The value of ^{42}K per lean body mass was the same upon completion of training as it was during the first measurement. Potassium deficiency, defined as a reduction of ^{42}Ke, did not occur during training in the winter. In the men who trained in the winter, total body potassium steadily increased from an initial value of 3,330 mEq to a final value of 3,716 mEq. When values for total body potassium over lean body mass were matched, there was a rise

from 53.3 to 56.4 mEq/kg. This represented a significant change and suggested that there was an increase in the potassium concentration in skeletal muscle as a result of training. As is pointed out below, subsequent studies in dogs confirmed this notion. The fact that the men who trained in hot weather did not show an increase in potassium per kilogram of lean body mass indeed suggested that muscle injury might have prevented such a change. Although none of the subjects became frankly hypokalemic, most values were in the low normal range, that is, between 3.4 and 3.7 mEq/liter at the time of peak potassium deficiency. The absence of frank hypokalemia possibly indicates coincident muscle injury. Other studies showed that aldosterone was produced excessively in terms of sodium intake. However, when expressed as a function of sodium excretion, both secretory rates and excretory rates of aldosterone were perfectly appropriate. Renin activity measured before the men arose each day was often markedly elevated and became more elevated following maintenance of an upright posture during the morning hours, as would be expected. There also occurred a substantial rise in total body water, an expansion of extracellular fluid volume, and an increase of inulin clearance from an average value of 101 ml/min per 1.72 m_2 of body surface area to a value of 123 ml/min (Knochel et al., 1974).

Serum creatine kinase activity was within normal limits at the time of initial measurement. However, this value and the value for creatine excretion rose markedly by week 2 of training (Knochel et al., 1974), suggestive of muscle injury. Subsequently, both values fell to the normal range. Other indices suggestive of skeletal muscle injury that peaked on week 2 of training included a drop in the total serum calcium concentration that was not associated with changes in the serum protein concentration and an elevation of serum phosphorus. Frank hyperuricemia occurred in all of these individuals. In addition, uric acid excretion into the urine became abnormally high and was compatible with major muscle injury or rhabdomyolysis (Knochel and Carter; 1976; Knochel et al., 1974). These values also peaked during week 2 of training. At the time of peak potassium deficiency, average values for potassium excretion into the urine were 72 mEq/day. This is considered to be greatly in excess of that anticipated in potassium depletion and suggests either an obligatory loss as a result of muscle injury or that losses were the result of renal tubular sodium-potassium exchange mediated by aldosterone.

The foregoing studies were interpreted to indicate that modestly severe potassium deficiency occurs as a result of intense training in hot weather. This did not occur under identical training conditions during cool weather. Although sweat cannot be collected accurately under such conditions, canteen counts confirmed water intakes of between 10 and 15 liters/day during hot weather. Since body weight did not change appreciably or fell,

and since urine volumes were seldom over 1.5 liters/day, the assumption was made that the subjects produced huge quantities of sweat. Because of data suggesting that the sweat potassium concentration under such conditions averages 9 or 10 mEq/liter, it was assumed that the major factor responsible for potassium deficiency in these subjects was sweating. A net loss of only 42 mEq/day average total loss of 463 mEq divided by 11 days would have been necessary to result in the potassium deficiency observed at the end of the third measurement of ^{42}K on day 11. The estimated loss in sweat was based upon a total intake of 100 mEq/day of potassium. On day 11, the average urinary excretion was 61 mEq. Allowing for an average unmeasured stool loss of 5 mEq/day, the unaccounted K loss was $100 - (61 + 5) + 42$ or 76 mEq/day. This quantity of K^+ could be lost by secreting an average of 8 or 9 liters of sweat volume per day. The brisk excretion of potassium into the urine, despite potassium deficiency, was compatible with an obligatory loss resulting from muscle cell injury or could have been mediated by renal tubular sodium-potassium exchange induced by aldosterone. The fact that potassium deficiency did not occur in men who trained in cool weather suggests that sweating was responsible for the bulk of potassium loss. Nevertheless, this does not completely exclude the possibility that skeletal muscle injury caused potassium loss, because it is known that training at such intensities results in much more severe skeletal muscle injury when conducted under hot rather than cool conditions.

Costill has performed several studies in which he examined muscle potassium content (samples obtained by needle biopsy) or by measuring losses in sweat and urine. He reported that he was not able to demonstrate a significant potassium deficit occurring in healthy young men who cycled or walked on a treadmill for 1 1/2 to 2 hours per day. These studies were conducted in environmental chambers maintained at 40° or 30°C dry bulb temperature and 23.5% or 46% relative humidity respectively (Costill, 1975; 1986). However, in his subjects, the total sweat production per day amounted to about three liters and the amount of work performed by these individuals is by no means comparable to that encountered by a military recruit in basic training who works day after day in hot weather. Training exercises under such conditions are exhausting and commonly exceed twelve hours per day. The temperatures in our studies (Knochel et al., 1972) were also very high with a daytime outdoor maximum varying between 100 and 108°F on days 1 - 5, and 96 to 100° between days 5 and 11. Thus, although the environmental temperatures were within the same range, on the basis of level of exercise performed I do not believe the studies are comparable.

Additional studies were conducted in our laboratory using experimental animals to examine the possible effects of potassium deficiency on several important modalities including muscle glycogen metabolism, carbohydrate

metabolism, glucose utilization, and muscle blood flow. A large body of evidence indicates that a normal concentration of potassium ions in skeletal muscle is a prerequisite for glycogen synthesis (Bergstrom and Hultman, 1966b; Gardner et al., 1950; Hastings, 1941; Knochel, 1977b; Losert, 1968; Torres et al., 1966). Our studies in dogs made potassium deficient by dietary deprivation in conjunction with administration of desoxycorticosterone, confirmed that muscle glycogen content falls to almost immeasurable values as a result of potassium deficiency (Knochel, 1987). Normal dogs also show the "supercompensation" phenomenon that was described by Bergstrom and Hultman in humans (Bergstrom and Hultman, 1966a). Thus, if a muscle is exercised to the point of exhaustion, glycogen stores become virtually zero. If glycogen content is then measured in that muscle daily for four or five days, the quantity increases to four or five times the original resting value. This is defined as glycogen supercompensation. The phenomenon is reproducible in the normal dog (Knochel, 1987). In contrast, stimulation of muscle contractions to the point of exhaustion by external electrodes followed by daily biopsy of the exercised muscle shows that the supercompensation phenomenon is eliminated by potassium deficiency (Knochel, 1987). Utilizing the isolated gracilis muscle preparation, we also showed that glucose utilization in potassium deficient muscle is perfectly normal (Knochel, 1987). However, electrical stimulation of the muscle shows reduced endurance that can be correlated exactly with reduction in muscle glycogen content. Finally, studies were conducted to measure the effect of potassium deficiency on skeletal muscle blood flow (Knochel, 1972). Stimulation of muscle cell contraction is associated with a release of potassium ions into the muscle interstitium at which site the local hyperkalemia acts as a vasodilator to trigger increased muscle blood flow with exercise. The hypothesis was made that in the presence of potassium deficiency, potassium would not be released adequately during contraction to increase muscle blood flow, and ischemic muscle damage would follow. Again, using the isolated gracilis muscle, we showed that electrically stimulated exercise of the normal muscle was associated with an increase of muscle K release from 0.4 to 32 μEq/100 g/min and, simultaneously, a rise of muscle blood flow from 6.2 ml/100 g/min to 24 ml/100 g/min. By contrast, K-deficient dogs showed a marked reduction in K release. During stimulated exercise, K-release rose from zero to only 2.1 μEq/100 g/min and blood flow from 6.0 to 7.8 ml/100 g/min (Knochel, 1972). If potassium were administered arterially to the contracting potassium deficient muscle, blood flow promptly increased. Finally, we showed that work conducted by potassium deficient muscle was initially equal to normal in terms of contractile strength but could not be sustained (Knochel, 1987). Following exercise to exhaustion, potassium deficient but not normal muscle becomes necrotic (Knochel,

1972). Observations in humans (Knochel, 1978; Knochel, 1982) have shown that potassium deficiency induced by a variety of mechanisms can be responsible for frank muscle necrosis. Thus, our finding that potentially serious potassium deficiency occurs during training in a hot climate infers that the associated muscle injury could be partially explained by potassium deficiency.

Mention was made previously that men who trained in cool weather showed an increase of potassium per kilogram of lean body weight, suggesting an increase in the muscle potassium concentration. Since serum potassium values in highly trained endurance runners may be frankly hypokalemic in the absence of potassium deficiency, the possibility was suggested that muscle cells may become electrically hyperpolarized as a result of training. A biologic reason why this might happen would be to help forestall or dissipate exercise-induced hyperkalemia. This possibility was studied both in humans and animals. In dogs, endurance training on the treadmill caused a reduction of the serum potassium concentration, and with electrical hyperpolarization of muscle cells there was an increase of resting membrane potential measured by Ling electrodes from a control value of 92 ± 5 mV to a training value of 103 ± 5 mV. The muscle potassium concentration rose from 139 ± 7 to 148 ± 14 mEq/liter, and serum potassium fell from 4.2 ± 0.2 to 3.9 ± 0.3 mEq/liter. Measurements of magnesium-dependent Na, K ATPase activity in sarcoplasmic membranes from the trained dogs compared with that in normal dogs showed a marked increase in enzyme activity (Knochel et al., 1985). Direct measurements of resting membrane potential (anterior tibial muscle) on six highly trained long-distance competitive runners from Texas Christian University showed an average value of 98.8 mV compared with normal resting values of 91.5 mV in age-matched untrained men. While the actual implications of such studies are far from clear, at least preliminary studies in dogs indicated that the capacity to dissipate hyperkalemia and to withstand otherwise fatal infusions of potassium chloride were produced by exercise training.

The foregoing data suggest that changes in potassium metabolism and balance play a critically important role in exercise and the ability to become trained. Potassium deficiency may occur as a result of intense training in hot weather. Comparable levels of potassium deficiency in experimental animals impair muscle blood flow during exercise and cause ischemic necrosis of skeletal muscle (rhabdomyolysis). Potassium deficiency also impairs energy storage by reducing glycogen synthesis in resting muscle or that which occurs in response to exercise. Finally, in proportion to reduced glycogen synthesis, exercise endurance is impaired. If physical training in the heat is of such intensity and duration to cause muscle injury, it would appear that potassium loss would be obligatory. At the present time, our understanding

of exertional rhabdomyolysis is much more clear than it was prior to publication of our data in 1972 (Knochel et al., 1972). Clearly, the fact that the highest level of CK activity in serum, the highest levels of creatine excretion, the most pronounced hyperuricemia and uricosuria, the hyper-phosphatemia and hypocalcemia occurred simultaneously with peak potassium deficiency, strongly suggests that muscle cell injury was the primary factor responsible for a reduction of total body potassium (Knochel, 1982). It seems highly likely that if nitrogen balance and phosphorus balance would have been measured at the same time, these elements would have been similarly negative, confirming that a reduction of cellular mass had occurred as a result of injury. I suspect, but cannot prove from our data that potassium losses probably exceeded proportionate losses of phosphorus and nitrogen, primarily due to the fact that K losses in sweat were substantial and the possibility that brisk sodium excretion into the urine would favor disproportionate loss of potassium via the action of aldosterone. Whether potassium supplementation could overcome a deficit such as this is unlikely. Indeed, administration of a high potassium intake or potassium supplements to a person in whom skeletal muscle cells are temporarily injured and thus unable to take up potassium ions may be fraught with the hazard of hyperkalemia and potential cardiotoxicity.

In this special case of training in hot weather, rather than toying with the idea of potassium supplementation, perhaps we should consider either reducing the intensity of training, or conducting such exercises in geographic areas that would not impose such levels of heat stress.

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11

Shift in Body Fluid Compartments After Dehydration in Humans

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INTRODUCTION

Maintenance of blood volume is important for optimal regulation of both arterial blood pressure and body temperature during exercise and thermal stress (Fortney et al., 1981a,b; Fortney et al., 1983; Nadel, 1984). A reduction of the central circulating blood volume, due either to hypovolemia accompanying dehydration or dilation of the peripheral vasculature, results in a fall in cardiac filling pressure and stroke volume and, if uncompensated, also in cardiac output (Fortney et al., 1983; Miki et al., 1983a). Among the possible compensations is the body's ability to mobilize water from the extravascular to the intravascular space (Miki et al., 1983b; Mohsenin and Gonzalez, 1984; Morimoto et al., 1981; Nose et al., 1983).

Senay (1979) recently reviewed the dehydration literature and reported that water appeared to be lost from the plasma at a rate one to five times that of other fluid compartments during dehydration. Costill (1977) ascribed the relatively greater plasma water loss to movement accompanying the major ions lost in sweat and urine, which are those of the extracellular

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compartment. There would then be less mobilization of water from the intracellular fluid (ICF) space due to the smaller increase of extracellular osmolality. Durkot et al. (1986) reported that in rats a higher water loss occurred from the extracellular fluid (ECF) space than from the ICF space during dehydration of 10% body wt. Water movement might be linked to the electrolyte losses from each compartment, as suggested by Nose et al. (1985). These results suggest the necessity of measuring electrolyte balance to analyze water balance between fluid compartments.

It is well known that sweat [Na^+] decreases during the process of heat acclimation (Kirby and Convertino, 1986; Locke et al., 1951). However, there is no experimental evidence that shows a relation between [Na^+] and water mobilization from the ICF space.

The purpose of this study was to clarify the effect of sweat [Na^+] on water mobilization from the ICF compartment in conditions of thermal stress. We hypothesized that a lower sweat [Na^+] would be accompanied by a smaller reduction in plasma water loss during dehydration.

METHODS

Ten volunteers (nine male and one female) participated in this study. Certain of their physical characteristics are shown in Table 11-1. Each subject gave informed consent and passed a physical examination to screen for medical reasons that would prevent participation. The experimental protocol was approved by the Human Investigation Committee of the Yale University School of Medicine. Experiments were performed in the spring months.

Table 11-1 Characteristics of subjects (n = 10)

	Age (years)	Wt (kg)	$\dot{V}_{O_2\,max}$[a] ($ml.kg^{-1}.min^{-1}$)	Blood Volume (ml/kg)	Plasma Volume (ml/kg)
Mean	27.8	68.9	50.2	81.2	46.5
Range	23-33	48.6-83.7	36.4-62.9	61.0-102.3	33.5-61.4

[a] Maximal aerobic power.

Design

About 1-2 weeks before the experiment, maximal aerobic power ($\dot{V}_{O_2\,max}$) (cycle ergometer) and plasma volume [Evans blue dye dilution (Greenleaf et al., 1979)] were measured on each subject. On the day of the experiment, subjects reported to the laboratory normally hydrated but without breakfast, then entered an environmental chamber and rested in the sitting position for 30 min at a thermoneutral temperature [28°C, <30% relative humidity (rh)]. After a control blood sample (5 ml) was taken, subjects emptied their bladders and entered another environmental chamber (36°C, <30% rh). Body weight was measured to the nearest 1 g. Subjects then sat in the contour chair of the cycle ergometer in a semirecumbent position and had electrocardiogram electrodes put in place and a vinyl bag for collecting sweat placed on one forearm. Exercise (40% $\dot{V}_{O_2\,max}$)began for an initial 30-min period, followed by alternating 5-min rest and 15 min exercise periods. Exercise continued until body weight decreased between 2 and 3%. Total exercise time was 90-110 min. Sweat from the forearm bag was collected every 30 min of exercise; the bag for collecting sweat was changed from one forearm to the other in consecutive collection periods to minimize the pore occlusion, which influences excretion rate and electrolyte concentrations in sweat (Sohar et al., 1965). Heart rate was monitored each 5 min and oral temperature was measured during each of the nonexercise intervals to ensure that subjects were not overly strained.

After the cessation of exercise, subjects voided for collection of urine samples, were weighed, and then entered an adjacent chamber (28°C, <30% rh) for a seated recovery period without any fluid supply. A butterfly catheter was inserted into a superficial forearm vein and a 5-ml blood sample was taken within 10 min of the termination of exercise. Blood samples were also taken at the 30th and 60th min thereafter. Body weight was measured at 30 min.

Blood samples were separated into a 4-ml aliquot, which was transferred to a heparinized tube and placed on ice to be centrifuged later, and a 1-ml aliquot, which was immediately treated for hematocrit (Hct) and hemoglobin (Hb) analysis.

Measurements

From each blood sample we determined plasma osmolality by freezing point depression (model 3DII, Advanced Instruments) and plasma electrolytes ($[Na^+]$ and $[K^+]$, flame photometry, Instrumentation Laboratory model 443; $[Cl^-]$, Cotlove chloride titrator). These were expressed in meq/kg plasma

H_2O by correcting for plasma solids. To calculate interstitial [Cl^-], we multiplied plasma [Cl^-] by the Donnan factor (1.05). We also measured microhematocrit, hemoglobin concentration (refractometry). Plasma solid concentration was determined by drying plasma in a heating chamber at 90°C for 24 h. We determined volume and electrolyte concentrations from each sweat and urine sample. Average electrolyte concentration in sweat was also determined from all samples.

Calculations

Total body water loss (ΔTW) was estimated from body weight loss. Total sweat loss was calculated by subtracting total urine loss from total body water loss, assuming that water loss due to respiration was negligible (Morimoto et al., 1981). Electrolyte losses in sweat and urine were calculated by multiplying the volume of water loss by the electrolyte concentration of each fluid, respectively. The change in plasma volume (ΔPV) during an experiment was calculated from changes in the Hct and Hb concentrations (Elkinton et al., 1946).

We made determinations of ECF and ICF water by the Cl^- method (Costill et al., 1976). This method requires the following assumptions: (1) Cl^- loss in sweat and urine comes only from the ECF space; (2) the Donnan factor for Cl^- between plasma and the interstitial fluid (ISF) space is 1.05; and (3) Cl^- loss from the plasma and ISF spaces is proportional to the water loss from each space. The calculation was as follows:

$$\Delta Cl^-_{ECF} = Cl^-_U + Cl^-_S$$

$$\Delta Cl^-_{ISF} = \Delta Cl^-_{ECF} - \Delta Cl^-_{Pl}$$

$$\Delta ISF = 1/1.05 \times \Delta Cl^-_{ISF}/\Delta Cl^-_{pl} \times \Delta PV$$

$$\Delta ECF = \Delta PV + \Delta ISF$$

$$\Delta ICF = \Delta TW - \Delta ECF$$

where subscripts Pl, ISF, ECF, U, and S indicate plasma, interstitial and extracelluar fluid spaces, urine, and sweat, respectively. The use of the Cl^- method in this experiment was based on the results of a previous experiment on rats (Nose et al., 1985): the decreases in distribution of ^{51}Cr-EDTA in various tissues after thermal dehydration were strongly correlated with their losses of sodium ($r = 0.97$, $P < 0.0001$), which itself is highly correlated with

Cl^- losses. Changes in the extracellular fluid space determined by the Cl^- method were almost identical to those determined by the ^{51}Cr-EDTA dilution method. Free water loss (ΔFW) during dehydration was calculated as follows:

$$\Delta FW = \Delta TW - \{([mosmol]_s \times vol_s) + ([moamol]_U \times vol_U)\}/P^0_{osmol}$$

$$= \Delta TW - (\text{cation loss} \times 2)/P^0_{osmo}l$$

$$\text{cation loss} = [\text{cation}]_S + vol_S + [\text{cation}]_U \times vol_U$$

$$\Delta TW = vol_S + vol_U$$

where P^0_{osmol} is the control plasma osmolality, subscripts s and u indicate sweat and urine, respectively, and [cation] denotes the sum of $[NA^+]$ and $[K^+]$. The amount of osmotically active substances lost from the body was estimated by doubling the cation loss because the main osmotically active substances in body fluids are Na^+ and K^+ and their combined anions. The concept of free water loss is analogous to "free water clearance" in renal function.

Statistics

One-way analysis of variance for repeated measures was used to determine differences between predehydration and postdehydration conditions, with significant differences between pre- and postdehydration at various times determined with Tukey's minimum significant difference (MSD) test (Sokal and Rohlf, 1981). The null hypothesis was rejected when P was <0.05. Regression formulas were calculated using Brace's method (Brace 1977). Values are represented as means ± SE of 10 subjects.

RESULTS

The amounts of water and electrolytes excreted in sweat and urine during the dehydration period are shown in Table 11-2.

Eighty-seven percent of the total Na^+ loss was excreted in sweat and only 13% in urine. Only 21% of the total cation loss was K^+. $[Na^+]$ and $[K^+]$ in sweat averaged 56.4 ± 7.3 meq/liter (ranging from 6.9 to 11.5 meq/liter), respectively.

Table 11-2 Water and electrolyte losses 60 min after dehydration (means ± standard errors)

		Electrolyte loss (meq/kg)		
	Volume (ml/kg)	Na^+	K^+	Cl^-
Sweat	21.6±1.5	1.04±0.12	0.20±0.04	0.97±0.12
Urine	0.9±0.9	0.15±0.18	0.11±0.03	0.17±0.03
Total	22.5±1.5	1.19±0.14	0.31±0.06	1.14±0.13

Figure 11-1 shows the Hct, Hb, and plasma solids before and after dehydration. Immediately after exercise, these increased from 42.7 ± 0.5% to 44.7 ± 0.5%, 14.8 ± 0.2 g/dl to 15.8 ± 0.2 g/dl, and 8.4 ± 0.1 g/dl to 9.1 ± 0.1 g/dl, respectively. These levels were maintained for the next 30 min (43.6 ± 0.5%, 15.5 ± 0.1 g/dl, and 8.8 ± 0.1 g/dl at 60 min). In all variables,

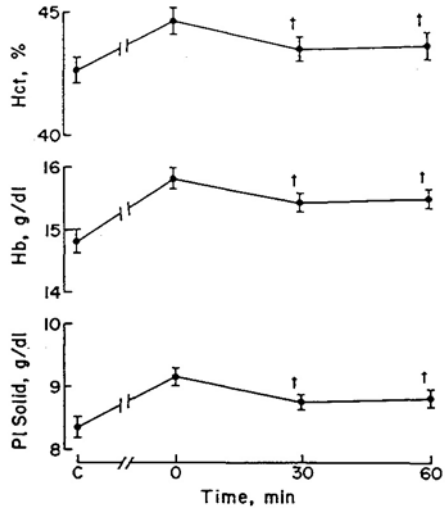

FIGURE 11-1 Hematocrit (Hct), hemoglobin (Hb) concentration, and plasma (Pl) solids are shown as means ± SE of 10 subjects before (C) and 0, 30, and 60 min after dehydration. Significant differences were observed for all variables between control and dehydrated conditions (0, 30, and 60 rain). + Significant differences between 0 min and the other 2 dehydrated conditions (30 and 60 min).

significant differences occurred between control and dehydrated conditions (0, 30, and 60 min) and between 0 min and the other two dehydrated conditions (30 and 60 min), but no significant differences occurred between 30 and 60 min. Plasma protein concentration paralleled changes in plasma solids.

