Naval Health Research Center

PROCEEDINGS HYDRATION AND HYPERHYDRATION ISSUES CONCERNING OPERATION DESERT SHIELD

D. M. HERRON (Ed.)

REPORT No. 91-5

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NAVAL MEDICAL RESEARCH AND DEVELOPMENT COMMAND
BETHESDA, MARYLAND

Proceedings

Hydration and Hyperhydration Issues

Concerning Operation Desert Shield

Edited by D.M. Herron

GEO-CENTERS, Inc.

Hacienda Old Town Hotel

San Diego, California

5-6 November 1990

Host:

Naval Health Research Center

San Diego, California

Sponsor:

Naval Medical Research and Development Command

Bethesda, Maryland

Report No. 91-5, supported by the Naval Medical Research and Development Command, Department of the Navy, under Work Unit No. 63706N 0095.004-6105. The views expressed in these proceedings are those of the participants and do not reflect the official policy or position of the Department of the Navy, the Department of Defense, or the U.S. Government.

Program Schedule

Monday, 5 November 1990

0830 - Introduction - Lyn Yaffe
Meeting Goal/Hyperhydration Mission

0915 - Hyperhydration - Participant discussion
Feasibility Comments
Essential Questions

1030 Break

1045 Immediate Deliverable Procedures
Availability/Safety/Efficacy
Generic Fluid Choices/Hyperhydration Volumes
Fluid Requirements During Hyperhydrated State
2-6 Hour Hyperhydration Periods
Loading Times and Requirements
Operational Scenarios

1230 Lunch

1330 Immediate Deliverable Procedures (continued)
Essential Questions/Studies to Make it a Reality

1530 Break

1545 Discussion (continued)

1630 Recap/Can Hyperhydration Work Now?
Second Meeting Day Focus

1700 First Day Meeting Adjournment

1900 Dinner

Program Schedule (continued)

Tuesday, 6 November 1990

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1030 Break

1045 Procedures for Small Operational Mission Groups
Procedures for Larger Operational Groups
Hyperhydration Impact on Personnel Performance in Chemical/Biological Protective Gear

1230 Lunch

1330 Possible Collaborative Efforts to Deliver Hyperhydration, if feasible, quickly for Simplest Mission Scenario

1530 Break

1545 Role of Naval Health Research Center in Coordinating Necessary Collaborative Studies for Rapid Delivery

1700 Second Day Meeting Adjournment

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Preface

These Proceedings represent the collective efforts of many participants who attended the meeting. In the final editing, I added, deleted, or changed material only as seemed necessary to provide consistency or continuity.

The conference was organized principally to answer two questions that have been raised as a result of Operation Desert Shield. The first deals with a short-term study to determine if there is a more appropriate fluid than water to keep our military men and women hydrated while on exercises in the desert environment. The second deals with a long-term study to determine the most effective means to hyperhydrate a soldier to provide him or her with increased performance and survivability in extended desert operations.

The conference was divided into five parts: (1) The introduction and background for the issues to be discussed were provided by CDR Lyn Yaffe, MC, USN, Bureau