Figure 11-2 shows the plasma electrolyte concentration before and after dehydration. Plasma osmolality increased significantly from 284 ± 1 to 290 ± 1 mosmol/kg H_2O. Changes in $[Na^+]$, $[Ka^+]$, and $[Cl^-]$ from 155 ± 1 to 160 ± 1, from 4.28 ± 0.08 to 4.47 ± 0.07, and from 116 ± 1 to 119 ± 1 meq/kg H_20 just after the dehydration (0 min) were significant. These all showed a tendency to return toward control levels between 0 and 60 min, but no significant differences occurred.

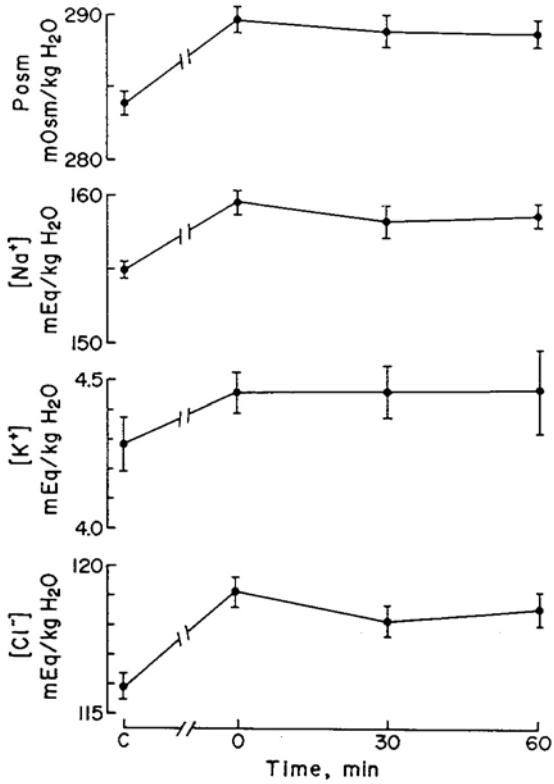

FIGURE 11-2 Changes in electrolyte concentrations and osmolality (P_{osmol}) in plasma after dehydration. Significant differences were observed for all variables between control and dehydrated conditions (0, 30, and 60 min).

Figure 11-3 shows the changes in the body fluid compartments after dehydration. The ΔTW was 20.3 ± 1.3 ml/kg body wt at time 0 and 22.5 ± 1.5 ml/kg body wt at 30 min, because the subjects continued to sweat after the dehydration until their body temperatures returned to the control level. We did not measure body weight at 60 min, because sweating was negligible after 30 min. Changes in the ICF space after dehydration were −8.7 ± 1.3 (0 min), −10.3 ± 1.2 (30 min), and −10.0 ± 1.2 (60 rain) ml/kg body wt. There were no significant differences between these values. Changes in ECF space were −11.6 ± 1.2 (0 min), −12.3 ± 0.7 (30 min), and −12.5 ± 0.9 (60 min) ml/kg body wt. There were no significant differences between these values. The ΔPV was −4.3 ± 0.6 ml/kg body wt (−9.4%) at time 0. This loss was partially recovered at 30 and 60 min, with ΔPV of −2.3 ± 0.4 (30 min) and −2.6 ± 0.5 ml/kg body wt (60 min). The differences were significant between the control and dehydrated conditions (0, 30, and 60 min) and between 0 min and the other dehydrated conditions (30 and 60 min). The change in the ISF volume, determined by subtracting the ΔPV from ΔECF, was −7.3 ± 1.0 ml/kg body wt at time 0 and decreased further to −10.0 ± 0.5 ml/kg body wt at 30 min and −9.9 ± 0.8 ml/kg body wt at 60 min. The difference was significant between 0 and 30 min but not between 30 and 60 min.

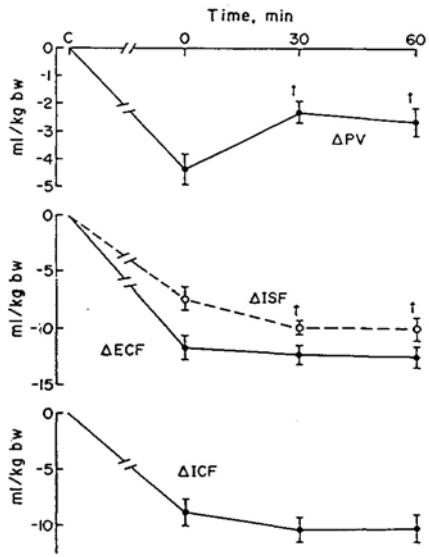

FIGURE 11-3 Changes in body fluid compartments after dehydration. Values are changes with respect to control values. ΔPV, ΔISF, ΔECF, and ΔICF denote changes in plasma, interstitial, extracellular, and intracellular fluid volumes. Significant differences were observed for all variables between control and dehydrated conditions (0, 30, and 60 rain). Significant differences between 0 min and the other 2 conditions (30 and 60 min).

Figure 11-4 shows the linear relationship between the change in P_{osmol} and in ΔFW during the steady state after dehydration ($r = -0.79$, $P < 0.01$). Individual points are the mean steady-state values between 30 and 60 min.

Figure 11-5 shows the change in ICF volume as a function of the change in P_{osmol} ($r = -0.74$, $P < 0.02$).

Figure 11-6 depicts a linear relationship between $[Na^+]$ in sweat and free water loss, normalized for total body water loss in each subject ($r = -0.97$, $P < 0.001$). It also shows that the loss in ECF was correlated with the $[Na^+]$ in sweat ($r = -0.80$, $P<0.01$). Changes in ICF would then be inversely correlated with the changes in $[Na^+]$ in sweat ($r = -0.80$, $P < 0.01$).

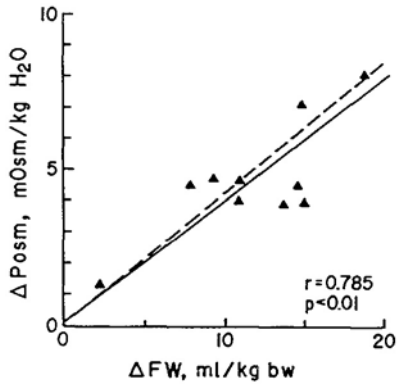

FIGURE 11-4 Relationship between loss of free water (ΔFW) and change in plasma osmolality (ΔP_{osm}). Solid line, regression line; dashed line, theoretical line.

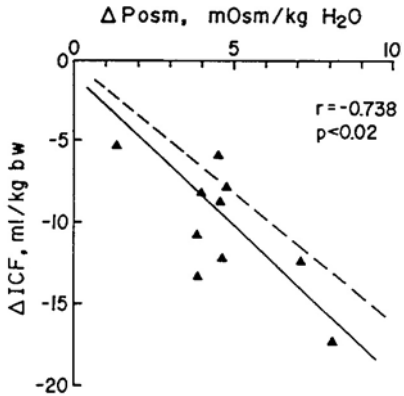

FIGURE 11-5 Relationship between changes in plasma osmolality (ΔP_{osm}) and intracellular fluid volume (ΔICF). Solid line, regression line; dashed line, theoretical line.

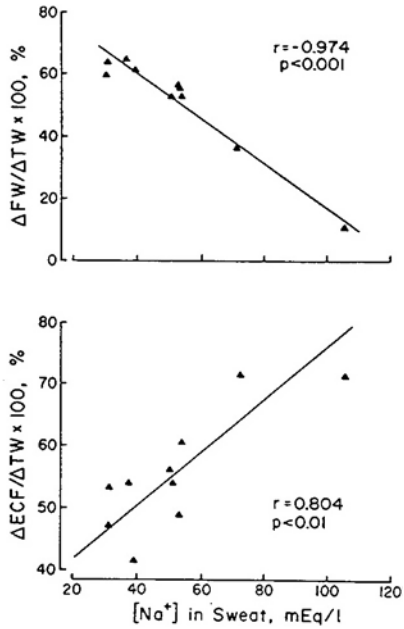

FIGURE 11-6 (Top): relationship between [Na^+] in sweat and loss of free water normalized by total body water loss (ΔFW/ΔTW). (Bottom): Relationship between [Na^+] in sweat and loss of extracellular or intracellular fluid normalized by total body water loss (□ECF/□TW).

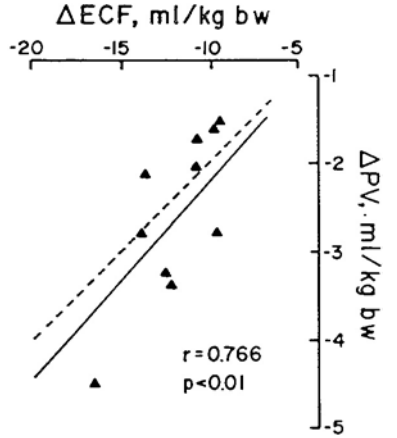

FIGURE 11-7 Relationship between loss of plasma volume (ΔPV) and loss of extracellular fluid (ΔECF). Solid line, regression line; dashed line, theoretical line.

Figure 11-7 shows that the decrease in PV was correlated with that in ECF volume ($r = 0.77$, $P < 0.01$).

DISCUSSION

The loss of plasma water during exercise in a hot environment is governed by several factors (Senay and Pivarnik, 1985). One of these is the shift of plasma water from the intra- to the extravascular fluid space caused by a change in the Starling forces accompanying increased perfusion pressure and capillary area. Another is plasma water movement accompanying whole-body dehydration due to the excretion of sweat. The decrease in plasma water must be compensated for, partly by shifting water from other fluid compartments, to maintain cardiac filling pressure and to provide for an adequate distribution of cardiac output (Nadel, 1984; Rowell, 1983). The purpose of this study was to investigate the water movement between fluid compartments during and after dehydration and to quantify the relationship between $[Na^+]$ in sweat and the maintenance of circulating blood volume.

Immediately after the dehydration exposure, we found plasma volume to be decreased by 9.4% with respect to the preexposure value, and this deficit recovered to −5.0% at 30 min and −5.6% at 60 min of recovery when the subjects had no access to fluids. The water losses from the ICF and ECF spaces were −8.7 and −11.6 ml/kg body wt, respectively, immediately after the exposure. There was a small additional water loss between 0 and 30 min of recovery due to the continued secretion of sweat. However, electrolyte concentrations in plasma were unchanged during the hour after the dehydration exposure. These results suggest that fluid movement between the ICF and ECF spaces was at a steady state at the end of the dehydration exposure and the partial recovery of the lost plasma volume between 0 and 30 min of recovery was from the interstitial fluid space rather than from the intracellular space.

Many investigators have documented the existence of fluid movement from the intra- to extravascular space during exercise; these data were recently summarized by Senay and Pivarnik (1985). Mohsenin and Gonzalez (1984) reported that interstitial fluid pressure in muscle immediately after maximal exercise was increased by 2.5 cm H_2O above base line, and this increase was sustained up to 14 min after the termination of exercise. Convertino et al. (1981, 1983) demonstrated that there was a linear relationship between the amount of plasma water loss and the relative exercise intensity (% $\dot{V}_{O_2\,max}$). Sjogaard and Saltin (1982) showed, from estimates of ECF space in humans using ^{3}H-inulin distribution, that this fluid movement was due primarily to increased filtration caused by the rise

in precapillary hydrostatic pressure during exercise rather than from an induced hyperosmolality of the ICF space.

The dashed line in Figure 11-4 is the theoretical line describing the relationship between free water loss and P^0_{osmol}, assuming that total body water is 65% of body weight (Wyndham et al., 1968) and plasma osmolality represents that of total body water in the equilibrium state. The equation is as follows:

$$\Delta P_{osmol} = (P^0_{osmol} \times TW^0 - \text{cation loss} \times 2)/$$
$$(TW^0 - \Delta TW) - P^0_{osmol} = P^0_{osmol}/TW^0 \times \Delta FW$$

where TW^0 indicates control values of total water volume (see Appendix this chapter). The amount of osmotically active substances lost from the body was estimated by doubling the cation loss (Na^+ and K^+). The slope of this relation was 0.41 (mosmol/kg H_2O)/(ml/kg body wt), which was almost identical to that of the best-fit regression line (solid line) from the experimental data. In other words, the increase of plasma osmolality during dehydration was a function of the loss of free water from the body.

The relationship between the change in plasma osmolality and the change in ICF volume is shown in Figure 11-5. The dashed line, again, is the theoretical line determined by assuming that the initial volume of the ICF space is 38% of body weight (Bass et al., 1955), that the potassium in urine and sweat comes from only the ICF space (Nose et al., 1985; Wallace et al., 1970), and that plasma osmolality represents that of the ICF space in the steady state. The equation is as follows:

$$\Delta P_{osmol} = (P^0_{osmol} \times ICF^0 - K^0 \text{ loss} \times 2)/$$
$$(ICF^0 - \Delta ICF) - P^0_{osmol}$$

where ICF^0 indicates the control values of ICF volume and K^+ loss is the K^+ loss in sweat and urine. The amount of osmotically active substance lost from the ICF space was estimated by doubling the K^+ loss. The slope of the theoretical line is −1.67 (ml/kg body wt)/(mosmol/kg H_2O). The slope of the regression line determined from the experimental data was −2.00 (ml/kg body wt)/(mosmol/kg H^2O). The difference between the two may be partially explained by the fact that ions other than K^+--i.e., Mg^{2+} and Ca2+--were lost from the ICF space into sweat and urine during dehydration. [Mg^{2+}] and [Ca^{2+}] in sweat have been reported to be 1.5-5.0 and 5.0-10 meq/liter, respectively (Durkot et al., 1986). On this basis, we estimated the losses in sweat to be 0.03 - 0.11 meq/kg for Mg^{2+} and 0.11 - 0.22 meq/kg body wt for

Ca^{2+}. Costill et al. (1976) reported that the Mg^{2+} loss during thermal dehydration of 2.2% of body weight was 0.07 meq/kg body wt. A second possibility for the difference between the theoretical and observed regression relations is that the K^+ lost from the ICF space partially accumulated in the interstitial fluid space without being excreted into the sweat and urine, but this seems rather unlikely. The plasma $[K^+]$ increased by 9.8% above the control value, which was entirely within the range of the expected increase in $[K^+]$ by extrapolation from the decrease of the ECF space after dehydration. It is obvious that the increase in the ICF space was highly correlated with the change in plasma osmolality and that water movement from the ICF space followed the osmotic gradient.

We also found a strong correlation between free water loss and the $[Na^+]$ in sweat over a wide range (Figure 11-6, top). The free water loss caused the increase in P_{osmol} (Figure 11-4), resulting in fluid mobilization from the ICF space (Figure 11-5) to maintain ECF volume (Figure 11-6, bottom). The dashed line in Figure 11-7 is a theoretical line drawn with the assumption that water losses from plasma and the ECF space were proportional to the initial volume of each compartment (Spector, 1956). The regression line determined from the experimental data (Figure 11-7, solid line) was practically identical to the theoretical line, and the slope relating ΔPV to ΔECF was 0.22.

The ratio of plasma water loss to total body water loss was 0.11 ± 0.02, which was approximately 60% higher than the theoretically expected value, assuming that body water was lost proportionally from each compartment (Spector, 1956). This is likely due to the fact that the major electrolytes excreted during thermal dehydration are Na^+ and Cl^-, which are the main electrolytes in the ECF. At a given level of dehydration, the $[Na^+]$ in sweat determines the volume of fluid mobilized from the intracellular fluid compartment, thereby determining the effective maintenance of circulating blood volume. This conclusion emphasizes the importance of producing a more dilute sweat in the heat adaptation process.

APPENDIX

The content of osmotically active substances in the body and their loss during dehydration are $P^0_{osmol} \times TW^0$ and $[mosmol]_{S+U} \times \Delta TW$, respectively, where P^0_{osmol} and TW^0 are control plasma osmolality and total water, and $[mosmol]_{S+U}$ and ΔTW are mean values of osmolality of sweat and urine and their total volume, respectively. Therefore plasma osmolality after dehydration (P'_{osmol}) is represented as follows:

$$\Delta P'_{osmol} = P^{0}_{osmol} \times TW^{0} - [mosmol]_{S+U} \times \Delta TW)/(TW^{0} - \Delta TW)$$

therefore the change in plasma osmolality (ΔPosmol) is as follows:

$$P_{osmol} = P'_{osmol} - P^{0}_{osmol}$$
$$= P^{0}_{osmol} \times TW^{0} - [mosmol]_{S+U} \times \Delta TW)/$$
$$[TW^{0} \times (1 - \Delta TW/TW^{0})] - P^{0}_{osmol}$$
$$= (P_{osmol} \times TW^{0} - [mosmol]_{S+U} \times \Delta TW)/$$
$$TW^{0} \times (1 + \Delta TW/TW^{0})] - P^{0}_{osmol}$$

because

$$\Delta TW/TW^{0} <<< 1$$
$$= (P^{0}_{osmol} - \Delta TW^{0}/TW^{0} \times [mosmol]_{S+U})$$
$$\times (1+ \Delta TW/TW^{0}) - P^{0}_{osmol}$$
$$= (P^{0}_{osmol} - [mosmol]_{S+U} \times \Delta TW/TW^{0}$$

because

$$[mosmol]_{S+U} \times (\Delta TW/TW)^{2} = 0$$
$$= P^{0}_{osmol} \times (1 - [mosmol]_{S+U}/P^{0}_{osmol}) \times \Delta TW/TW^{0}$$

whereas

$$\Delta FW = \Delta TW \times (1 - [mosmol]_{S+U}/P^{0}_{osmol})$$

therefore

$$\Delta P_{osmol} = P^{0}_{osmol}/TW^{0} \times \Delta FW$$

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12

Role of Osmolality and Plasma Volume During Rehydration in Humans

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INTRODUCTION

Humans have a prolonged period of delayed rehydration after thermal dehydration. This phenomenon has been known as involuntary dehydration since 1974 (Rothstein et al., 1947), and a number of studies have been conducted to better understand its cause (Greenleaf and Sargent, 1965; Greenleaf et al., 1983; Mack et al., 1986). Dill et al. (1933) suggested that thirst is primarily a function of the sodium chloride concentration in plasma rather than plasma volume. Greenleaf (1982) stated that two factors unique to humans contribute to the involuntary dehydration: excessive extracellular fluid loss due to Na^+ loss into sweat and the upright posture. Recently, Morimoto et al. (1981b) found that the degree of involuntary dehydration in humans was reduced when a glucose-electrolyte solution rather than water was ingested during thermal dehydration. However, their results may have

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been biased by the presence of glucose in their rehydration solution because taste of glucose-electrolyte solution may have influenced drinking behavior. More recently, Nose et al. (1985, 1986) demonstrated that the degree of involuntary dehydration was reduced in rats supplied with water containing 0.45 or 0.9% NaCl to compensate for the loss of electrolytes during thermal dehydration phenomenon.

There has been other evidence demonstrating the importance of the plasma volume change in involuntary dehydration. Nose et al. (1986) reported that in rats 17-20% of the ingested water remained in the vascular space, which is twice as much as expected, assuming that ingested fluid is distributed proportionally among the body compartments. These results also suggested to us that the high retention of ingested fluid in the vascular space might diminish volume-dependent dipsogenic stimulation despite the incomplete restoration of the total water deficit.

The purpose of this study was to assess the involuntary dehydration phenomenon in humans. We wished to examine the distribution and fate of the water ingested during rehydration to determine the mechanisms that contribute to the high retention of ingested fluids in the vascular space. Our hypothesis was that the disproportionately high recovery of plasma volume, with respect to total body water, contributes to the removal of the dipsogenic drive. Furthermore, removal of the osmotic stimulus accompanying plasma volume dilution limits the rate of body fluid restitution.

METHODS

Design

Six male volunteers were studied. Their physical characteristics are shown in Table 12-1. With a few exceptions, to be described below, the procedures and analytic techniques were the same as in the preceding chapter and as in Nose and colleagues (1988a). We induced a dehydration of 2.3% body weight by exposing subjects for 90-110 min to simultaneous heat [36°C, <30% relative humidity (rh)] and exercise (40% maximal aerobic power) stress in the seated position.

Table 12-1 Characteristics of Subjects (n = 6)

	Age (years)	Wt (kg)	$\dot{V}_{O_2\,max}$[a] ($ml.kg^{-1}$ min^{-1})	Blood Volume (ml/kg)	Plasma Volume (ml/kg)
Mean	28.3	68.3	51.8	82.1	47.4
Range	23-33	56.5-83.7	36.4-62.9	61.0-102.3	33.5-61.4

[a] maximum aerobic power.

After dehydration, a 60-min recovery without fluid was imposed to allow the body fluid compartments to stabilize. Recovery was in a thermoneutral environment (28°C, <30% rh) and subjects were in the seated position throughout. A butterfly catheter was inserted into a superficial forearm vein within 10 min of the termination of exercise. Blood samples were taken directly after catheter placement and at 30 and 60 min of recovery. There were no differences in plasma osmolality (P_{osmol}) or plasma volume between 30 and 60 min after the termination of exercise, thereby confirming that a new steady state had been achieved.

During the next 180 min, subjects rehydrated with water plus capsules ad libitum. Two series of rehydration experiments were performed on each subject: (1) with tap water (H_2O-R) and (2) with 0.45% NaCl solution (Na-R). Subjects were given a capsule containing either 0.2 g sucrose/100 ml water during H_2O-R or 0.45 g NaCl/100 ml water during Na-R. Water temperature was approximately 15°C. The minimum allowable drinking volume at a time was 100 ml because subjects were expected to take one capsule per 100 ml. Sodium and potassium concentrations in tap water were undetectable by flame photometry and the osmotic activity of the sucrose solution was approximately 4% of the 0.45% NaCl solution so that the gain of osmotically active substances in H_2O-R was ignored. Ingestion of salt in capsule form was necessary to avoid any influence of taste on drinking behavior.

Blood samples were taken at 10, 20, 30, 60, 120, and 180 min of the rehydration period, and urine was collected at 60, 120, and 180 min of rehydration.

Measurements

From each blood sample we determined P_{osmol} (freezing point depression, model 3DII, Advanced Instruments) and plasma electrolytes

([Na^+] and [K^+], flame photometry, Instrumentation Laboratory model 433; [Cl^-] Cotlove chloride titrator). These were expressed in meq/kg H_2O after correction for plasma solids. We also measured microhematocrit, hemoglobin concentration (cyanomethemoglobin), plasma protein concentration (refractometry), and plasma solid concentration (dry weight method).

Calculations

Total water loss due to dehydration was estimated from body weight loss. Net fluid gain was calculated by subtracting total urine loss from water intake, assuming that respiratory water loss and sweat loss at rest were negligible. Electrolyte losses in sweat and urine due to dehydration were calculated by multiplying the volume of water loss by the concentration of each fluid, respectively (see Nose et al., 1988a). Net electrolyte gain was calculated by subtracting electrolyte loss in urine from electrolyte intake. The change in plasma volume (ΔPV) during an experiment was calculated from changes in hematocrit and hemoglobin concentrations (Elkinton et al., 1946). The change in extracellular fluid (ΔECF) space after 180 min of rehydration was determined by Cl^- distribution, assuming that Cl^- is equally distributed throughout the ECF space (Nose et al., 1985).

$$\Delta Cl^-_{ECF} = Cl^-_{In} - Cl^-_{U} - Cl^-_{S}$$

$$\Delta Cl^-_{ECF} = \Delta Cl^-_{ISF} + \Delta Cl^-_{Pl}$$

$$\Delta ISF = 1/1.05 \times \Delta Cl-_{ISF}/\Delta Cl-_{Pl} \times \Delta PV$$

$$\Delta ECF = \Delta PV + \Delta ISF$$

$$\Delta ICF = \Delta TW - \Delta ECF$$

where ICF denotes intracellular fluid space, ISF denotes interstitial fluid space, TW indicates total body water, and subscripts Pl, ISF, ECF, In, U, and S indicate plasma, interstitial and extracellular fluid spaces, intake, urine, and sweat, respectively.

Statistics

Two-way analysis of variance (ANOVA) for repeated measures was used to determine differences between H_2O-R and Na-R, with significant differences between the two groups at various times determined with Tukey's minimum significant difference (MSD) test (Sokal and Rohlf, 1981). Specific trend analysis for each treatment was performed with a one-way ANOVA for repeated measures with significant differences between each time also determined with Tukey's MSD test. The null hypothesis was rejected when

$P < 0.05$. Regression formulas were calculated by Brace's method (Brace, 1977). All values are reported as means ± standard errors of six subjects.

RESULTS

The total body water deficits immediately before rehydration in the two conditions (H_2O-R and Na-R) were 23.7 ± 0.9 and 21.7 ±1.0 ml/kg body weight. Since the difference in deficit between the two conditions was not significant, the data were pooled and the body water loss during dehydration therefore averaged 22.7 ± 0.7 ml/kg body wt ($n = 12$).

Figure 12-1 shows the cumulative amounts of fluid intake, urine output, and net fluid gain during rehydration. The cumulative fluid intake increased sharply for the first 30 min in both recovery conditions and then slowly

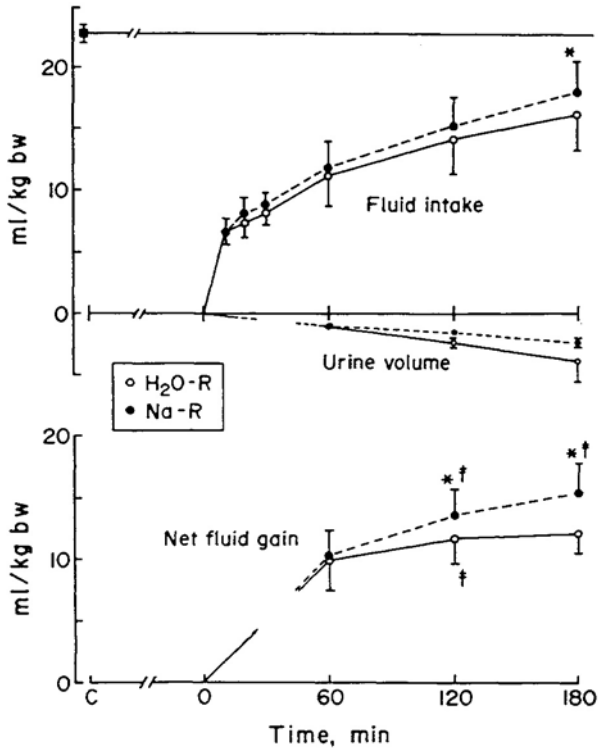

FIGURE 12-1 Cumulative amount of fluid intake, urine volume, and net fluid gain during 180 min of rehydration. Values are means ± SE of 6 subjects. ▪, Body water loss as difference from prerehydration. □ and ·, Tap water (H_2O-R) vs. NaCl Na-R recovery conditions, respectively. * H_2O-R vs Na-R ($P < 0.05$); + 60 vs 120 and 180 min ($P < 0.05$).

increased to 16.1 ± 2.9 ml/kg body wt in H_2O-R and 17.8 ± 2.8 ml/kg body wt in Na-R after 180 min of rehydration. By 180 min the cumulative fluid intake for Na-R was significantly greater than for H_2O-R. Urine volume tended to be greater during H_2O-R than Na-R, but this difference was not statistically significant. When the urine volumes are taken into account, the net fluid gain at 180 min was 15.3 ± 2.4 ml/kg body wt in Na-R and 12.1 ± 1.6 ml/kg body wt in H_2O-R. The difference in net fluid gain was significant at 120 and 180 min. Net fluid gain during Na-R increased significantly between 60 and 180 min, whereas net fluid gain during H_2O-R showed no significant increase after 60 min.

Figure 12-2 shows the changes in hematocrit (ΔHct), hemoglobin concentration (ΔHb), and plasma solids during rehydration. After 60 min of rest without fluids after dehydration, Hct, Hb, and plasma solids were increased significantly. These variables returned to control relatively slowly XXX

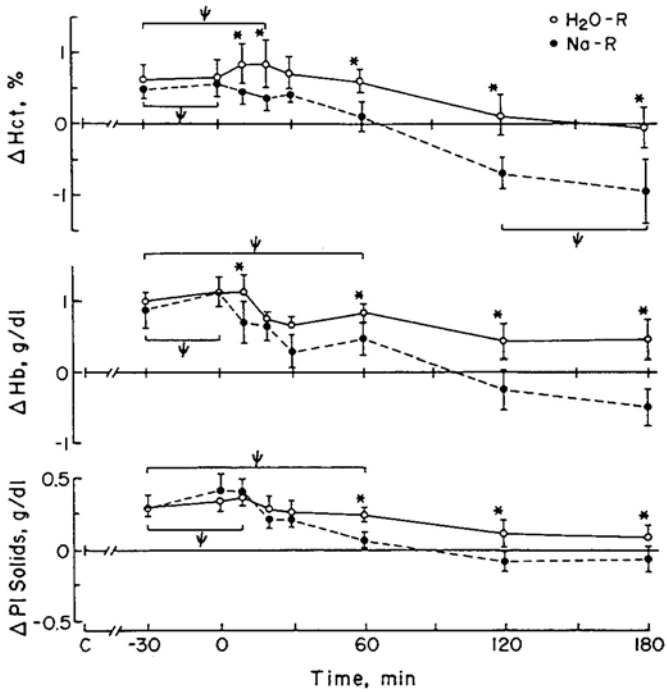

FIGURE 12-2 Changes in hematocrit (ΔHct), hemoglobin (ΔHb), and plasma (ΔPl) solids shown as differences from control values (C). Symbols and other abbreviations as in Figure 12-1. ψ indicates values that are different from control. ($P < 0.05$)

during H_2O-R; Hct was restored after 30 min of rehydration and Hb and plasma solids were restored after 120 min of rehydration. On the other hand, these variables returned to the control levels more rapidly during Na-R than during H_2O-R, with significant differences being maintained between the two rehydration conditions throughout the 180 min. During Na-R, Hct fell significantly below the control values after 120 min. Changes in plasma protein concentration were almost identical to changes in plasma solids. Total protein content, calculated from plasma protein concentration and PV, was 3.4 ± 0.2 g/kg before dehydration in both groups, and, at 180 min of rehydration, 3.4 ± 0.3 g/kg and 3.5 ± 0.2 g/kg in H_2O-R and Na-R, respectively.

Figure 12-3 shows the changes in plasma electrolytes during rehydration. During Na-R, plasma electrolytes tended to decrease, but P_{osmol} remained significantly above the control concentration until 120 min of rehydration, [Na^+] until 60 min, [K^+] until 30 min, and [Cl^-] until 10 min. On the other

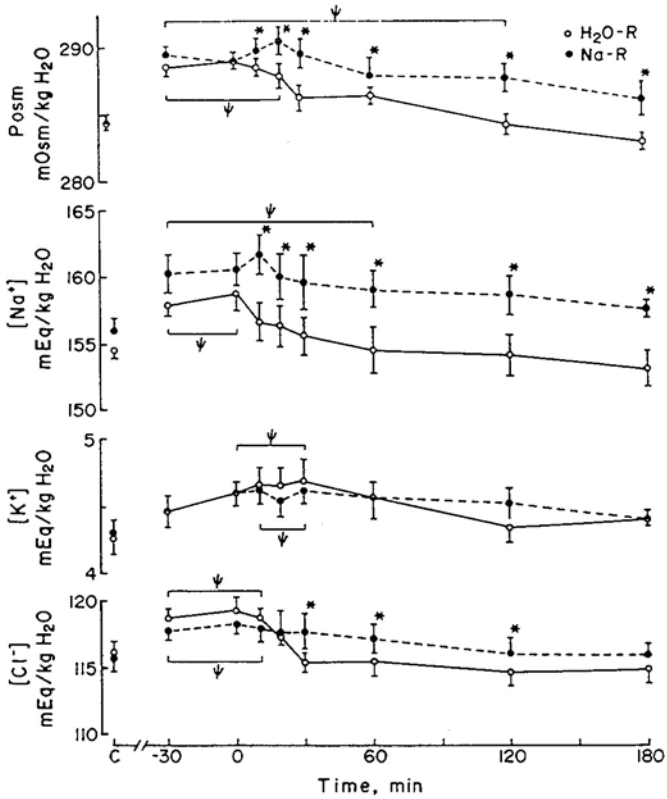

FIGURE 12-3 Osmolality (P_{osmol}) and Na^+, K^+, and Cl^- concentrations in plasma during rehydration. Symbols and other abbreviations as in Figure 12-1 and Figure 12-2.

hand, plasma electrolytes decreased significantly at the beginning of H_2O-R, and significant differences between the two conditions were maintained for P_{osmol} and $[Na^+]$ throughout the rehydration period. No significant differences in $[K^+]$ occurred between the two conditions throughout the rehydration period.

Figure 12-4 shows the changes in plasma volume from predehydration values. After dehydration, the PV deficit was 2.28 ± 0.51 and 2.14 ± 0.60 ml/kg body wt in the H_2O-R and Na-R experimental conditions, respectively. During H_2O-R, PV increased slowlybut remained significantly lower than the control PV until 60 min. PV restoration was faster during Na-R and returned to the control level by 20 min. By 180 min of rehydration, the changes in PV with respect to control were −0.5 ± 0.8 and 1.58 ± 0.63 ml/kg body wt in H_2O-R and Na-R, respectively.

Free water clearance (C_{H_2O}) was significantly increased (less negative) during H_2O-R but decreased slightly (more negative) in Na-R (Table 12-2). These differences in C_{H_2O} , between the recovery conditions were significant. In addition, the loss of osmotically active substances and osmotic clearance (C_{osmol}) was greater in Na-R than in H_2O-R (Table 12-2).

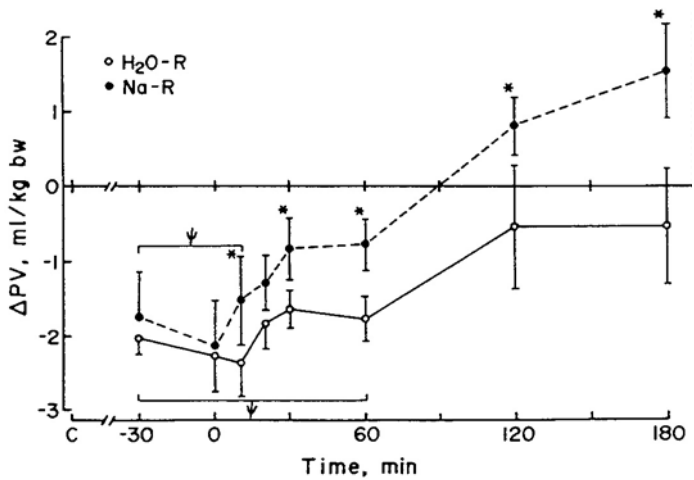

FIGURE 12-4 Changes in plasma volume (ΔPV) shown as differences from control values. Symbols and abbreviations as in Fig. 12-1 and Fig. 12-2.

Table 12-2 Renal Function After Dehydration and Rehydration

	Dehydration	Rehydration, min		
		60	120	180
Urine flow, μl · kg^{-1} · min^{-1}				
H_2O-R	9.7 ± 1.6	8.9 ± 0.9	21.0 ± 11.4	25.9 ± 17.2
Na-R	9.0 ± 1.2	8.4 ± 1.3	11.5 ± 2.8	12.1 ± 3.5
$[Osmol]_U$ × urine flow, μosmol kg^{-1}min^{-1}				
H_2O-R	7.9 ± 0.9	8.6 ± 0.9	8.2 ± 1.0	7.1 ± 0.7
Na-R	7.5 ± 0.5	7.5 ± 0.5	9.3 ± 1.3	9.3 ± 1.0*
C_{osmol}, μl · kg^{-1} · min^{-1}				
H_2O-R	27.5 ± 3.0	29.9 ± 3.2	28.7 ± 3.5	25.3 ± 2.6
Na-R	25.9 ± 1.7	26.1 ± 1.8	32.4 ± 4.4	33.3 ± 3.0*
C_{H_2O}, μl · kg^{-1}· min^{-1}				
H_2O-R	−17.8 ± 2.2	−21.0 ± 2.4	−7.7 ± 11.1	0.6 ± 16.2
Na-R	−16.9 ± 1.2	−17.7 ± 1.3	−21.0 ± 4.2*	−21.7 ± 3.8*

Values are means ± SE. H_2O-R and Na-R, rehydration conditions with tap water and 0.45% NaCl solution, respectively; $[osmol]_U$, urine osmolality; C_{osmol}, osmotic clearance; C_{H_2O}, free water clearance. *Significant differences between H_2O-R and Na-R groups ($P < 0.05$).

Table 12-3 Electrolyte Balance After Dehydration and at 180 min of Rehydration

	Dehydration		Rehydration	
	H_2O-R	Na-R	H_2O-R	Na-R
Na^+ loss	−1.01 ± 0.15	−1.18 ± 0.12	−1.28 ± 0.17	−1.48 ± 0.13*
K^+ loss	−0.31 ± 0.03	−0.31 ± 0.03	−0.54 ± 0.05	0.58 ± 0.03*
Cl^- loss	−0.95 ± 0.11	−1.09 ± 0.14	−1.28 ± 0.12	−1.53 ± 0.03*
Na^+ intake				+1.40 ± 0.22
Cation balance	−1.32 ± 0.15	−1.49 ± 0.13	−1.81 ± 0.17	−0.66 ± 0.14

Values are means ± S.E. in meq/kg body wt. H_2O-R and Na-R, rehydration conditions with tap water and 0.45% NaCl solution, respectively. *Significant differences between H_2O-R and Na-R ($P < 0.05$).

During Na-R, subjects consumed 119% of the Na^+ lost during dehydration, whereas during H_2O-R they consumed no electrolytes. Because of the K^+ and Na^+ losses in urine during rehydration, the net cation balance at the

end of the rehydration period was −0.66 meq/kg body wt in Na-R, whereas it was −1.81 meq/kg body wt in H_2O-R (Table 12-3).

Fluid and electrolyte balances during rehydration are summarized in Figure 12-5. The means are plotted with standard error bars at 60-min intervals from the dehydrated condition (0 min) to rehydrated conditions (60, 120, and 180 min) in both groups. The intersection of the *x*- and *y*-axes represents the predehydrated condition (control) and the solid line indicates the isotonic line, $y = 0.15x$. The area above the isotonic line reflects hypertonic body fluids, and the area below the line represents hypotonic body fluids. In both recovery conditions, H_2O-R and Na-R, fluid and electrolyte balance moved toward the theoretical isotonic line. Only in H_2O-R did the fluid balance reach the isotonic line. The degree of involuntary dehydration after 180 min of drinking was primarily determined by the cation deficit.

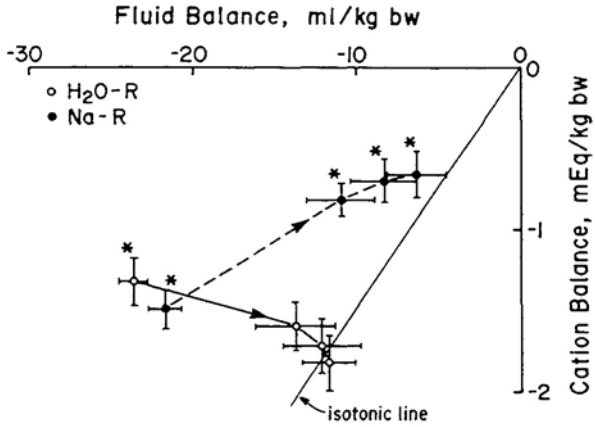

FIGURE 12-5 Recoveries of fluid and electrolyte balance during rehydration. Means of 6 subjects are shown with SE bars of 60-min intervals during rehydration. The theoretical isotonic line is $y = 0.15x$. * Points significantly different from isotonic line ($P < 0.05$). Abbreviations as in Figure 12-1.

Changes in the body fluid compartments after dehydration and 180 min of rehydration are summarized in Figure 12-6. The values are shown as differences from the predehydration values. After dehydration and after the 60-min period of body fluid stabilization, change in total body water (ΔTW), change in intracellular fluid space (ΔICF), ΔECF, and ΔPV were −2.2 ± 0.7, −10.2 ± 1.0, −12.6 ± 0.8, and −2.2 ± 0.4 ml/kg body wt, respectively.

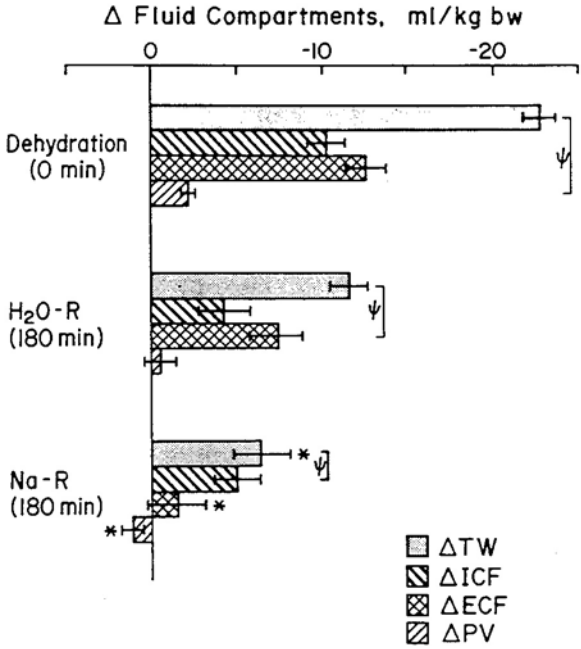

FIGURE 12-6 Changes of fluid compartments shown as differences from control values. Values are means ± SE of 12 subjects in dehydration and 6 subjects in each recovery condition at 180 min of rehydration. All recovery values are significantly different from dehydration values ($P < 0.05$) * Tap water (H_2O-R) vs. NaCl (Na-R) recovery conditions ($P < 0.05$): ψ different from control ($P < 0.05$). ΔTW, change in total body water; ΔICF, change in intracellular fluid space; ΔECF, change in extracellular fluid space; ΔPV, change in plasma volume.

After 180 min of rehydration the fluid deficits in all compartments were significantly reduced. The TW and ICF space were still significantly lower than predehydration values in both recovery conditions. The ECF space recovered in Na-R, whereas it did not in H_2O-R. Significant differences between H_2O-R and Na-R occurred in ΔTW, □ECF, and ΔPV (Figure 12-6).

Figure 12-7 shows the relationship between the recoveries in PV (rPV) and total body water (rTW) (top) and between the rPV and ECF space (rECF) after 180 min of rehydration (bottom). Values are shown as

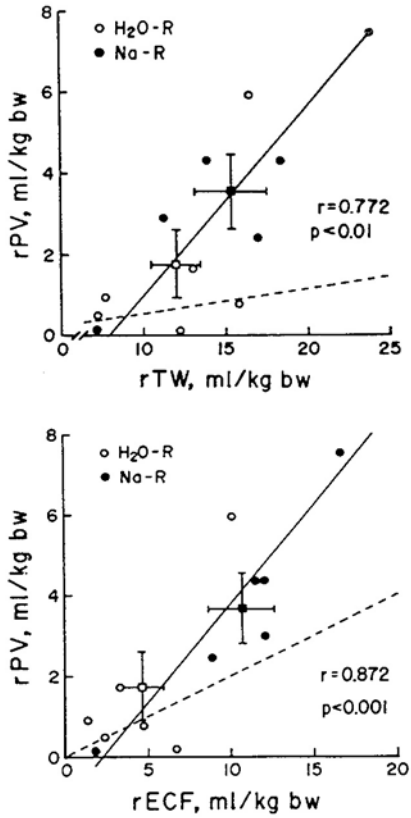

FIGURE 12-7 Relationship between recoveries in plasma volume (rPV) and total body water (rTW) (*top*) and between recoveries in plasma volume (rPV) and extracellular fluid volume (rECF) (*bottom*) during rehydration with tap water (H_2O-R) and 0.45% NaCl solution (Na-R). ----, Theoretically expected lines, constructed under the assumption that distribution of ingested fluid between two compartments is proportional to their initial volumes. Individual data at 180 min of rehydration are plotted as differences from prerehydration values, as are means ± SE of each group.

differences from the prehydration values in each subject, and the means of each group with standard error bars are also shown.

Since there were no significant differences between the regression formulas between the recovery conditions, all data were pooled for the following analysis. The rPV was closely correlated not only with the rTW ($y = 0.47 \times x - 3.8$; $r = 0.77$, $P < 0.01$), but also with the rECF space ($y = 0.48 \times x - 1.09$; $r = 0.87$, $P < 0.001$) during rehydration. The ratios of rPV to rECF were not significantly different between the two groups during rehydration, averaging 0.36 ± 0.11 and $0.29 + 0.04$ for H_2O-R and Na-R, respectively, but the ratio of rPV to rTW was significantly greater in Na-R (0.21 ± 0.05) than that in H_2O-R (0.12 ± 0.05).

The dashed lines in Figure 12-7 (top and bottom) are the theoretical lines, assuming that the distribution of ingested fluid between the two compartments was proportional to their initial volumes (Spector, 1956). All the data points except three are located above the theoretical lines, which means a greater relative recovery of PV than TW or ECF space.

DISCUSSION

It is well known that the regulation of fluid intake is influenced by both P_{osmol} and volume, as well as by oropharyngeal and gastric factors (Fitzsimons, 1979; Rolls and Rolls, 1982), but the relative importance of these factors in rehydration remains unknown. Since the early phase of rehydration is the time during which water and electrolytes move dynamically among fluid compartments to attain new steady states, transient changes in P_{osmol} and/or PV might influence drinking behavior.

Drinking: The Early Phase of Rehydration (0 to 60 min)

Even though the changes in P_{osmol} and PV were quite different between H_2O-R and Na-R until 60 min of rehydration bottom (Figure 12-3 and Figure 12-4), fluid intake and net fluid gain were identical during this period (Figure 12-1). During H_2O-R, P_{osmol} and $[Na^+]$ began to decrease immediately after the onset of drinking. $[Na^+]$ returned to the control level within 10 min and P_{osmol} returned by 30 min. During Na-R, P_{osmol} remained elevated after 60 min. Thus, if an elevated P_{osmol} were the only factor contributing to the dipsogenic drive, drinking should have been greater during Na-R. PV restoration at 60 min of H_2O-R was only 17% of that lost, whereas at 60 min of Na-R, PV restoration was 60% of that lost. Thus, the rates of fluid

intake in the different recovery conditions, while similar, were driven by different factors.

Other occurrences may have further contributed to the similarity in the rates of fluid intake despite the apparent differences in volume and osmotic drives in the two recovery conditions. The importance of preabsorptive tension in the early termination of drinking has been reported by several investigators (e.g., Rolls and Rolls, 1982). Thrasher et al. (1981) reported that in dogs oropharyngeal stimuli were important not only for the inhibition of drinking but also for the suppression of arginine vasopressin release. Similar results have been reported in humans (Geelen et al., 1984; Seckl et al., 1986). Rolls et al. (1980) suggested the importance of gut distension in the early termination of fluid intake based on subjective feelings reported by the subjects.

Drinking: The Later Phase of Rehydration (61-80 min)

Significant differences in fluid intake between H_2O-R and Na-R occurred at 180 min. P_{osmol} and $[Na^+]$ in Na-R remained elevated at 120 min. On the other hand, in H_2O-R P_{osmol} returned to the control level by 30 min. The increase in urine flow and C_{H2O} in H_2O-R after 120 min reflected the return of P_{osmol} to its control level, thereby causing net fluid gain to remain constant. During Na-R subjects restored PV to the control value by 30 min; during H_2O-R, PV was restored by 120 min.

Thus two issues should be considered in attempting to understand the greater cumulative fluid intake at 180 min during Na-R. The first is the persistent existence of an osmotic drive for drinking in Na-R and the early removal of this drive in H_2O-R. The second is that the PV recovery in the H_2O-R seemed to be sufficient to diminish the volume-dependent dipsogenic drive. In support of this latter notion, we found that plasma renin activity and plasma aldosterone returned to control levels by 180 min in H_2O-R (Nose et al., 1988b).

The fluid and electrolyte status in H_2O-R returned to the theoretical isotonic line by 60 min of rehydration (Figure 12-5). At this time, the subjects still had a 49% deficit in TW, of which 64% was attributed to inadequate replacement of ECF and 86% to inadequate replacement of ICF (Figure 12-6). During Na-R, subjects almost returned to the isotonic line by 180 min, and they did so closer to the origin. After 180 min the deficit to TW was 30%, which was nearly all attributed to the ICF deficit, since the subjects regained 95% of the Na^+ loss (Table 12-3). After 180 min the ICF space deficits were 4.2 and 5.3 ml/kg body wt ($P < 0.05$) in H_2O-R and Na-R (Figure 12-6), and the K^+ losses were 0.54 and 0.58 meq/kg body wt,

respectively (Table 12-3). In other words, the ICF space losses had an average [K^+] of 130 meq/kg H_2O-R in Na-R. Thus 70%-80% of the lost ICF space can be explained by the movement of water after the loss of K^+, assuming that [K^+] in ICF is initially 165 meq/kg H_2O (Nose et al., 1985). These results indicate that the ICF space deficit in both recovery conditions was almost entirely due to the K^+ loss. The larger ECF space deficit in H_2O-R was due to the greater loss of Na^+. In other words, the degree of rehydration in each compartment was determined by the ability to restore the ions lost from each compartment.

Recovery of PV

Costill and Sparks (1973) reported that rehydration with a glucose-electrolyte solution resulted in a better recovery of PV than with tap water after thermal dehydration. Mack et al. (1986) obtained similar results using dilute NaCl solutions. In this study, we found increases in PV of 1.6 and 3.5 ml/kg body wt after 180 min in H_2O-R and Na-R, respectively. This was equivalent to 12 and 21% of the net fluid gain and 36 and 29% of the increases in ECF space, respectively (Figure 12-7). It is reasonable to assume that the greater restoration of PV in Na-R was due simply to the greater restoration of the ECF space. Another possibility is that the gut absorption rate of a hypotonic NaCl solution may have been faster than that of tap water. Nose et al. (1986) reported that rats rehydrated with 0.45% NaCl solution tended to regain blood volume more rapidly than with tap water. Maximum changes in blood volume occurred 14 min after the onset of rehydration when drinking tap water and 9 min after the onset when drinking the NaCl solution. Hunt and Pothak (1960) investigated the effects of solutes on gastric emptying in resting humans and demonstrated that gastric emptying was three times faster when subjects drank a dilute saline solution (100-300 mosmol/kg H_2O) than when drinking distilled water. An improved gastric emptying may contribute to a more rapid restoration of blood volume when subjects drink dilute saline.

Figure 12-7 shows that the recovery of PV after 180 min of rehydration was relatively greater than the recovery of TW in both recovery conditions. The recovery of PV was also greater than the recovery of the ECF (Figure 12-7, bottom). Although the precise reason for the selective retention of ingested fluid in the vascular space is not clear, the movement of fluid between the intra- and extravascular compartments should follow the Starling forces (Gauer et al., 1970; Isogai et al., 1982; Morimoto et al., 1981a). The time to reach a steady state depends on the transvascular filtration coefficient for water, which is influenced by the availabel capillary

surface area in different conditions (Miki et al., 1983; Nose, 1982). Nose et al. (1983) reported that after thermal dehydration in rats, the splanchnic blood volume was well maintained, in contrast to that of skin and muscle. It is possible that a redistribution of blood flow to maintain the central blood volume changes the effective capillary surface area and influences fluid movement between intra- and extravascular spaces during rehydration. Thus, the rate of blood volume restoration should be determined by both the rate of fluid movement from the gastrointestinal tract to the intravascular space and the rate of fluid shifts between the intra- and extravascular spaces. The selective retention of ingested fluid in the vascular space may have diminished the volume-dependent dipsogenic stimulation in spite of the persistent existence of a TW deficit.

In summary, during recovery from moderate (2.3% body wt) whole-body dehydration, a delay in rehydration is caused by both the electrolyte deficit from the intra- and extracellular spaces and the removal of a volume-dependent dipsogenic drive due to the selective retention of ingested fluid in vascular space.

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13

Palatability and Fluid Intake

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INTRODUCTION

People consume fluids in response to a variety of physiological, psychological, and environmental stimuli. In this paper, I discuss some of the physiological changes that can affect fluid intake in man and why people drink spontaneously when they have free access to water. The sensations accompanying dehydration are also considered, as is rehydration and its accuracy in restoring fluid deficits. Finally, the effects of palatability of the availabel fluids on thirst satisfaction and consumption are discussed.

PHYSIOLOGICAL THIRST STIMULI

During fluid restriction, both the cellular and extracellular body fluid compartments are depleted. Changes in both compartments are associated with thirst and drinking. There is clear experimental evidence that dehydration of the cellular compartment is a potent thirst stimulus. For example, the effects of double-blind intravenous infusions of hypertonic saline (0.45 M) and isotonic saline (0.15 M) were compared in seven healthy young men (Phillips et al., 1985b). Only the hypertonic saline significantly increased

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plasma sodium and osmolality, subjective ratings of thirst, and water intake. The main sensations associated with the infusions were a dry and unpleasant-tasting mouth. The increase in plasma sodium (4.2 meq/liter) associated with thirst and drinking was well within the physiological range and was similar to the changes seen after exercise, thermal dehydration, and water deprivation.

The evidence for a role for hypovolemia in dehydration-induced drinking is more equivocal. Fluid deprivation decreases plasma volume, and such volume changes would be detected by receptors in and around the heart and kidneys. When the kidneys detect hypovolemia, renin is released, and it acts on a substrate in the plasma to increase the formation of angiotensin. Angiotensin II has been found to be a potent thirst stimulus in most species (Rolls and Rolls, 1982), but we have found that it stimulates drinking in humans only at supraphysiological levels (Phillips et al., 1985a). More experiments are needed to define the situations in which hypovolemia is a thirst stimulus in humans and to determine its mechanism of action.

SENSATIONS ASSOCIATED WITH DEHYDRATION

The idea that thirst is associated with unpleasant oral sensations dates back to the ancient Greeks. However, only recently have there been systematic attempts to characterize these sensations. Visual analog scales, which are 100 mm lines on which subjects indicate how they currently feel in relation to a very specific question (e.g., how dry is your mouth now?) have been critical in this assessment. We found, for example, that after 24 h without fluids, healthy young men showed a marked increase in ratings of thirst, how pleasant it would be to drink water, dryness of the mouth, and unpleasantness of the taste in the mouth. The changes in the sensations were significantly correlated with subsequent water intake (Rolls et al., 1980). Recently, there has been a detailed examination of the sensations accompanying graded levels of dehydration induced by restricting food and fluid intake and imposing a regimen of moderate heat-exercise stress. The number and intensity of unpleasant sensations reported increased with the level of dehydration. Sensations that showed a significant linear trend in intensity were a dry and irritated mouth; a bad and chalklike taste in the mouth; a dry, scratchy, and warm throat; chapped lips; feeling weary, dizzy, lightheaded, sleepy, tired, irritable, and thirsty; having a headache and loss of appetite; and thinking of drinking (Engell et al., 1987). It is not clear from this study whether the more general sensations are associated with a lack of caffeine that would result from fluid restriction (i.e., no coffee or tea). This

study also showed that these thirst sensations contributed to the differential fluid intake that followed the various levels of deprivation.

AD LIBITUM THIRST AND DRINKING

Although increased thirst and fluid intake follow depletions of body fluids, it is not clear whether, when liquids are freely availabel, people would wait for a significant depletion before drinking. To investigate whether thirst and drinking during free access to water occur in response to body fluid deficits, blood samples and visual analog-scale thirst ratings were obtained from five young men at hourly intervals and when they were thirsty during a normal working day. Although there were significant increases in ratings of thirst, pleasantness of drinking water, mouth dryness, and unpleasantness of the taste in the mouth when subjects were thirsty enough to drink compared with the ratings during intervening intervals, there were no concomitant changes in body fluid variables. Subjects drank mainly in association with eating. The results indicated that during free access to water, humans become thirsty and drink before body fluid deficits develop, perhaps in response to subtle oropharyngeal cues (Phillips et al., 1984a).

Several other recent studies have confirmed that when food and a variety of fluids are consumed freely, most of the fluid intake is associated with eating (de Castro, 1988; Engell, 1988). In one of these studies, de Castro (1988) concluded that in such situations, spontaneous fluid intake is in excess of requirements and is determined primarily by eating, with excess fluid being eliminated by the kidneys.

REHYDRATION

Although fluid intake is normally closely associated with food intake, most of the controlled studies of rehydration have been conducted with no food availabel. This does not negate the importance of these studies but indicates that they should be extended to encompass the more naturalistic situation in which food and fluid are both availabel. It is likely that during the early stage of rehydration, little food would be consumed, but that as rehydration continues, the consumption of food would encourage further fluid intake.

It was found that following acute thirst stimuli, such as hypertonic saline infusions or 24 h fluid deprivation, healthy young individuals drank sufficient room temperature tap water in an hour to restore the body fluids to prestimulus levels (Phillips et al., 1985b; Rolls et al., 1980). It is

important to note that drinking slowed before plasma dilution had become significant. The attenuation of drinking was attributed to changes in sensations, such as stomach fullness and decreased mouth dryness (Rolls et al., 1980). In contrast to these young men, healthy elderly individuals do not experience normal thirst following fluid deprivation and do not rapidly restore their body fluids to predeprivation levels (Phillips et al., 1984b). In future studies, special consideration should be given to those factors that influence rehydration in the elderly.

A number of studies indicate that prolonged dehydration in situations such as intense exercise or thermal dehydration in a desert environment is associated with voluntary dehydration in which insufficient fluid is consumed to restore body fluids (Hubbard et al., 1984). It is clear, however, that the taste and temperature of the availabel fluids can influence the rate of rehydration.

TASTE OF DRINKS

The taste of the availabel drinks is a major determinant of the amount consumed. There are many factors that influence how good a particular drink tastes to an individual. For example, the cultural background of the individual (Rozin and Vollmecke, 1986), previous experience with the drink (Pliner, 1982), and the time of day (Birch et al., 1984) can affect palatability. Even within an individual, palatability is not constant. Dehydration can increase the pleasantness of fluids, whereas rehydration decreases the pleasantness (Rolls and Rolls, 1982). The decrease in pleasantness can, however, be specific to the particular fluid being consumed, so if the goal is to increase fluid intake, switching to a different drink will help to maintain consumption (Rolls, 1986). It has been shown that variety can increase fluid consumption. Nondeprived subjects, under the pretext of a tasting experiment, consumed three drinks successively, with a 10-min period allowed for each drink, under three different conditions: three different flavors (low-calorie orange, lemon, and lime drinks), one flavor only, or water alone with no flavor. More (22%) was consumed in the three-flavor condition than in the no-flavor condition, and more (99%) was consumed in the one-flavor condition than in the no-flavor condition (Rolls and Rolls, 1982).

It is well known that adding sweeteners to drinks leads to increased fluid intake (Rolls, 1987). Soft drinks are consumed in large quantities in the absence of physiological need. This excess fluid does not matter as long as the kidneys are functioning normally, but palatable drinks can potentially induce dangerous overhydration when kidney function is impaired (Rolls et al., 1978). Surprisingly little is known about the effects of soft drinks on the

satisfaction of thirst. This lack of information meant that claims such as "sugary soft drinks can leave you thirstier than ever" made in the press (Brody, May 13 and 20, 1987) could not be confirmed or denied.

We (Rolls et al., 1990) have recently determined the effects on ratings of thirst of two volumes (8 and 16 oz.) of three drinks: lemonade sweetened with sucrose (8.3%), lemonade sweetened with aspartame (0.045%), and tap water, all of which were served at 9°C. Fourteen male subjects were tested in all six conditions as well as in a no-drink condition. The drinks were consumed with a lunch of sandwiches. Surprisingly, the subjects ate the same amount of food regardless of the type or volume of drink availabel. The drinks did, however, have differential effects on ratings of thirst measured immediately after the end of the meal. The suppression of thirst was greater with the 16-oz. drinks than with the 8-oz. drinks. The type of drink availabel also affected the ratings of thirst, in that the water and aspartame-sweetened drinks were equally effective in reducing thirst and were both more effective than the same volume of the sucrose-sweetened drink. The subjects were unable to tell the difference between the aspartame- and sucrose-sweetened drinks in a sensory evaluation test at the end of the study. It is not clear how these different effects on thirst would affect subsequent fluid intake.

A recent study indicates that adding too much sugar to beverages can decrease acceptability. Trained athletes reported that glucose-electrolyte drinks containing 12% glucose caused significantly more nausea and fullness than either 6% glucose or water. Because of the possibility of stomach upset, they were less likely to choose the more concentrated drink during training or competition (Davis et al., 1988).

TEMPERATURE OF DRINKS

As with the taste of drinks, the preferred temperature depends on a number of factors, which include culture and learning (Zellner et al., 1988) and the physiological state of the individual (Sandick et al., 1984). Several studies indicate that finding the optimal temperature for availabel fluids will improve rehydration. In a French study (Boulze et al., 1983), men were dehydrated by mountain climbing or sweating in a vaporarium. During rehydration, when offered water from 0 to 50°C, subjects drank the most when the water was 15° C; this was the preferred temperature. In an American study (Sandick et al., 1984), subjects drank the most of the coldest water (5°C) during rehydration after exercise. In a study in which the effects of both the flavor and temperature of the availabel beverages on rehydration after a simulated desert walk were examined, it was found that consumption of cold, flavored, iodinated water elicited over twice the percent rehydration

(80.5% versus 37%) than when warm iodinated water was ingested (Hubbard et al., 1984). There is a need not only for more studies on temperature and intake, but the effects of the temperature of various fluids on the rate of rehydration should also be determined.

CONCLUSIONS

Although the termination of drinking ultimately depends on the restoration of fluid and electrolyte losses, the early slowing of drinking during rehydration is attributed to a reduction of the sensations associated with thirst (Rolls et al., 1980; Sandick et al., 1984). It is known that the taste and temperature of beverages can affect these sensations, but as yet, this information has not been translated into the development of optimal drinks that will ensure fluid balance in different environments.

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14

Solute Model or Cellular Energy Model? Practical and Theoretical Aspects of Thirst During Exercise

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INTRODUCTION

Most physiologists would agree that repaying the water debt incurred through evaporative cooling is part of the physiological cost of work in the heat. Pitts et al. (1944) emphasized that during work in the heat, men never voluntarily drink as much water as they lose and usually replace only two-thirds of the net water loss. Rothstein et al. (1947) observed that this occurred even when water was availabel and called this phenomenon voluntary dehydration. Some physiologists feel that voluntary dehydration occurs because ". . . thirst is an inadequate stimulus to drinking" (Ladell, 1965, p. 253). On the other hand, Vokes (1987) contends that ". . . one of the best examples of a perfectly functioning homeostatic system is water balance" (Vokes, 1987, p. 383). One of our goals is to reconcile the fact that under certain conditions both of these statements are correct. We will also try to switch the reader's interest from water to salt for, although man may drink, ". . . water cannot be held until the missing osmoles are made good"

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(Ladell, 1965, p. 284). This may be seen as at least one explanation of why thirst is inadequate, and there are others.

Common sense would dictate that it is quite useless to estimate a "normal" fluid intake because we are dealing with a homeostatic system designed to equate water requirements with the various losses (respiratory, urinary, skin, and sweat). Let us look briefly at these as a partial inventory of our water demand. Under normal conditions, respiratory water loss is about 200 ml/day, but it can be around 350 ml/day for men working in a dry climate and can approach 1,500 ml/day for men working at high altitudes in cold air (Ladell, 1965). The insensible perspiration may be as low as 500 ml in a moist climate, and with a minimum urine volume (<300 ml/day), a person can barely meet obligate losses on 1,000 ml of water per day. The obligate urine volume varies with the diet and is high on a high-protein diet and low on a carbohydrate diet. A more reasonable figure for urine volume represents a maximum of 1.4 osmol of metabolic end products (mostly urea and surplus electrolyte) per liter of urine on a mixed European-style diet. Thus, the greatest rate of water loss, by far, is represented in a healthy individual by eccrine sweating, which most physiologists would agree can be sustained at something over 1 liter/h. This makes sense, because the maximum rate of gastric emptying has been estimated between 15 and 20 ml/min or 900 to 1,200 ml/h (Davenport, 1982).

According to Ladell, ". . . thirst is primarily a sensation, which often serves as a drive to drink, but the drive and the sensations are not necessarily identical" (Ladell, 1965, p. 271). Ladell (1965) has further introduced a concept of free circulating water, equivalent to some 2 liters, which does not appear to participate in the osmotic balance of the body. This suggests that the drive to drink would not come into play until this free circulating water is expended. This interesting notion actually delivers two important ideas: (1) There is an inherent delay in the onset or drive of thirst. If this could be explained, it would then be more accurate to describe thirst as delayed rather than inadequate. (2) The delay is a manifestation of the body's osmotic control.

HYPERTONICITY, ANTIDIURETIC HORMONE RELEASE, AND THIRST

Although the solute composition of the extracellular compartment is markedly different from that of the intracellular space, the total osmolalities (solute concentration, not content) (Conway and McCormack, 1953) are very similar. This is because most cell membranes are freely permeable to water. Thus, one can approximate intracellular fluid osmolality by measuring the

plasma osmolality (Feig and McCurdy, 1977). The major intracellular osmotic solutes are potassium, magnesium, organic phosphates, and protein. The major osmotic solutes in extracellular fluid are normally sodium and its anions, chloride, and bicarbonate. They are referred to as impermeant but are kept on the proper side of the membrane by molecular size, electrical charge, or active pumps. Net movement of water is determined by the osmolalities of the intra- and extracellular compartments (Peters, 1944).

The osmolal concentration or osmolality (usually in milliosmoles per kilogram of water) is an indiscriminating summation of all the particles, ions, and molecules present in a solution. It is usually measured by freezing point depression or change in vapor pressure. Measured osmolality should be differentiated from effective osmolality (i.e., the concentration of solutes that will create an osmotic force in vivo). For example, sodium is the major determinant of the effective osmolality of the extracellular fluid because its concentration is high and it acts as if it is restricted from entering cells (Guyton, 1986). In contrast, urea permeates cells freely and does not exert an osmotic force if it is elevated in either compartment. The addition of an impermeant solute to the extracellular space causes a net intracellular fluid volume depletion and creates, by definition, a hypertonic state (Feig and McCurdy, 1977). Freezing point depression does not distinguish between permeant and impermeant solutes by measuring osmolality. Thus, an elevated plasma osmolality must be checked by calculation of tonicity before it is interpreted as hypertonicity. For example, 2 × plasma sodium (meq/liter) + plasma glucose (mg/dl/18) = approximate tonicity.

Normally, intracellular fluid contains about two-thirds of the total body solute, and one-third is in the extracellular fluid. Since water distributes according to the amount of impermeant solute in each compartment, the intracellular fluid contains two-thirds of total body water (TBW) and extracellular fluid contains about one-third of TBW. Assume, for ease of calculation, that the average 70-kg adult is 60% water (TBW = 42 liters) and two-thirds (28 liters) is intracellular and one-third (14 liters) is extracellular (3.5 liters of plasma and 10.5 liters of interstitial fluid). Note by calculation (Feig and McCurdy, 1977) that the intravascular or plasma volume is equivalent to one-twelfth of the total body water (3.5:42 as 1:12) and that the plasma volume is one-fourth the extracellular volume (3.5:14 as 1:4). Thus, by definition, if a pure water loss occurs (no salt loss), two-thirds comes from the intracellular water, one-third comes from the extracellular water, and one-twelfth comes from the intravascular water. In practice, less than one-twelfth of the water loss usually comes from the plasma space because of increased plasma protein oncotic pressure (Feig and McCurdy, 1977). It also follows that if the extracellular space loses 4 liters

of isotonic saline, three-fourths would come from the interstitial fluid and one-fourth would come from the plasma fluid.

Gilman (1937) demonstrated that intravenous infusions of hyperosmotic sodium chloride elicited drinking but that equally hyperosmotic solutions of urea stimulated thirst poorly. Since urea could diffuse into cells but sodium would produce shrinkage, an osmotic basis for thirst was established. Other solutes that cause the withdrawal of water from cells, such as sucrose and sorbitol, were equally effective in producing thirst when infused intravenously (Holmes and Gregersen, 1950a,b). These observations reinforced the important role of cellular dehydration in triggering thirst and drinking behavior. The classic work of Verney (1947) demonstrated that water diuresis in dogs could be inhibited by intracarotid infusions of hypertonic sodium chloride and, therefore, that both thirst and antidiuresis were linked to the osmotic withdrawal of water from cells. Verney (1947) deduced that the inhibition of water diuresis resulted from neurohypophyseal secretion of vasopressin, which was later confirmed (Wade et al., 1982). According to Andersson (1978), the most potent stimulators of antidiuretic hormone (ADH) release and thirst are absolute and relative dehydration. Although ADH is released as a function of the body osmolality (Robertson and Athar, 1976; Robertson and Mahr, 1972), it is equally well correlated with plasma sodium (Olsson et al., 1978).

Andersson (1978) suggested that sodium itself is the crucial factor in the osmotic control of water balance and proposed that the centrally located osmoreceptors are responding to specific changes in the cerebrospinal fluid (CSF) sodium concentration subsequent to perturbations in the extracellular fluid osmolality. This was supported by the observation that hypertonic sucrose did not stimulate thirst and ADH when infused into the third ventricle (Olsson, 1969). Intracerebral infusions of hypertonic sucrose can inhibit ADH release by dilution-reduction of the CSF sodium concentration, which argues against a receptor location outside the blood-brain barrier. Andersson (1978) recognized that there is the possibility that both elevated sodium and cellular dehydration trigger a biochemical process involved in the receptor-excitation mechanism. Andersson (1978) further suggested that angiotensin II might be an activator of a cationic transporting enzyme. Angiotensin II (Gutman et al., 1972), L-norepinephrine (Desaiah and Ho, 1977), and prostaglandin PGE1 (Limas and Cohn, 1974) interact with sodium, possibly at the level of Na-K-adenosine triphosphatase (ATPase), in stimulating ADH and thirst.

The ADH of humans and most other mammals is arginine vasopressin, which is produced by the neurohypophysis. Under physiological conditions, ADH release is apparently controlled primarily by plasma osmolality, but the osmoregulatory system appears to display large individual (Robertson, 1977;

Robertson et al., 1976) differences (biological variability?) in both sensitivity and threshold. However, this could be analogous to the apparent differences in the onset of sweating, which depends on an acclimatization response to repeated exposures. Within any one individual, the plasma vasopressin response (ADH release) is linearly related to plasma osmolality across the same range within which thirst is stimulated (Robertson et al., 1976). Generally, the range of body fluid osmolality in a person in good health is between 280 and 295 mosmol/kg of water or 287 ± 2% (Feig and McCurdy, 1977). At a plasma osmolality of 280 mosmol/kg of water, ADH release is completely inhibited (Feig and McCurdy, 1977) and the urine osmolality is minimal (< 100 mosmol/kg of water).

According to Robertson and Berl (1985), the full range of urinary concentrations can be achieved by changing the plasma ADH concentration to between 0.5 and 5.0 pg/ml. The most important action of ADH is to conserve body water by increasing the renal reabsorption of solute-free water, which increases the urine concentration and decreases the urine flow. Although there is wide variation in individual thirst threshold, Vokes (1987) estimated its average value at 295 mosmol/kg of water. Thus, at the thirst threshold (the highest plasma osmolality that occurs normally), the increased ADH concentration elicits maximum urinary concentration [urine osmolality (U_{osmol}) > 800-1000 mosmol/kg of water].

According to Feig and McCurdy (1977), the mathematical relationship between variables across this physiologic range can be expressed by the following equations:

$$0.34 \times \text{change in plasma}_{osmol}\ (P_{osmol}) = \text{change in plasma ADH (in pg/ml)},$$

$$\text{change } U_{osmol} = 95 \times \text{change in } P_{osmol}.$$

Thus, a 1-mosmol plasma change increases urine osmolality by almost 100 mosmol, and at the thirst threshold (295 mosmol/kg of water), urine volume is reduced 10- to 20-fold. Therefore, it can be appreciated that ADH and thirst play key roles in maintaining the water balance, primarily by regulating the plasma osmolality over a very narrow range (Vokes and Robertson, 1985) bounded on the lower end by the osmotic threshold for ADH releases (280 mosmol/kg) and on the upper end by the osmotic threshold for thirst (295 mosmol/kg). This lack of complete parity between an increase in osmolality and the behavior of thirst--(1) seeking water, (2) drinking water, (3) ceasing to drink, and (4) absorption and distribution (Adolph et al., 1954)--could represent an importation adaptation which frees people and animals from the necessity to irritate themselves repeatedly in response to minor increases in osmolality (Stricker and Verbalis, 1980,

p. 261). Thus, thirst does not become prominent until the osmotic dehydration exceeds the renal capacity to deal with it physiologically.

EXAMPLE 1: FREE CIRCULATING WATER

Ladell (1965) has introduced the idea of free circulating water that is equivalent to some 2 liters of TBW but does not appear to participate in the body's osmotic balance. Let us examine this in light of the current mechanism for thirst stimulation. If we assume that a pure water deficit does not alter the total body solute, then hypertonicity will be proportional to the volume of water lost (Feig and McCurdy, 1977):

(normal TBW) × (normal P_{osmol}) = present TBW) × (present P_{osmol}).

We also assume parity between a liter and a kilogram of water: If a man begins to lose pure water at the lowest normal plasma osmolality (Feig and McCurdy, 1977) of 280 mosmol/kg of water (fully hydrated), we can calculate about how much water will be lost before the average threshold (Vokes, 1987) for thirst is reached at 295 mosmol/kg water:

(normal TBW) × (normal P_{osmol}) = (thirst TBW) × (thirst P_{osmol}),

(42 liters) × (280 mosmol/kg) = liters x (295 mosmol/kg)

(11,760 mosmol/295 mosmol/kg) = liters = 39.9 liters = TBW at the thirst threshold,

(42 liters-39.9 liters) = 2.1 liters = TBW deficit.

This calculation suggests that, on average, 2.1 liters of water would be lost before reaching the thirst threshold. This assumes that a person begins losing water when that person is fully hydrated, which is more common practice in research than in other activities. This figure appears to confirm the prior observation by Ladell (1965) that there is free circulating water equivalent to some 2 liters that does not appear to participate in the osmotic balance of the body. This calculation provides futher support to the two arguments (1) that thirst is delayed rather than inadequate and (2) that the delay is a manifestation of the body's osmotic control.

EXAMPLE 2: PURE WATER DEFICIT IN THE HYDRATED STATE: IMPACT ON REHYDRATION

Let us examine the impact of the thirst threshold on rehydration in a common situation (TBW loss = 6% of body weight or 4.2 liters; begin from fully hydrated state).

Dehydration

First, let us calculate how high the plasma osmolality would be driven without fluid intake.

(normal TBW) × (normal P_{osmol}) = (dehydrated TBW) × (dehydrated P_{osmol}),

(42 liters) × (280 mosmol/kg) = (42 liters − 4.2 liters) × (? mosmol/kg)

(11,760 mosmol/37.8 liters) = 311.1 mosmol/kg = dehydrated P_{osmol}.

Rehydration

(dehydrated TBW) × (dehydrated P_{osmol}) = (thirst TBW) × (thirst P_{osmol})

(37.8 liters) x (311.1 mosmol/kg) = (295 mosmol/kg) x (? liters)

(11,760 mosmol/295 mosmol/kg) = 39.9 liters = rehydrated TBW.

Thus, at the thirst threshold (a plasma osmolality of 295 mosmol/kg), a TBW of 39.9 liters is theoretically achieved. Since the prior, dehydrated TBW was 37.8 liters, there was a net gain in TBW of 2.1 liters (39.9 liters − 37.8 liters). This suggests that only 50% (2.1 liters × 100/4.2 liters) of the fluid deficit would be rehydrated before the thirst threshold is reached. Under these conditions, thirst is not inadequate. The rehydration deficit is an inherent feature of the offset between the thirst set point relative to the renal diuresis set point in the fully hydrated condition. For example, it is not uncommon to assess a fully hydrated condition by having test subjects consume water until urine specific gravity declines to some target end point. Thus, fully hydrated test subjects before dehydration will almost certainly never fully rehydrate after dehydration. This calculation appears to confirm the early assertion of Pitts et al. (1944) that subjects rarely consume sufficient water to replace the deficit. Since only one-twelfth or less of this deficit (2.1 liters/12 = 175 ml) comes from plasma (3.5 liters:42 liter as 1:12), given its high oncotic pressure, there is very little impact on cardiovascular performance.

EXAMPLE 3: PURE WATER DEFICIT PRODUCING CLINICAL SHOCK

Clinical shock from pure water loss generally requires a sodium above 170 meq/liter (Feig and McCurdy, 1977). This water deficit can be calculated by the following formula equation *(Yarbrough and Hubbard, 1989):

Water deficit (liters) = TBW or (0.6 × wt in kg) − [TBWX desired (Na)/ measured (Na)],

water deficit = 42 liters − [(42 liters) × (140 meq/liters)/(170 meq/liters)] =

42 liters − 34.6 liters = 7.4 liters

Thus, in a pure water deficit sufficient to produce shock, one might estimate a minimum loss of some 7.4 liters. Since one-twelfth of this deficit is coming from the plasma (7,400 ml/12 = 616 ml), there is a decline in plasma volume of about 18% (616 ml × 100/3,500 ml). One rarely sees a pure water deficit since salt is usually lost as well. The percent body weight loss in this example is 10.6% (7.4 liters × 100/70 kg).

EXAMPLE 4: PURE WATER DEFICIT IN THE HYPOHYDRATED STATE: IMPACT ON REHYDRATION

If the subjects losing water are hypohydrated at the thirst threshold with a thirst plasma osmolality of 295 mosmol/kg of water (thirst TBW = 39.9 liters) and then lose 4.2 liters (6% of initial body weight), their plasma osmolality could rise to:

(thirst TBW) × (thirst P_{osmol}) = (dehydrated TBW) × (dehydrated P_{osmol}),

(295 mosmol/kg) × (39.9 liters) = (39.9 liters − 4.2 liters) × (? mosmol/kg),

(11,770 mosmol/35.7 liters) = 330 mosmol/kg water.

The dehydrated plasma osmolality could be 330 mosmol/kg and the dehydrated TBW could be 35.7 liters. If they drink until the starting thirst threshold is reached (rehydrate), they should consume:

(dehydrated TBW) × (dehydrated P_{osmol}) = (thirst TBW) × (thirst P_{osmol}),

(35.7 liters) × (330 mosmol/kg) = (? liters) × (295 mosmol/kg),

(11,781 mosmol/295 mosmol/kg) = 39.9 liters (thirst TBW).

Thus, at the thirst threshold (a plasma osmolality of 295 mosmol/kg), a TBW of 39.9 liters would be achieved. Since the dehydrated TBW was 35.7 liters, an intake of 4.2 liters was required to reach the thirst threshold. This suggests that, by beginning the dehydration in the hypohydrated state at the thirst threshold, a nearly 100% rehydration of the dehydration deficit but only 66.7% of the total deficit (6.3 liters) could be expected. Therefore, rehydration results will depend on whether test subjects show up hydrated (50% rehydration) or hypohydrated (100% rehydration) for an experiment producing a 6% loss in body weight as body water.

EXAMPLE 5: HYPOTONIC WATER DEFICIT IN THE HYDRATED, NON-HEAT-ACCLIMATIZED STATE

Assume that the subject is unacclimatized to heat and produces a hypotonic sweat (0.43% NaCl = 1/2 isotonic saline) as the source of body water deficit. He begins work in the heat in a fully hydrated, normal condition (plasma osmolality = 280 mosmol/kg of water) and then loses 6% of body weight (4.2 liters) as sweat.

Solute Deficit

We first compute the impact of the solute loss (sweat NaCl) on the total solute content of the body. The total of 11,760 mosmol (280 mosmol/kg × 42 liters) is reduced by an amount equivalent to the solute content of the lost sweat. Assume that 1/2 isotonic saline is equivalent to an osmolality of 140 mosmol/kg (0.5 × 280 mosmol/kg), then:

(140 mosmol/kg of sweat) × (4.2 liters) = 588 mosmol of lost solute.

The new salt-depleted total solute content is 11,172 mosmol (11,760 mosmol − 588 mosmol).

Dehydration

The new salt-depleted TBW will be 37.8 liters (42.0 liters − 4.2 liters). The new salt-depleted, dehydrated plasma osmolality will be 295.6 mosmol/kg (11,172 mosmol/37.8 liters). Assume that one-half of the fluid loss is pure water (2.1 liters) and the other half is isotonic saline. The plasma would contribute one-twelfth of the pure water deficit, or 175 ml. The extracellular space would lose 2.1 liters of isotonic saline, of which the

plasma contributes (3.5:14 as 1:4) 2,100 ml × 1/4 = 525 ml. If we add the 175 ml from the pure water portion (525 ml + 175 ml = 700 ml), we see that the plasma has lost 20% of its volume (700 ml × 100/3,500 ml) which, as seen above, is close to the shock threshold. Thus, a 4.2 liter sweat loss has theoretically as much impact on the plasma (volume −20%) as a much greater volume (7.4 liters) of pure water loss (−18%).

Rehydration

If the subject drank pure water until the plasma osmolality reached the thirst threshold (295 mosmol/kg), he or she would reach a thirst TBW of:

(dehydrated TBW) × (dehydrated P_{osmol}) = (thirst TBW) × (thirst P_{osmol}).

Assume the dehydrated condition to be a TBW of 37.8 liters and a salt-depleted, dehydrated plasma osmolality of 295.6 mosmol/kg of water. Assume the plasma osmolality to be 295 mosmol/kg at the thirst threshold.

(37.8 liters) × (295.6 mosmol/kg) = (? liters) × (295 mosmol/kg),

(11,172 mosmol/295 mosmol/kg) = 37.88 liters of TBW.

The subject would increase his or her TBW by only 80 ml (37.88 liters – 37.8 liters) before the thirst threshold was reached. This is equivalent to only 1.9% of the initial water deficit (80 ml x 100/4,200 ml). In contrast to a similar volume of pure water loss from a hydrated starting point, a hypotonic deficit reduces the expected percent rehydration from 50% to 1.9%. This example serves to indicate the impact of solute loss on rehydration. Under these conditions, thirst is not inadequate. The problem is the missing solute. Any fluid intake under these conditions would probably be stimulated by the volume deficit.

EXAMPLE 6: HYPOTONIC WATER DEFICIT IN THE HYDRATED, HEAT-ACCLIMATIZED STATE

Assume that a subject was producing a sweat of minimum sodium concentration (a very hypotonic sweat; 0.17% NaCl = 0.2 isotonic saline) due to heat acclimation and a low-salt diet (high aldosterone levels). He subsequently loses 6% of his body weight (4.2 liters) after beginning work in the heat, fully hydrated.

Solute Deficit

His solute content would be 280 mosmol/kg × 42 liters = 11,760 mosmol, and his solute loss would be equivalent to the sweat solute concentration (280 mosmol/kg × 0.2 = 56 mos/kg) × sweat volume (4.2 liters) = 235 mosmol. His salt-depleted total solute content would be 11,760 mosmol − 235 mosmol = 11,525 mosmol.

Dehydration

His salt-depleted, dehydrated TBW would be 37.8 liters; therefore, the plasma osmolality would be: 11,525 mosmol/37.8 liters = 305 mosmol/kg of water. This deficit is equivalent to 839 ml (1,000 ml × 235/280) of isotonic saline or 0.84 liters of saline. The plasma contributes 25% or 210 ml of this deficit (839 ml/4). The remaining deficit is pure water (4,200 ml – 839 ml = 3,361 ml), of which the plasma contributes one-twelfth or 280 ml. The total plasma deficit is 490 ml (280 ml + 210 ml) or 14% (490 ml × 3,500 ml) of the plasma volume.

Rehydration

If the subject drank until the plasma osmolality reached the thirst threshold, then:

(dehydrated TBW) × (dehydrated P_{osmol}) = (thirst TBW) × (thirst P_{osmol}),

(37.8 liters) × (305 mosmol/kg) = (? liters) × (295 mosmol/kg),

(11,525 mosmol/295 mosmol/kg) = 39.07 liters.

The subject would consume 1.27 liters (39.0 liters – 37.8 liters) in reaching the thirst threshold. This represents 30.2% replacement of the total deficit (1.27 liters × 100/4.2 liters). Approximately 100 ml of this 1.27 liters would be returned to the plasma (1.27/12) and would reduce its deficit to 11%, 490 ml – 100 ml or 390/3,500 ml.

Thus, heat acclimation could be expected to improve cardiovascular stability by reducing the solute loss, thereby preserving some plasma volume (390 ml versus 750 ml deficits). Moreover, it should have a pronounced impact on rehydration (30.2% versus 1.9%).

EXAMPLE 7: HYPOTONIC WATER DEFICIT IN THE HYPOHYDRATED, HEAT ACCLIMATIZED STATE

If the same subject began work slightly hypohydrated at the thirst threshold at a plasma osmolality of 295 mosmol/kg, he would have a TBW of 39.9 liters (2.1 liter deficit).

Solute Deficit

His total solute content would be 11,760 mosmol (295 mosmol/kg × 39.9 liters). His or her solute loss would be equivalent to the sweat solute concentration (56 mosmol/kg) x sweat volume (4.2 liters) = 235 mosmol. The salt-depleted solute content would be 11,525 mosmol.

Dehydration

After losing a 4.2 liter volume of sweat (39.9 liters − 4.2 liters = 35.7 liters), the salt-depleted plasma osmolality would be 323 mosmol/kg (11,525 mosmol/35.7). The extracellular fluid deficit due to salt loss would be equivalent to 0.84 liters of saline (235/280 × 1,000 ml of isotonic saline), of which the plasma contributes 25% or 210 ml. The pure water deficit equals 5,460 ml [3,360 ml (4,200 ml − 840 ml) + 2,100 ml]. The plasma contributes 665 ml (5,460 ml/12 = 455 ml + 210 ml). Thus without drinking there would be a 19% deficit (665 ml × 100/3,500 ml) in plasma volume.

Rehydration

If the subject drank until the thirst threshold was reached, then:

(dehydrated TBW) × (dehydrated P_{osmol}) = (thirst TBW) × (thirst P_{osmol}),

(35.7 liters) × (323 mosmol/kg) = (? liters) × (295 mosmol/kg),

(11,531 mosmol/295 mosmol/kg) = 39.09 liters.

The subject would consume 3.39 liters (39.09 liters − 35.7 liters) in returning to the thirst threshold. This represents an 81% replacement of the dehydration deficit (4.2 liters) or a 54% replacement of the total deficit (6.3 liters). This again would be an important consideration for studies in which the initial hydration status of the subjects was not known, for the resultant

rehydration value could be 54% or 81% rehydration of the experimental body weight change. With drinking, the subject would consume 3.39 liters. Approximately 282 ml of this would be returned to the plasma (3,390 ml/12) and would reduce (668 ml – 282 ml) its deficit to 386 ml. Thus, with drinking there would be an 11% deficit in plasma volume (386 ml × 100/3,500 ml).

The evaporative loss by a nonsweating man is made up of the respiratory water loss and the insensible perspiration and is called the insensible water loss (Ladell, 1965). It is not really possible to give a firm figure for either the respiratory water loss or for the insensible perspiration, because the lower the atmospheric water vapor pressure, the greater the loss. Although the temperature and humidity of the expired air do not vary greatly (Osborne, 1913), the increased water content (90% saturated) (Burch, 1945; McCutchan and Taylor, 1951) relative to the inspired air represents an inevitable loss. Under normal conditions, respiratory water loss is about 200 ml/day but may be around 350 ml/day for men working in a dry climate and may approach 1,500 ml/day for men working at high altitudes in cold air (Ladell, 1965). The insensible perspiration may be as low as 500 ml in a moist climate. It is clear from these examples that the dessication producing a relatively pure water loss would be a slow process. For example, even at minimum water losses per day (1,500 ml/24h), it would take nearly 5 days to reproduce the situation in example 3 (see Table 14-1). This does not fit most military scenarios except abandonment in a life raft or some involuntary confinement. Note the large increase in plasma osmolality or sodium (170 meq/liter) in this case and the enormous loss of fluid necessary to produce an 18% deficit in plasma volume. This is why shock from primary water depletion is relatively rare.

A pure water deficit producing a 6% loss in body weight (Table 14-1, example 2), primarily through nonsweating means, would probably have to occur through work in the cold at high altitude. The large respiratory water loss (approximately 1,500 ml/day) would make this another unlikely military scenario. Even more unlikely is the 6% loss in body weight superimposed on a preexisting deficit (−3%) at the thirst threshold (9%, total; example 4). Even if these examples overestimate the times required to produce this form of primary water depletion, they serve to illustrate the highly unlikely prospect of ever being militarily relevant.

The first hypotonic sweat losses calculated (example 5) for nonacclimatized individuals are striking for several reasons. First, it takes a relatively short time to produce a severe loss in plasma volume (−20%, 4 h) versus a similar deficit via pure water routes (−18%, 5 days; example 3). The calculated values are at equilibrium concentrations, and plasma osmolality (and, therefore, thirst) would be greater before the extracellular water debt

was paid by intracellular losses. This indicates why thirst and rehydration experiments should not be started until the equilibrium state has been achieved. Second, the equilibrium plasma osmolality does not reflect the volume loss because of the concurrent salt losses. The pure water loss is absorbed just in reaching the thirst threshold. Under these conditions, the only inclination to drink at equilibrium times would be due to volume depletion signals. Third, the percent change in the extracellular fluid volume (2.8 liters x 100/14 liters) equals the percent change in plasma volume (−20%). Finally, this model assumes no gain in solute from a prior meal. This strongly reinforces the concept of skipped meals in the etiology of this condition and further lends support for electrolyte replacement as soon as even one meal is missed.

The advantages conferred by heat acclimation on reducing electrolyte losses are seen (example 6) if one assumes equivalent volume losses. In actuality, either the times to achieve a 4.2 liter deficit would be shorter or the volumes lost would be greater. The 50% reduction in total sweat sodium losses (294 versus 118 meq) reduces the plasma volume deficit from severe to moderate levels and, at the same time, improves the osmotic drive for thirst (80 versus 1,270 ml). The impact of sodium reduction through sweat is further appreciated when one estimates that a 9% body weight loss in the acclimatized state (example 7) is roughly equivalent to a 6% loss in the nonacclimatized condition (example 5).

THIRST AND METABOLISM: THE ENERGY DEPLETION MODEL

It is interesting to note that hypoglycemia stimulates many hormones, including vasopressin, in both rats (Baylis and Robertson, 1980) and humans (Baylis et al., 1981). According to Vokes (1987), the mechanism is secondary to an intracellular glucopenia, since a similar effect can be induced with 2-deoxyglucose (Vokes, 1987; Vokes and Robertson, 1986). Hypoglycemia has recently been identified as a serious complication of heat stroke and, along with dehydration, it could play a significant role in heat stroke pathophysiology. In this regard, we have recently attempted to identify the cellular site or location where the physical effects of heat are translated to the physiological manifestations of heat strain (Hubbard et al., 1987). The underlying mechanisms (cellular site) as well as the theoretical rationale could share a common application with thirst research and are reviewed here.

Table 14-1 Effect of Pure Water Loss, Hypotonic Sweat Loss, and Heat Acclimation on Thirst and Rehydration

Condition (Example)	Water Loss (liter or % Body Weight Loss)	Salt Loss (mosmol or meq)	PV Loss (ml/ECF Loss)	PV	P_{osmol} (mosmol)	Estimated Rehydration	Incidence
Voluntary dehydration, euhydrated (example 2)	4.2.L 6.0%	--	350 ml 1.4 L	−10%	311	2.1 L 50%	~3 days work in cold, high altitude
Shock, involuntary dehydration (example 3)	7.4 L 10.6%	--	616 ml 2.47 L	−18%	350	--	Life raft, confinement, 5 days
Voluntary dehydration, nonacclimated, euhydrated (example 4)	6.3L 9.0%	--	525 ml 2.1 L	−15%	330	4.3 L 66.7%	~4 days at cold, high altitude
Voluntary dehydration, nonacclimated, euhydrated (example 5)	4.2 L 6.0%	588/ 294	700 ml 2.8L	−20%	295.6	80 ml 1.9%	~4 h of work in heat
Voluntary dehydration, nonacclimated, euhydrated (example 6)	4.2 L 6.0%	118	490 ml 1.96 L	−14%	305	1.3 L 30.2%	~4 h of work in heat

Voluntary dehydration, nonacclimated, euhydrated (example 7)	6.3L 9.0%	235/ 118	668ml 2.66L	−19%	323	3.39L 54%	~4 h of work in heat

Following is a list of the hypothetical characteristics of such a site.

- Common feature of all cells, especially nerves and muscles
- Temperature sensitive
- Related to cell volume changes
- Functionally related to the acclimatization response
- Functionally related to tolerance and fatigue
- Ability to generate heat
- Potential for inducing irreversible change

The key factors in this list all relate in some way to the sodium pump, a change in membrane permeability to sodium, a stimulation of metabolism and especially glycolysis, and a resultant energy drain upon the cell. For example, consider those factors in the following list that tend to increase intracellular sodium and to drive the sodium pump in a hyperthermic person.

- Active transport hydrolyzes one ATP per three Na ions translocated for two K ions
- Heat increases kinetic energy and ion diffusion stimulating Na permeability
- Heat increases intracellular acidity and a Na-H exchange
- Heat storage results in hypohydration and increased extracellular Na
- Increased extracellular Na increases Na permeability
- Hypohydration increases basal metabolism
- Heat increases the neural stimulation frequency required to maintain force
- Each molecule of acetylcholine stimulates a 50,000 cation flux at the receptor
- Increased neural stimulation increases Na flux in nerves and muscles
- Heat and exercise produce regional ischemia
- Regional ischemia induces regional acidosis and increased Na flux
- A doubling of cellular Na results in an eight fold increase in ATP hydrolysis

Thus, all these factors that stimulate the influx of sodium into the cell increase ATP utilization, heat production, and lactate formation and produce an energy drain on the cell. We refer to this concept as the energy depletion model of heat stroke pathophysiology (Hubbard et al., 1987). Therefore, if these mechanisms produce an intracellular glucopenia, this could account for part of the increased ADH release and thirst associated with hyperthermia and could account for the generalized increase in

hormone release. In this regard, it is also interesting to note that Andersson (1978) suggested that the thirst receptors are also sensitive to temperature and that local warming of the preoptic region elicits drinking in water-fed goats, whereas preoptic cooling inhibits it. This is exactly the behavior we would expect from a sodium pump-mediated process. For example, membrane leakage of sodium and potassium ions and the resultant active transport may account for nearly half of the basal metabolism of the brain (Astrup, 1982; Whittam, 1962). Hypothermia provides clinical protection from circulatory arrest by thermally restricting Na channels, delaying energy depletion, delaying potassium efflux, and stabilizing the cell membrane (Astrup et al., 1981).

If extracellular fluid osmolality decreases, water must enter cells and the cellular volume increases; conversely, if extracellular fluid osmolality increases, because of the addition of solutes that penetrate cell membranes poorly, water must leave the cells and the cellular volume decreases. Thus, the basic physiological mechanisms that control the osmolality of the extracellular fluid affect cell volume. The maintenance of cellular volume also depends on the energy metabolism of the cell (Robertson, 1953). Tissues incubated in a medium similar to extracellular fluid maintained a normal volume while respiring but swelled when metabolism was inhibited (MacKnight and Leaf, 1977). Swelling was associated not only with the uptake of water but with extracellular solutes as well (Mudge, 1951). Thus, two factors can cause or contribute to an increase in cellular volume: a decrease in extracellular osmolality or a decrease in the energy metabolism of the cell. These two factors must be borne in mind when interpreting factors that elicit thirst or appear to inhibit it.

Water itself appears to cross cell membranes very rapidly. This process could be considerably slower in vivo than in vitro experiments would suggest. The gain in water and solute when metabolism is depressed is expected from a Gibbs-Donnan system with the presence of nonpermanent polyvalent macromolecules restricted to one side of the membrane (MacKnight and Leaf, 1977). Calculations show that there is an excess of osmotic pressure in that compartment contributed by the polyvalent macromolecule itself and its associated counterions. Only if the excess osmotic pressure is counterbalanced by some additional solute restricted to the opposite compartment will a steady state be achieved. It is the active extrusion of sodium in metabolizing tissues that allows stabilization of cellular volume. Since this transport of sodium out of the cell takes place against an electrochemical gradient, work or active transport is required. The energy comes from the metabolism of the cell, and any inhibition of metabolism will result in the accumulation of sodium in cells like those in the kidney (Leaf, 1956; MacKnight and Leaf, 1977; Mudge, 1951), the liver (Elshove and Van Rossum, 1963; Heckmann

and Parsons, 1959), skeletal muscle (Kleinzeller and Knotkova, 1964; Rixon and Stevenson, 1956), cardiac muscle (Page et al., 1964), and brain (Bourke and Tower, 1966; Franck et al., 1968).

As discussed by MacKnight and Leaf (1977), a central question confronting physiologists in the mid-1950s was not why did cells swell when their metabolism was inhibited, but was restated (Manery, 1954) as why cells did not swell given their high content of intracellular proteins and other macromolecules that exert an osmotic pressure? As recognized by Leaf (1956) and as explained by MacKnight and Leaf (1977, p. 520) ". . . so long as the rate at which a substance crossed the membrane from the extracellular fluid into the cell was equaled by the rate at which it was passed from cell to the extracellular fluid, that substance in effect would be held in the extracellular compartment and could offset the intracellular swelling force." These authors postulated that the active extrusion of sodium from the cells allowed stabilization of cellular volume in metabolizing tissues. It follows from this that sodium is leaking into cells at all times and therefore accounts for a substantial amount of the cells' basal metabolic rate (Astrup, 1982; Siesjo and Wieloch, 1985; Whittam, 1962; Whittam and Willis, 1963). It also follows that if the thirst receptor were a sodium receptor, then it could interpret an increase in the sodium concentration and leak rate as an increase in energy demand. This would add significance to the observation that thirst can be induced by brain heating and can be inhibited by brain cooling. If this were true, it would lead to further insight; that is, thirst could be sensing energy demand and, therefore, could be intimately related to metabolism and hunger!

For example, Gutman (1963) injected hydrochlorothiazide (an inhibitor of active Na^+ transport) in nephrectomized rats and observed reduced drinking in response to a load of hypertonic saline. Injections of ouabain had a similar effect (Bergman et al., 1967; Gutman et al., 1971). Ouabain apparently inhibits ADH release (Gutman et al., 1971). It was also very interesting to note that glycerol (Albers and Koval, 1972) and deuterium oxide (D_2O) (Ahmed and Foster, 1974) are two weaker inhibitors of Na-K-ATPase. D_2O had the same inhibitory effects when it was used as the solvent for hypertonic saline in goats (Leksell et al., 1976; Rundgren et al., 1977). Infusions of glycerol (Olsson et al., 1976, 1978) were found to suppress dehydrative thirst and ADH secretion much more effectively than corresponding glucose infusions. This could suggest that thirst is more easily attenuated by inhibiting the activity of the Na-K-ATPase than by raising the glucose levels within the cell.

For example, if sodium were leaking into the cell at a higher rate, there would be a greater turnover of availabel ATP producing more ADP and P_i to stimulate metabolism, possibly glycolysis in the vicinity of the cell

membrane. Inhibiting the Na-K-ATPase would likely reduce this source of metabolic stimulation, and ATP demand would fall and concentrations would increase. Thus, low thirst would correlate with low pump activity and higher energy (ATP) levels within the cell (high thirst would correlate with high rates of sodium entrance, high rates of ATP hydrolysis, lower ATP levels, higher ADP and P_i levels, and stimulated glycolysis). In this model, high thirst correlates with high pump activity and lower steady-state ATP levels. If the cellular trigger for thirst were related to lower ATP levels (energy depletion), then this might explain the analogous condition of high ADH release (Baylis and Robertson, 1980; Baylis et al., 1981) with either intracellular glucopenia or 2-deoxyglucose (2dG). If glucose were either unavailabel (glucopenia) or unable (2-DG) to fuel glycolysis, then steady-state ATP levels would fall (energy depletion), thereby stimulating ADH release and thirst. Depending upon the situation (glucose concentration, insulin, etc.), elevated glucose levels might elevate the ATP levels and inhibit thirst, but even higher levels might deplete ATP levels by producing excess hexose phosphates. This difficult concept is summarized in Table 14-2.

Table 14-2 Effect of Cellular Energy Levels on Thirst and ADH Release

High Thirst; High ADH Release	Low Thirst; Low ADH Release
Increased metabolic demand	Low or normal metabolic demand
• Elevated plasma Na, increased Na leaks, hyperthermia • Increased pumping • Lower ATP levels • Increased glycolysis/lactate	• Low plasma Na, low leaks, cold • Decreased pumping • Elevated ATP levels • Elevated glucose
Inhibited metabolism	Inhibited Na-K-ATPase
• Intracellular glucopenia, 2dG • Lower ATP levels • Reduced blood volume/flow • Reduced substrate/oxygen availability	• Ouabain, hydrochlorothiazide • Glycerol, deuterium • elevated ATP level

Table 14-2 provides logic that thirst and ADH release can both be defined or regulated in terms of energy balance rather than the more common approach using water deficits and elevated osmolalities. This concept is relatively sophisticated and useful because it unifies a number of observations that on the surface are either unrelated or difficult to interpret

with the existing model (hyperosmolality). Table 14-2 also provides an interesting perspective on the potential for unravelling physiological regulation by stimulating metabolic demand or by reducing the substrate availability fueling it. Selective inhibition studies then tend to identify key enzymes or regulators in the system, or at switching points. For example, reducing the activity of the pump enzymes with ouabain might make more ATP availabel for other uses such as muscular contractility. Therefore, this model would predict that a reduction of blood volume and flow and attendant reductions in substrate availability and use would stimulate thirst. This explains the apparently inappropriate thirst found in those with salt depletion that tends to confound the hyperosmolality model.

Other recent experiments (Thrasher et al., 1980) infused equally hyperosmotic solutions of sodium, sucrose, urea, and glucose intravenously. All solutions appeared to raise CSF osmolality and sodium concentrations, but only saline and sucrose stimulated thirst. These results appear to question the specificity of the receptor for sodium but are compatible with centrally located osmoreceptors, since urea and glucose do not cause cellular dehydration. These results, however, do not rule out the possibility that either glucose or urea are interfering with some biochemical event in the receptor-response pathway, nor is it clear, if a proper equilibrium had been established, why they should raise CSF sodium in the first place. It is likely that this debate will continue.

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15

Environmental Issues That Influence Intake of Replacement Beverages

John E. Greenleaf[1]

INTRODUCTION

Water is the major constituent by weight and volume in the human body. The volume of water in normal healthy people is regulated to within ±0.22% (±165 g) of the body weight each day (Adolph, 1943), and plasma volume varies by less than ±0.6% (±27 ml) of the blood volume (Greenleaf et al., 1979). Such precise regulation underscores the degree of integrated coordination for maintenance of the volumes of cellular water (33 liters, 41% of body weight) and extracellular water (20 liters, 25% of body weight) in an 80-kg man as well as the importance of water for life. Muscle cells contain more water than fat cells, and men have a greater percentage of their weight as muscle than women; thus, men have a greater percentage of intracellular water than women. The rate of increase of total body water volume in infants and children is essentially the same until puberty, when female total body water levels off at about 28 liters and male total body water volume increases to about 44 liters (Figure 15-1, upper half). There is a gradual decline in the percentage of body water content to body weight

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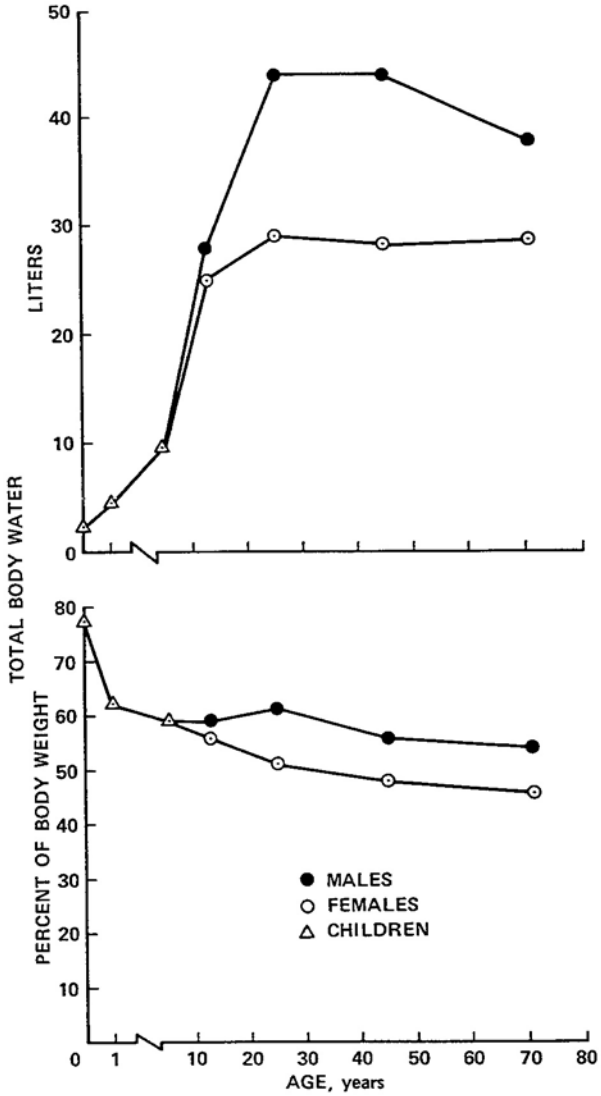

FIGURE 15-1 Total body water in relation to age. Source: Edelman et al. (1952), by permission of SURGERY, GYNECOLOGY & OBSTETRICS.

in both males and females with increasing age (Figure 15-1, lower half) (Edelman et al., 1952; Galagan et al., 1957).

Water content is the volume of liquid in the body at any given time; it is a more or less static quantity. Water balance is the difference between water intake and water outgo, which is a dynamic process. The major avenue of water intake is oral from food and liquid that are consumed. A typical water balance in a resting man would be as follows: Input equals 1,000 ml of beverage, plus 1,400 ml of food water, plus 250 ml of water of oxidation for a total of 2,650 ml; output equals 1,500 ml of urine water, plus 50 ml of fecal water, plus 1,000 ml of insensible water, plus 0 ml of sweat water for a total of 2,550 ml. The water balance then equals 2,650 ml minus 2,550 ml = + 100 ml. Water loss by sweating is increased by exposure, singly and in combination, to hot and dry environments and by increasing levels of metabolism (exercise).

The osmotic and oncotic pressures of the cellular and extracellular fluids are important for the control of fluid movement within the body. The effective osmotic content is composed of the electrolytes sodium, chloride, and bicarbonate in the extracellular fluids and potassium, phosphate, and some protein in the cellular fluids (Greenleaf and Harrison, 1986). Thus, body water volume and distribution are controlled, in part, by fluid compartment osmotic concentrations. Also, body water volume, distribution, and osmotic concentration are primary mechanisms for stimulating thirst and drinking.

PHYSIOLOGICAL FACTORS AFFECTING FLUID INTAKE AND SATIATION

There are three major circumstances that stimulate drinking: (1) a deficit of body water (hypohydration), (2) an excess of osmoles (electrolytes) in the cellular and extracellular fluid (ECF) compartments, (hyperosmolality), and (3) consumption of dry food (prandial) (Adolph, 1967).

Hypohydration

In general, the greater the water deficit, the greater the amount of fluid an individual takes in when fluid levels are between normal euhydration and about 6% body weight (water) loss. The level of body hydration is changing continuously because water is being lost continuously (urine and insensible) while it is being gained intermittently in food and drink. Drinking may be stimulated not only from an increase in the osmotic concentration of body

fluids but also from reduced body fluid volume. In stressful laboratory situations, total voluntary water intake is related directly to the severity of the total stress (Figure 15-2). When the stress factors (heat, exercise, and dehydration) were separated statistically, it was concluded that voluntary drinking in a hot (49°C) environment was 146% greater than that in a cool (24° C) environment; when a person was previously hypohydrated, drinking was 109% greater than that when the person was fully hydrated; and drinking during exercise was only 41% greater than that when at rest (Greenleaf and Sargent, 1965). Thus, heat exposure resulted in the greatest drinking, while exercise stimulated the least drinking. In a normally active subject, drinking begins when body weight (water) is reduced by about 0.8% (600 g). In previously hydrated subjects in stressful environments, there was a threshold for sweating of about 75 g/h, below which fluid loss was replaced promptly by drinking; in a hot environment, the sweating threshold for drinking was about 275 g/h (Greenleaf and Sargent, 1965). Thus, the more stressful the total environment, the greater the water deficit before drinking begins. This delay in drinking during dehydration has been called voluntary

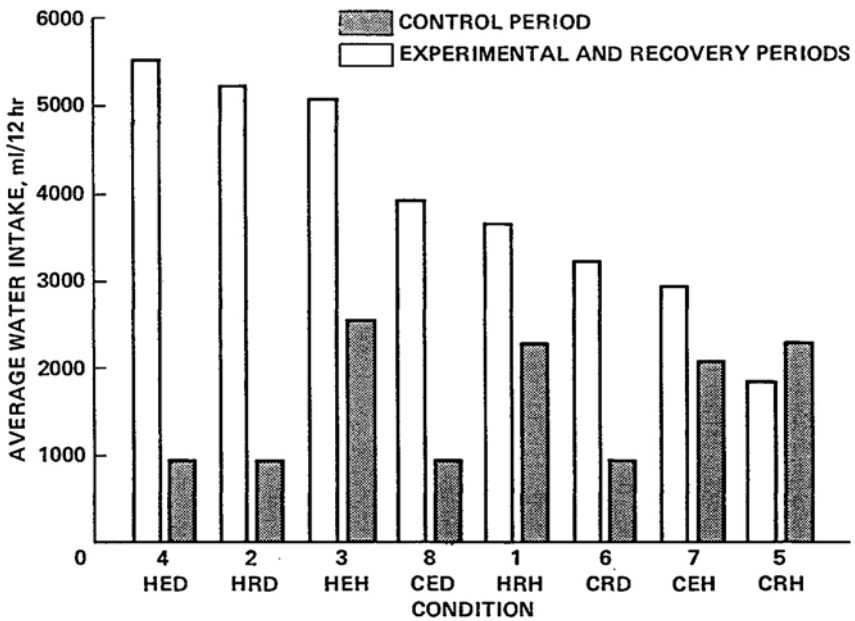

FIGURE 15-2 Average voluntary water consumption for the control periods (days 1-4) and the eight experimental (4 h) and recovery (3 h) periods. Combinations of conditions of heat (H), exercise (E), and dehydration (D) and of cool (C), resting (R), and hydration (Hy). Source: Greenleaf (1966), with permission.

dehydration (Adolph and Associates, 1947; Greenleaf and Sargent, 1965), but a more appropriate term would be involuntary dehydration or involuntary hypohydration, because the delay in drinking is not cognitive; the stimulus is just insufficient (Greenleaf, 1966).

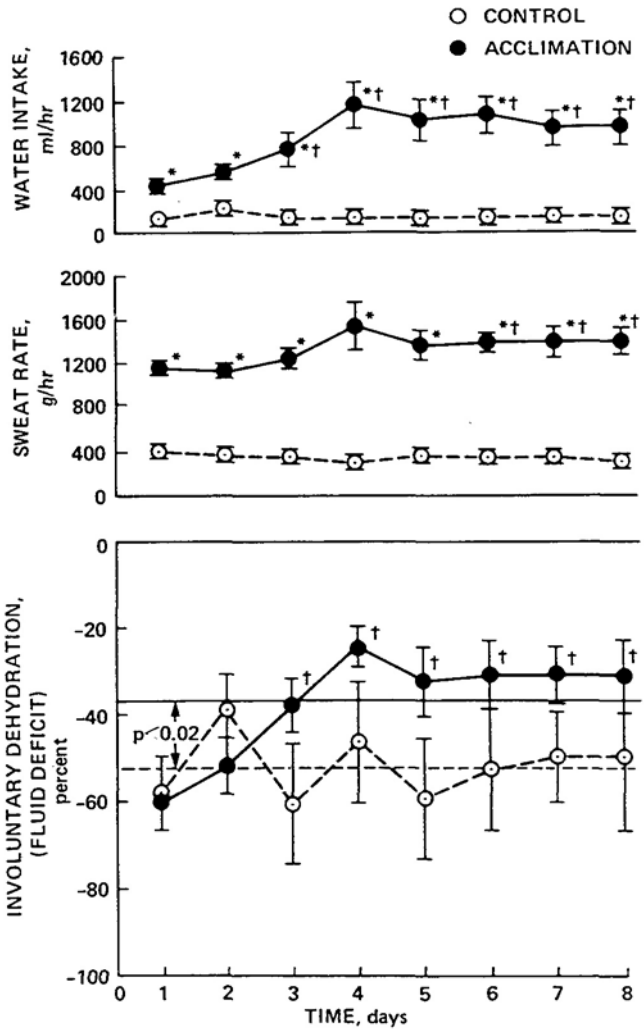

FIGURE 15-3 Mean (± standard error) water intake, sweat rate, and involuntary dehydration (fluid deficit) during the daily 2-h exercise (75 W) acclimation exposure in the control (ambient temperature, 28.8°C) and hot (ambient temperature, 39.8°C) environments. Dashed and solid lines are mean levels for the eight control and acclimation datum points, respectively. *Significantly different ($P < 0.05$) from control data; †Significantly different ($P < 0.05$) from the day-1 data point. Source: Greenleaf et al. (1983), with permission.

If environmentally induced body strain is reduced by exposure to intermittent bouts of exercise (acclimation) in a hot environment (Figure 15-3), the increase in the rate of voluntary water intake during the 2-h stress periods exceeds the rate of increase of water loss (sweating), so the level of involuntary dehydration (fluid deficit) is reduced significantly (Greenleaf et al., 1983). The maximal reduction in involuntary dehydration occurs after 4 days (8 h) of acclimation. Accompanying this reduction is a significant decrease in time to the first drink, a significant increase in the number of drinks, and a significantly greater average volume per drink that is unchanged during the eight acclimation exposures (Figure 15-4). The latter was probably due to the greater thirst-stimulating effect of heat exposure compared with that of exercise.

Osmotic Factors

Ingestion of hyperosmotic solutions (those greater than 290 mosmol/kg) of salt (NaCl) induces drinking in volumes directly proportional to the salt concentration. If the salt solutions are given through a stomach tube so that the swallowing mechanism is bypassed, a smaller volume of fluid is consumed more slowly, and the volume of water consumed is usually less than the volume required to dilute the hyperosmotic solutions to isosmoticity. An intake of fluid less than that required to achieve isosmoticity (involuntary dehydration) may be a compromise between full restitution of isosmoticity and full restoration of extracellular (plasma) volume. That is, if the extra water required to reduce the hyperosmotic solution to isosmoticity was consumed, a hypoosmotic hypervolemia would result, which may be more difficult to correct than would a slight hyperosmotic hypovolemia, which the body seems to prefer. The former would require increased sweating and urinary fluid losses with their accompanying electrolyte losses (osmoles), while the latter requires only consumption of pure water. The fewest number of osmoles (NaCl) that is necessary to induce drinking in satiated humans is that which increases the extracellular fluid volume by about 1.2% (Wolf, 1950). In an 80-kg man, the ECF volume averages 20 liters; thus, 1.2% of 20,000 ml equals 240 ml. A satiated ECF osmolality of 285 mosmol/kg would require ingestion and assimilation of 0.285 x 240 ml = 68.4 mosmol to induce drinking. This is equivalent to (6.245 g of NaCl/liter x 68.4 mosmol)/285 mosmol/kg = 1.5 g of NaCl. Consumption of fluids containing osmotic substances that do not penetrate cells easily (e.g., NaCl and KCl) provoke greater drinking than does consumption of equivalent fluids containing substances that do penetrate cells (e.g., sucrose

and urea). In general, dissolved solutes increase fluid consumption if they are present in hyperosmotic concentrations and decrease drinking if they are present in hypoosmotic concentrations. Hyperosmotic concentrations require a greater volume of water to excrete the additional solute.

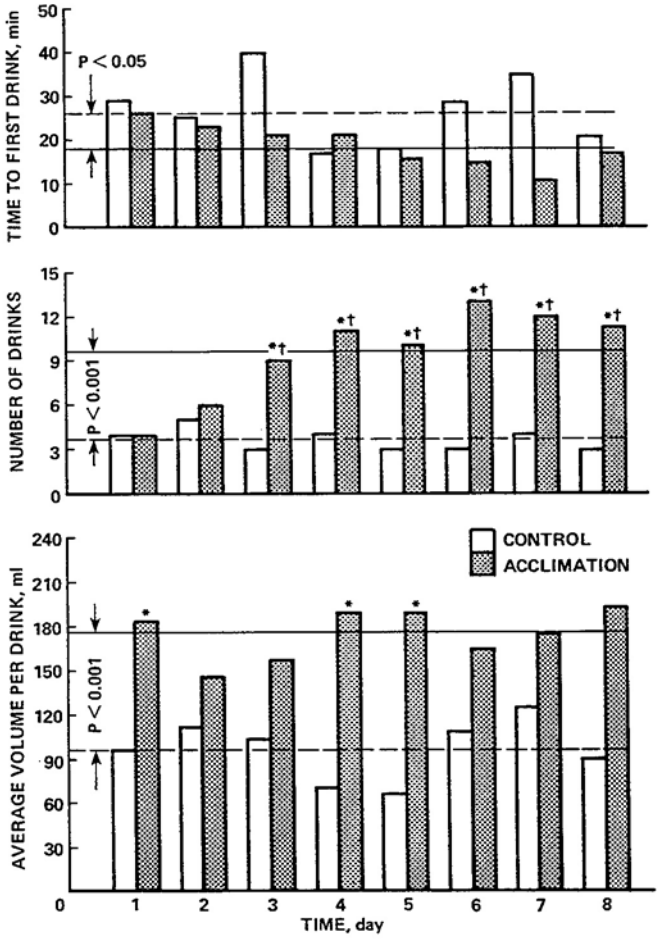

FIGURE 15-4 Mean drinking parameters during the daily 2-h exercise (75 W) acclimation exposures in the control (ambient temperature, 23.8°C) and hot (ambient temperature, 39.8°C) environments. Dashed and solid lines are mean levels for the eight control and acclimation days, respectively. *Significantly different ($P < 0.05$) from control data; Significantly different ($P < 0.05$) from the day-1 data point. Source: Greenleaf et al. (1983), with permission.

Prandial Factors

The intake of food may induce drinking under three circumstances. First, when dry food is eaten, drinking is promoted to dilute the food; when moist food is eaten, a smaller drinking response is provoked. Second, removal of the salivary glands of rats induces prandial drinking related perhaps to mouth dryness in humans. The absence of salivary glands in humans induces frequent drinking of small volumes of water, but has no significant effect on average daily fluid intake or normal water and salt metabolism (Steggerda, 1941). Third, damage to the lateral thalamic area of the brain in rats can stop all drinking except that which accompanies the eating of dry food. Prandial drinking appears to respond to the call for lubrication of the mouth and throat, and it may disturb rather than preserve the body water balance.

Satiation

Water that is swallowed satiates with a smaller volume than does water placed in the stomach through a tube; drinking is dramatically reduced following artificial placement of water in the stomach. If the volume of water placed in the stomach equals half the water deficit, the intake is reduced by half in most species. Inflation of a balloon in the stomach has the same immediate effect on fluid consumption as does the artificial placement of water. The act of swallowing produces some satiation for a limited period, as does stomach distension, and both together act to terminate drinking. However, only the distribution of water into and through the circulation of blood produces satiation. Water intake involves participation of the nervous system. An increase in the temperature of the hypothalamus stimulates drinking, while a decrease in the temperature inhibits drinking (Andersson et al., 1964). Cholinergic stimulation (which tends to calm the body) facilitates drinking, while adrenergic stimulation (which tends to excite the body and call it into action) inhibits drinking (Grossman, 1967). In short, people drink more when they are calm than when they are excited. Taste and smell are obviously important for the replenishment of water deficit. Sweet substances are almost universally preferred by both vertebrates and invertebrates; when food is abundant and the choice is wide, man eats primarily for palatability and secondarily for nutritional benefit (Epstein, 1967).

The control of drinking shares equally with the control of water output via sweating and the kidneys for maintenance of water balance and body weight. The kidneys can correct only for an excess of fluid in the body. If the body is hypohydrated, the kidneys will concentrate the urine to about 1,400

mosmol/kg of H_2O and continue to do so until they fail or until water is ingested. Thus, drinking is the only practical way of alleviating hypohydration. Water intake is primarily a response to a deficiency of water inside the body and not directly to stimuli from outside the body. However, external factors can influence the internal physiological state, which in turn can modify drinking.

FACTORS AFFECTING MINIMAL, MAXIMAL, AND AVERAGE BEVERAGE AND TOTAL FLUID INTAKES

Minimal Fluid Intakes

The lowest volume of fluid required to prevent physical deterioration is that which will provide 300 ml of urine/day. Under low-stress conditions (sedentary work in a cool environment), this volume (beverage plus food) is about 1,000 ml/day (Johnson, 1964b). The longest documented period any person has survived without any water is 18 days (Wolf, 1958).

Maximal Fluid Intakes

In persons with diabetes insipidus (damage to the brain that results in the inability of the kidneys to retain water), water intakes of 35 to 41 liters/day have been reported (Richter, 1938). Habener et al. (1964) have studied the responses of normal men to prolonged high fluid intakes. Four men measured their daily fluid intakes without dietary restrictions for a 2-week control period, and the intakes ranged from 1,310 to 2,550 ml/day. Then, the daily water consumption for each subject was increased by 2 liters/week until 8 liters was added; the maximum intake was 7.43 to 9.57 liters/day. Body weight remained constant at these high intake levels. The important conclusion is that these levels of water consumption did not change the serum osmotic concentration, which suggests that they were not harmful. The only untoward symptoms were mild nausea, diarrhea, lassitude, and light-headedness; these symptoms passed after cessation of drinking for a few hours. The men mentioned a slight increase in thirst upon arising in the morning.

Factors Affecting Average Beverage and Total Fluid Intakes

Some of the factors affecting beverage and total fluid intake in man are presented in Table 15-1. Most of the environmental and some of the nutritional-chemical factors have been discussed previously.

Table 15-1 Factors Affecting Average Beverage and Total Fluid Intake

Nutritional-Chemical	Socioeconomic-Psychological	Environmental
Protein content	Cost of drink	Temperature
Carbohydrate	Taste	Pressure
Fat content	Smell	Humidity
Osmotic concentration	Color	Wind speed
Electrolyte concentrations	Sound (fizz, etc.)	Gravitation
Drugs	Appearance (packaging)	
Acidity (pH)	Religious preference	
Carbonic acid concentration	Customs and mores	
Temperature	Masculine/feminine ratio[a]	
Color of drink	Viscosity	

[a] Some drinks may appeal more to men, others to women.

ENVIRONMENTAL AND OTHER EXTERNAL FACTORS AFFECTING FLUID INTAKE

It was stated above that fluid intake is related to the level of water deficiency in the body. It should be reiterated that water lost insensibly (from the respiratory tract and skin) is pure water and contains no osmoles (salt). Sweat and urinary fluids contain salts and contribute to both water and salt loss. Various environmental factors such as temperature, humidity, radiation, and atmospheric pressure affect mainly sweating and urinary water loss, while physical exercise affects, in addition, increased respiratory water loss from the increased expiratory volume and frequency of breathing.

Temperature

The relationship between environmental temperature and fluid intake is presented in Figure 15-5 (lower curve). Water intake increases at an ambient temperature of about 27°C, the temperature at which sweating begins. Thus,

the increased water intake when temperatures are above 27°C tends to compensate for sweat loss. There is also a cold diuresis (increased urinary output), but its effect seems to be well regulated by fluid intake because the curve is nearly level from −30°C to 16°C (Figure 15-5, lower curve). The upper half of Figure 15-5 shows the water intake requirements of young men in the heat (between 35°C and 50°C) at four levels of energy expenditure: resting (2,000 kcal/day), light work (2,800 kcal/day), moderate work (3,500

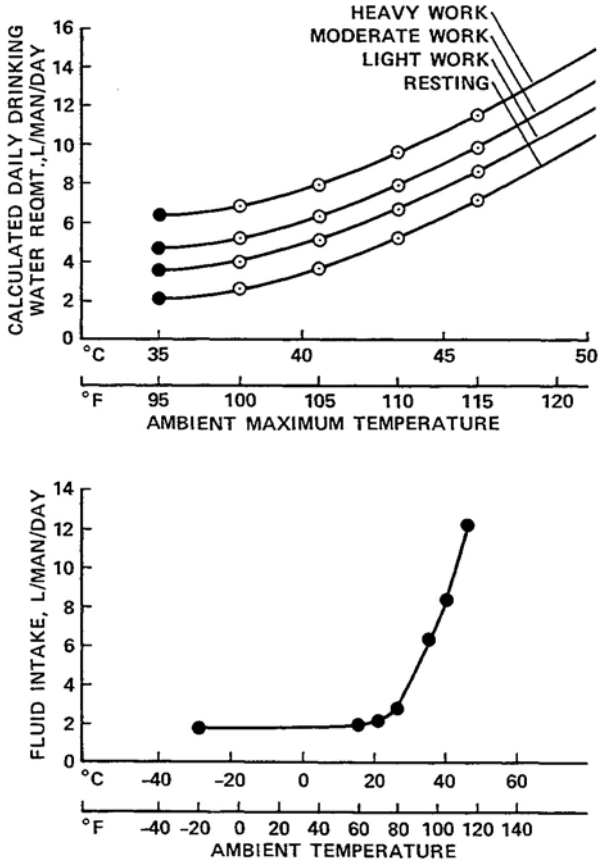

FIGURE 15-5 Beverage requirements of men in relation to environmental temperature and work intensity. Sources: Top panel, Nelson et al. (1943); bottom panel, Nelson et al. (1943) and Welch et al. (1958), with permission.

kcal/day), and heavy work (4,500 kcal/day). The range of daily drinking water requirements is 2 liters at rest at 35°C to 15 liters during heavy work at 50°C.

Greenleaf et al. (1966) have performed a statistical analysis of the relationships among 22 selected metabolic variables for their value in predicting voluntary water consumption in 87 young male military recruits in basic training living in a hot, moist environment. The equation for estimating water consumption is as follows:

Predicted water intake (ml/day) =

−11,502.40	+ 1.15 [mean daily urinary volume, (ml/day)]
	+ 45.81 [serum osmolality (mosmol/kg of H_2O)]
	− 18.72 [resting pulse rate (beats/min)]
	+ 4.39 [mean daily urinary Cl (meq/day)]
	− 18.86 [mean daily urinary K (meq/day)]
	+ 1.77 [rate of sweating (ml/hr)]

The predicted water intake had a multiple correlation coefficient of 0.79 with the measured water intake. The subjects were allowed unrestricted consumption of water; other beverages such as cocoa, tea, and coffee were allowed only at meal times, and their volumes were added to the water intake. The average liquid intake over the 6-day period was 3,256 ± 900 ml/day, and the range was 1,950 to 5,850 ml/day.

Humidity

The effects of humidity on water intake have not been studied intensively, but lower humidities would allow greater evaporation of sweat under high temperatures and a greater insensible water loss at lower temperatures. Presumably, the faster the water is lost, the greater the drinking, except for the problem of involuntary dehydration when, under stressful conditions, water intake lags far behind water loss. In some circumstances it takes 2 days to recover the lost fluid (Greenleaf et al., 1967).

Barometric Pressure

Gee at al. (1968) measured fluid consumption in 12 men exposed for 16 days to a simulated space cabin pressure of 258 Torr (8,230 m). Water intake varied from 1.2 to 5.6 liters/man/day despite the relatively equal food

intakes and activity levels. Daily urinary outputs ranged from 0.5 to 4.4 liters/man/day, insensible water loss increased by 50%, from 0.8 to 1.2 kg/man/day, and total body water decreased from 44.4 to 41.6 liters. In general, people going to increased altitudes incur negative water balances (Consolazio et al., 1968). Studies of mountain climbers are contaminated with the concomitant fluid perturbations caused by cold exposure, by physical exercise, and usually by inadequate food intake. The negative fluid balance of mountain climbers is often very great, and large body weight and fluid losses (to 9.6 kg) have been reported (Nevison et al., 1962). Most investigators have reported hypovolemia of 6% - 21% during 2-3-week exposures to 2,000-4,500 m altitudes (Alexander et al., 1967; Dill et al., 1974; Krzywicki et al., 1971; Surks et al., 1966), with a 29% decrease observed after 18 weeks at 5,790 m altitude (Pugh, 1962). On the other hand, Krzywicki et al. (1971) found in well-fed men a small increase in extracellular fluid volume of 1.3 liters after they spent 6 days at 4,300 m. Also, Greenleaf et al. (1978) observed no significant change in plasma volume or fluid balance during 8 days at 2,287 m in well-fed and well-hydrated men. Thus, hypovolemia and hypohydration observed at high altitudes appear to be related to involuntary dehydration and to food deficits (anorexia).

Consumption of Food

Intakes of food and water are closely related (Johnson, 1964a); food intake is reduced during water deprivation, and water intake is reduced during starvation (Andersson and Larsson, 1961). Subjects undergoing acute starvation for 10 days with water, tea, and coffee given ad libitum exhibit an immediate increased loss of water by the kidneys followed by a lessening of the diuresis (Consolazio et al., 1967). The fluid intake declined progressively as starvation continued, and water balance was achieved on day 9 when the fluid intake and output were the same. Fluid intake increased greatly when food was eaten during the recovery period. Thus, food has a water-retaining effect.

FACTORS AFFECTING REHYDRATION BEVERAGE COMPOSITION AND SELECTION

Beverage Composition

Starkenstein (1927) conducted the first comprehensive laboratory study of the thirst-quenching properties of various concentrations of carbonic acid

and salt solutions. Some of the more important observations and conclusions are as follows:

Water Intake Under Normal Conditions

1. The temporary thirst-quenching properties of such drugs as cocaine and opium are the result of elimination of the unpleasant sensation of being thirsty.
2. The cholinergic class of drugs (pilocarpine, etc.) exert their thirst-quenching effects by causing an increased secretion from organs and glands that move water to dehydrated regions of the body.
3. Thirst is not always quenched by drinking pure water, but depends upon the composition of the water (osmotic concentration) and the ability of the body to hold water.
4. Retention of ingested fluids depends on the osmotic concentration of the drink and the osmotic concentration of the blood. If sugar is given with water, the osmotic effect of the sugar is lost when the sugar is metabolized.
5. Urinary excretion is influenced by the acidity (pH) of the drink. The lower the pH (greater acidity), the greater the amount of urine excreted. The addition of carbonic acid to water lowers the pH. Therefore, fluids with high concentrations of carbonic acid are less suitable for quenching thirst than are those with a lower carbonic acid content.
6. The ability to retain ingested water does not depend solely on the water's salt concentration (osmotic concentration) and its relation to the osmotic content of the blood, but on the combined result of its salt and carbonic acid concentration. When the carbonic acid concentration decreases (pH increases), urinary excretion decreases. However, this pH effect is operative only with hypotonic solutions (those more dilute than blood plasma). Retention of isotonic solutions cannot be counteracted by increasing the acidity.
7. Under normal temperatures, diuretics (caffeine) merely rechannel the otherwise extrarenally excreted water into the kidneys.
8. Caffeine can stimulate thirst, especially when a person is sweating.

Water intake following resting-thermal dehydration

1. Distilled water cannot quench thirst when the loss of water by sweating is high.
2. Tap water has no effect on sweat excretion at low sweat rates but greatly increases sweat excretion that is already at a higher than normal rate.
3. The increase in water content that is usually produced by the intake of a NaCl solution can be nullified by profuse sweating.

4. Renal activity is inhibited neither by profuse sweating at room temperature nor with intake of a saline solution. When one drinks pure water, renal secretion is markedly reduced because of sweating.
5. Drinking of saline solution inhibits sweat excretion in people in a steam bath, while drinking of saline solution increases renal excretion in hot as well as at normal temperatures.

In conclusion

1. The best fluid for quenching thirst is 0.7% to 0.9% saline (isotonic solution), for the body retains it to a higher degree than it does any other fluid. In addition, the ingested salt is able to inhibit excessive sweating and thus prevent additional water loss and further development of thirst. Optimal drinks for workers in hot environments are slightly hypotonic solutions.
2. To be suitable for the quenching of thirst, a fluid must not only have the proper ingredients but it should also taste good. The taste of drinking water is determined not only by its temperature and its hardness (mineral content) but also by its acidity (carbonic acid content).
3. Acidified isotonic salt solutions can be used effectively as tasty liquids for the quenching of thirst.
4. The so-called soda waters (artificial seltzer waters) are not suitable for the quenching of thirst for they are rich in carbonic acid, which stimulates diuresis and sweating.

Beverage Selection

The only reasonably complete study of voluntary beverage selection (Sohar et al., 1962) was conducted on 19 fit young men (18-21 years old) who marched 370 miles from Eilat in the south of Israel to Metulla in the north of Israel in 24 days; this included 3 days of rest. They marched 17 miles/day, and each person carried a load of 16 kg. The various drinks investigated were warm tap water (20°-30°C), cold tap water (10°-16°C), cold sweetened lemon tea, water with sweetened citrus syrup, pasteurized bottled milk, soda water, a bottled citrus drink, carbonated lemonade, Malton (a cola), and beer. All drinks except tap water were kept between 10°C and 16°C. One 650-ml bottle of beer or citrus juice was given to each man at lunch, regardless of any other drinking. Tea and coffee were provided ad libitum at dinner.

The drink preferences were taken 11 times during the 24-day march and were divided into four groups: the most preferred drinks to the least preferred drinks.

Table 15-2 Beverage Preferences during Marching in the Heat

	Men who Preferred the Beverages (n)	
Beverage	Most	Least
Citrus juice	3	0
Citrus syrup	3	0
Cold lemon tea	2	1
Cold water	2	1
Soda water	1	1
Malton (cola)	0	0
Milk	0	0
Beer	0	1
Carbonated lemonade	0	3
Warm water	0	4

The results in Table 15-2 indicate that the most preferred drinks were cold and sweetened and tasted of citrus. That carbonated lemonade was one of the least preferred drinks suggests that the carbonation--and not the citrus taste--was the offensive agent.

General observations on the drinking behavior of the men are as follows:

1. When forced to drink carbonated beverages, the men would shake their bottles to release the gas. They maintained that the gas content made it difficult to drink the beverage in large quantities.
2. Milk was tried only once, and it produced diarrhea in four of five men and so was discontinued.
3. Beer was tried only once because it produced intoxication very easily in the hot environment.
4. During 2 days when the choice of all drinks was free, citrus juice was the leader, making up one-third to one-half of the total beverage consumption. On both days, warm water was preferred to all the varieties of carbonated drinks offered.
5. At the end of the total experiment, each man was questioned as to his beverage preference when it was necessary to drink large amounts during a short period of rest. Of 19 men, 17 preferred citrus juice or water with citrus syrup, while only 2 preferred a carbonated drink. The carbonated drink gave the men a feeling of fullness in the stomach and prevented the ingestion of large quantities.
6. Cold water (10°-16°C) was preferred to warm water (20°-30°C) six out of seven times.

Table 15-3 Beverage Chemical Composition

Beverage	Osmol/kg[a]	pH[b]
Olympade (Coca Cola, can)	842	2.4
Beer (Olympia)	830	4.2
Sport cola (Canada Dry)	808	2.1
Fanta grape (Coca Cola)	800	2.7
Fanta orange (Coca Cola)	790	2.6
Bitter lemon (Schweppes)	788	2.6
Hi-C orange (Coca cola)	754	2.6
Hi-C grape (Coca Cola)	727	2.6
Hi-C citrus cooler (Coca Cola)	725	2.3
Cola (Pepsi Cola)	706	2.5
Orange juice (frozen) (Minute Maid)[c]	674	3.7
Mountain Dew (Pepsi Cola)	645	3.3
Sport Cola (Canada Dry)	644	2.4
Frozen orange juice (Whole Sun)[c]	590	4.0
Cola (Coca Cola)	586	2.5
Cola (Shasta)	585	2.5
Cola (Royal Crown)	569	2.6
Sprite (Coca Cola)	566	2.9
Rootbeer (Mug)	532	3.9
Dr. Pepper	510	3.1
Seven-up	484	3.2
Ginger ale (Canada Dry)	477	2.7
Ginger ale (Vernors)	456	3.5
Olympade (bag) (Coca Cola)[c]	394	2.9
Lemonade (frozen) (inute Maid)[c]	389	2.4
Tang (General Foods)[c]	366	3.0
Gatorade (lime) (Stokley)	336	2.8
Olympade (Coca Cola)	335	2.2
Gatorade (orange) (Stokley)	320	2.8
Normal human serum or plasma	**290**	**7.3**
Fresca (Coca Cola)	99	2.3
Tab (Coca Cola)	84	2.4
Wink (Canada Dry)	72	2.8
Coffee (perked for 6 min) (Maxwell House)[c]	72	4.9
Fresca (Coca Cola)	58	2.6
Diet cola (Pepsi Cola)	41	2.6
Diet cola (Royal Crown)	38	2.7
Club soda (fresh) (Canada Dry)	36	5.4
Coffee (instant) (Folgers)[c]	35	4.9
Club soda (flat) (Canada Dry)	27	8.5
Coffee (freeze dried) (Taster's Choice)[c]	26	5.0
Tea (bag) (Lipton)[c]	8	5.5
Tea (loose) (Lipton)[c]	7	5.6

Club soda (flat) (Canada Dry)	27	8.5
Coffee (freeze dried) (Taster's Choice)[c]	26	5.0
Tea (bag) (Lipton)[c]	8	5.5
Tea (loose) (Lipton)[c]	7	5.6
Tea (instant) (Lipton)[c]	6	6.7
Demineralized water (Ames)	6	5.5
Tap water (Ames)	5	8.3

[a]Advanced instrumentation osmometer
[b]Research pH meter (Beckman Instruments)
[c]Prepared following the manufacturer's directions (1 cup = 8 oz.)

consumption at a time of physical effort. Milk, beer, or the various carbonated drinks may be preferred when small quantities are ingested during leisure periods, but they were not consumed in large quantities as well as the nonalcoholic, noncarbonated sweetened, cold, citrus fruit beverages were.

The osmotic and hydrogen ion concentrations of some current beverages are presented in Table 15-3. They are listed in descending order of osmotic concentration. In general, beer and the colas had the highest osmolality, while club soda and the diet drinks with artificial sweeteners had lower osmolalities. With the exception of club soda, all the manufactured beverages had hydrogen ion concentrations below 4.3. The beverages became more alkaline (the pH increased) as the carbonation escaped (see club soda).

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16

Changes in Plasma Volume During Heat Exposure in Young and Older Men

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INTRODUCTION

Dilation of blood vessels during exposure to high ambient heat was noted in 1795 by a physician accompanying British soldiers during their occupation of colonial India. The observations of this physician were quoted in 1955 in a review article on heat acclimation, "In passing from a cold to a hot climate the first thing that occurs is the effect produced by the simple increase of heat on the human frame. Expansion of the fluids and consequent fullness of the vessels is constantly observed to take place." (Bass et al., 1955, p. 323). This farsighted physician denounced the concept that European peoples could not safely perform exertions in the heat and said that " . . . while exertions of a single day have often been harmful, bad effects from the greatest exertions in the hottest weather were extremely rare after the campaign had been continued for a few days." (Bass et al., 1955, p. 323).

Hemodilution after a sudden increase in climatic temperature was reported by Barcroft in his fellow passengers during a voyage from England to Peru (Barcroft et al., 1922). Glickman et al. (1941) found that heat-

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induced hemodilution occurs within the first few hours of a controlled laboratory heat exposure. The time course of the changes in plasma volume of men quietly sitting in the heat were described in detail by Bass and Henschel (1956). The hemodilution usually is weak (less than a 5% increase in plasma volume) and transient. Without fluid replacement, it disappears after approximately 30-45 min. It may not appear in subjects who have been dehydrated before the heat exposure (Sawka et al., 1984) or in subjects who have been anesthetized or have suffered transection of the spinal cord below the level of the medulla (Bass and Henschel, 1956). The transient increase in plasma volume during acute heat exposure provides a fluid reservoir for sweat production and attenuates the decrease in central blood volume as sweating continues and as blood flow is redistributed from the core to the skin. Without this initial increase of plasma volume, body temperature would increase more rapidly and heat tolerance would be reduced. With adequate fluid and electrolyte replacement, the expansion of plasma volume persists and plays a key role in reducing cardiovascular strain during the early stages of heat acclimation (Wyndham et al., 1968).

Figure 16-1 illustrates the dynamic plasma volume responses of hydrated healthy young subjects to an acute 3-h heat exposure without fluid replacement. The plasma volume responses can be divided into three stages: initial hemodilution (stage 1), rapid hemoconcentration (stage 2), and slower hemoconcentration (stage 3). Several theories have been offered to explain these plasma volume responses.

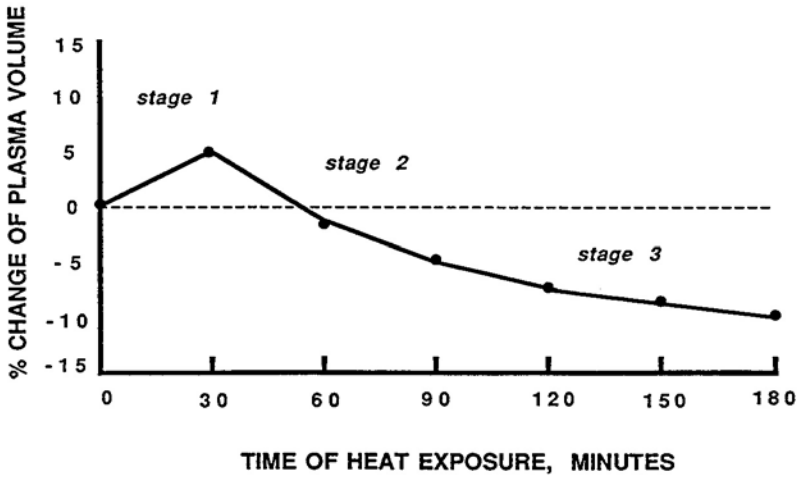

FIGURE 16-1 Pattern of plasma volume response of healthy young men during a 3-h passive heat exposure. See text for explanation of the stages of plasma volume response.

Stage 1

The initial increase in plasma volume, which occurs within minutes of heat exposure, is most likely due to a direct effect of heat, which causes venodilation. Dilation of blood vessels was first noted by Jackson (1795). Later, Bass and Henschel (1956) theorized that expansion of the vascular bed without an increase in blood volume results in the rapid displacement of fluids from the interstitial compartment to the plasma. More recently, Harrison (1986) elaborated on this theory. According to Harrison, acute heat exposure initially results in venodilation without an accompanying vasodilation. As the veins dilate, pressure in the venous end of the capillaries decreases, reducing capillary filtration and increasing fluid reabsorption. Plasma volume expansion occurs rapidly and continues until the balance between the arteriolar and venous tone is restored or reversed by vasodilation.

Stage 2

Active sweating and cutaneous vasodilation begin after approximately 4-6 min of heat exposure, depending on changes in core and skin temperatures, the hydration state, and the degree of heat acclimation of the subject (Nadel, 1985). As the sweat rate increases, the plasma volume decreases, since sweat is formed from fluid in the capillaries that perfuse the sweat glands. Cutaneous vasodilation has opposing effects on plasma volume. Vasodilation restores and possibly reverses the balance of arteriolar to venous constriction. This slows and possibly reverses the reabsorption of extracellular fluid across the cutaneous capillaries. However, a sudden increase in cutaneous perfusion stimulates lymph flow. According to Wasserman and Mayerson (1952), and later Senay (1970), a sudden increase in cutaneous perfusion increases protein transport from the lymph vessels to the vascular compartment. As the plasma protein content increases, the water-binding capacity of the plasma increases in a ratio of approximately 15 ml of serum water for each 1 g of protein added to the plasma (Rocker et al., 1976). Therefore, the initial effect of vasodilation may be to further increase plasma volume (this may contribute to the stage 1 hemodilution). However, after the priming action on lymph protein is completed, vasodilation increases the capillary surface area for fluid exchange, counteracts the effect of the venodilation, and causes a rapid decrease in the plasma volume.

Stage 3

The rapid decrease in plasma volume during stage 2 compromises cardiac filling, stimulating cardiopulmonary volume receptors, which attenuate the vasodilatory reflex and inhibit sweating (Nadel, 1985). Stimulation of the cardiopulmonary receptors also stimulates secretion of antidiuretic hormone (ADH) (Moore, 1971; Segar and Moore, 1968), which reduces free-water clearance and conserves plasma water (Khokhar et al., 1976). ADH may also affect the sweat glands directly, to inhibit sweating (Nadel, 1985). When central blood volume is decreased, arterial blood pressure may fall, stimulating the sinoaortic baroreceptors and thereby causing a redistribution of blood flow away from splanchnic vascular beds (Abboud et al., 1979). This reduction in splanchnic blood volume may be important in conserving plasma water. Horowitz (1984) has demonstrated the importance of restricting splanchnic perfusion for conserving body fluids by comparing the heat stress responses of various species of rats. Since the splanchnic capillaries are among the most porous capillaries of the body to proteins and fluids, a species that can significantly reduce splanchnic blood flow will be most successful in conserving plasma volume and surviving during severe water restriction. Horowitz (1984) reported that the desert rat species *Psammomys obesus* withstood dehydration for over 48 h at least partly because of its ability to almost completely reduce splanchnic vascular permeability. If such findings can be extrapolated to man, then, reducing splanchnic blood flow during heat exposure is a positive step toward conserving plasma proteins and water.

The increase in plasma osmolality also reduces the rate of plasma volume loss during heat exposure. Sweat is a hypotonic secretion, and therefore, as sweat production continues, the plasma becomes more and more hypertonic. This increase in plasma osmolality inhibits sweating (Fortney et al., 1984) and attenuates the rate of water loss from the vascular compartment.

EFFECT OF AGE ON BODY FLUIDS

Aging has been defined as an inability to adapt to changing environmental conditions (Piscopo, 1985). Several investigators (Leaf, 1984; Miller, 1987; Phillips et al., 1984) have observed that elderly individuals have difficulty maintaining body fluid balance. Physiological alterations in water and sodium regulation result in an increased danger of both dehydration and overhydration in the elderly (Crowe et al., 1987). Leaf (1984) observed that nursing home patients have an increased susceptibility to dehydration, and

Spangler et al. (1984) reported that as many as 25% of nursing home patients may be chronically dehydrated. However, these findings do not prove that there is an age-related change in fluid regulation, since the results may have been complicated by a restricted access to fluids or by the prevalent use of medications that alter body fluids. The extent of dehydration in healthy, active older individuals has been debated. One study by Phillips et al. (1984) reported normal hydration in elderly subjects, while another study by the same group found elevated baseline sodium concentrations and plasma osmolalities in healthy older subjects (Crowe et al., 1987).

Miller (1987) recently reviewed potential mechanisms for the occurrence of body fluid disturbances during the normal aging process. Lindeman et al. (1960) found that renal concentrating capacity in response to dehydration decreases with age, becoming evident between approximately 45 and 50 years of age. Rowe et al. (1976) substantiated this observation in men after 12 h of dehydration.

The regulation of plasma sodium also appears to be affected by the normal aging process. Epstein and Hollenberg (1976) studied the renal response to sodium restriction in individuals from 18 to 76 years of age. Renal sodium excretion decreased by 50% after 18 h in subjects younger than 30 years, after 24 h in subjects between 30 and 60 years of age, and after 31 h in subjects older than 60.

Impaired fluid and electrolyte balance in the elderly also may be due to an inability to detect changes in body hydration. Phillips et al. (1984) compared thirst perception between a group of young men and a group of men 67 to 75 years of age. The subjects were dehydrated for approximately 24 h, until both groups had a similar decrease in body weight. Following dehydration, the older subjects were not as thirsty as the younger subjects, based on their responses to a visual analog thirst scale, despite a greater increase in plasma osmolality.

Increased secretion of ADH in response to osmotic stimuli and decreased secretion in response to hypovolemic stimuli occur with aging (Bevilacqua et al., 1987; Ledingham et al., 1987). During water restriction, Phillips et al. (1984) found a greater increase in ADH in older subjects, despite a similar loss of plasma volume. Helderman et al. (1978) infused hypertonic saline into young and older individuals and found a greater release of ADH into the plasma of older subjects compared with that in the plasma of the young subjects. This increased responsiveness of ADH is believed to compensate for the reduced sensitivity of the kidneys of older subjects to ADH.

Baseline concentrations of atrial natriuretic factor (ANF) increase with increasing age (Wambach and Kaufmann, 1988; Yamasaki et al., 1988). The consequences of these changes in ANF regulation on body fluid responses

are not known. Specific high-affinity binding sites for ANF have been found in many areas of the body, including the kidneys, the adrenal gland, smooth muscles of blood vessels, and the hypothalamus. Increases in plasma ANF have been shown to inhibit aldosterone production in the adrenal zona glomerulosa (Laragh and Atlas, 1988) and thus might contribute to the altered sodium regulation that occurs with aging. ANF also has an antagonist role to many of the actions of angiotensin II. It inhibits water intake induced by the administration of angiotensin II to the central nervous system. It has the potential to block the formation and secretion of both ADH and angiotensin II (Kramer, 1988; Laragh and Atlas, 1988), and it modulates sympathetic activity by inhibiting epinephrine release and reducing baroreceptor responsiveness. We are just beginning to understand the role of ANF in the regulation of body fluids and electrolytes.

HYPOTHESIS

On the basis of two facts, that (1) acute heat exposure provokes rapid changes in body fluids and (2) older individuals have an impaired ability to regulate body fluids, we hypothesized that older subjects would have difficulty maintaining plasma volume and osmolality during prolonged heat exposure. By comparing the time courses of body fluid responses to heat exposure of young and older individuals, the mechanisms for altered body fluid regulation in older healthy men may become apparent.

Study Description

The experiment outlined below is described in more detail in Miescher and Fortney (1989).

The plasma volume, protein, and osmolality responses of six young men (age, 24-29 years) were compared with those of five older men (age, 61-67 years). The subjects were normotensive, non-smokers who were not taking any medications. The subjects had an average level of aerobic fitness for their age (Astrand, 1960). Each subject had an active life-style but did not participate in routine exercise training or sports. The two groups were matched for height, body surface area, and surface area/weight ratio (Table 16-1).

The tests were performed in the winter months in Baltimore. The subjects reported to our laboratory at 8 a.m. after a light breakfast and after

Table 16-1 Age and anthropometric characteristics of older and younger mena

Subjects	Age (yr)	Weight (kg)	SA[b] (m^2)	SA/Wt (m^2/kg)	VO_{2max}[c] (ml/kg/min)
Older men (n = 5)	64.0[d]	73.0	1.9	0.026	38.8[e]
±SEM	± 1.0	± 2.3	± 0.04	± 0.000	± 2.3
Younger men (n = 6)	26.0	69.3	1.8	0.027	52.1
±SEM	± 0.7	± 3.1	± 0.05	± 0.000	± 2.2

[a]All values are mean ±SEM.
[b]Surface area.
[c]maximal oxygen consumption.
[d]$p < 0.05$, older versus younger.
[e]$p < 0.01$, older versus younger.

abstaining from caffeine beverages for at least 10 h. They were given 200 ml of water to drink when they arrived. They changed into shorts and were provided with a rectal thermistor, an Exersentry heart rate monitor, and venous catheter. They rested for 30 min in a cool room (25°C) before moving to a hot, dry heat chamber (45°C, 25%) for 180 min of heat exposure without fluid replacement. The subjects reclined to a sitting position in a webbed chair, and blood samples were drawn by a free-flowing technique just before they entered the heat chamber and every 30 min during the heat exposure. From each blood sample, hematocrit (microhematocrit technique), hemoglobin concentration (cyanomethemoglobin method), and total protein concentration (refractometry) were determined. Also, measurements of body weight, rectal temperature, and heart rate were obtained at 30-min intervals.

Following 30 min of baseline rest, the older men had significantly lower rectal temperatures (Figure 16-2) and higher plasma osmolalities, despite similar hematocrits, hemoglobin concentrations, and plasma protein concentrations (Figure 16-3).

During the 180-min heat challenge, rectal temperatures rose in both groups, but the rise was significantly greater in the older men (Figure 16-2). The decreases in body mean weight were similar in both groups (1.52% in the older subjects and 1.55% in the younger subjects), yet the change in xxxxxx

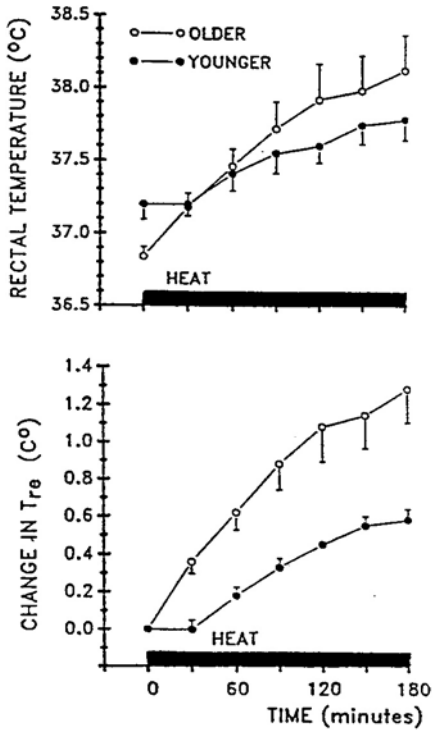

FIGURE 16-2 Rectal temperature responses and changes in rectal temperature for young (n = 6) and older (n = 5) men during a 3-h passive heat exposure. Values are the means ± standard errors of the mean.

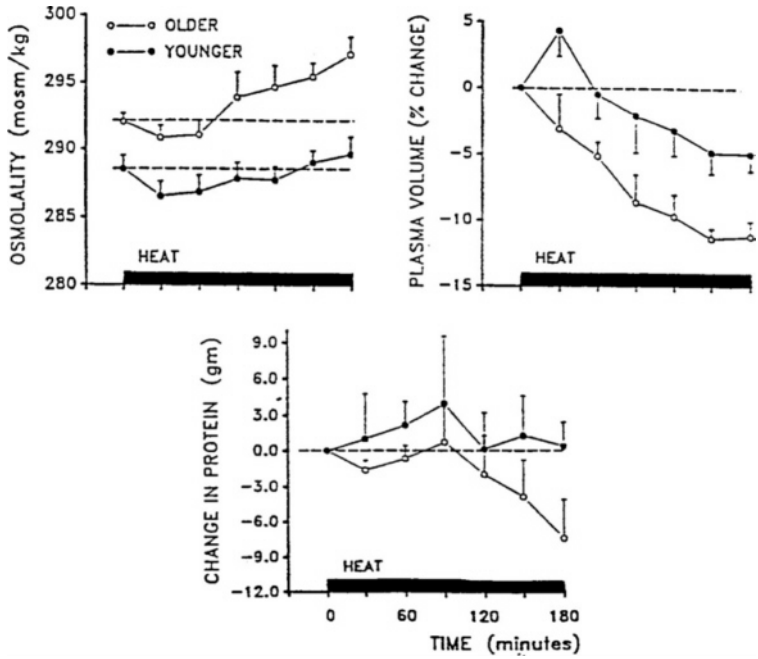

FIGURE 16-3 Plasma osmolality, percent changes in plasma volume, and absolute changes in plasma proteins in young (n = 6) and older (n = 5) men during a passive 3-h heat exposure. Values shown are the means ± standard errors of the mean.

plasma volume in the older subjects was significantly greater during the heat exposure (Figure 16-3). Every young subject hemodiluted during the first 30 min of heat exposure, while only one older subject hemodiluted. The increases in plasma osmolality were similar in both groups during the heat exposure, although the older group maintained significantly higher plasma values. The total protein concentration increased or remained the same during the initial 90 min of heat exposure; it then stabilized in the younger men and decreased in the older men.

DISCUSSION

Compared with the younger men, the older men in this study showed an impaired ability to maintain their core temperature and plasma volume during a passive heat challenge. By carefully examining the time course of the changes in body fluids during the 180-min heat exposure, we may be able to identify potential causes for these age-related differences.

The most striking difference in the plasma responses of the two groups was the lack of hemodilution during the first 30 min of heat exposure in the older men. Since hemodilution is thought to be due to a transient imbalance of venous and arteriolar tone (Harrison, 1986), this finding suggests that with increasing age, the veins become less responsive to environmental changes. Changes in the structure of cutaneous veins might increase wall stiffness or increased sympathetic tone might prevent venous relaxation in response to body heating as part of an overall change in the autonomic nervous function.

Differences in the fitness levels of the two groups may have contributed to the heat response differences. The maximum oxygen consumption of the older men was significantly lower than that of the younger men, as would be expected in an older population with a similar life-style (Astrand, 1960). Although we did not specifically assess daily energy requirements, neither group participated in regular exercise or had jobs that required hard physical labor. If a significant training effect had been present, then a more sensitive sweating response would have maintained lower temperatures in the trained group. The absolute rectal temperatures were not significantly different after the first 30 min of heat exposure, and the total body weight loss of the two groups was similar. Therefore it is unlikely that the differences in body fluids in this study were due to a training difference.

Our finding of elevated plasma osmolality in healthy older subjects under resting conditions agrees with the findings of Crowe et al. (1987). However, it is unclear whether the higher osmolalities indicate that the older men were dehydrated or whether they resulted from an age-related

difference in sodium regulation. Baseline dehydration could explain the failure of the older men to hemodilute during acute heat exposure (Sawka et al., 1984). However, if the older men were dehydrated, then they should have had higher resting hematocrits and plasma protein concentrations.

The similar rate of loss of plasma volume during the final 2 h of heat exposure suggests that the mechanisms responsible for fluid shifts during these stages of heat exposure were not altered by age. The total body sweat loss was similar for the two groups and, therefore, probably contributed equally to the hemoconcentration response. However, the greater loss of plasma proteins in the older men during the final hour of heat exposure suggests that older men may have greater difficulty restricting splanchnic blood flow during prolonged heat exposure (Horowitz, 1984). If the heat exposure had been extended in this study, greater differences in plasma volume might have occurred.

We conclude that a difference exists in the ability of young and older healthy men to maintain plasma volume during passive heat exposure. This difference may contribute to the greater rate of rise in core temperature in the older group and, therefore, might affect heat tolerance. Our findings suggest that future studies should focus on age-related changes in vascular responsiveness to uncover mechanisms of greater heat strain in the elderly.

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Index

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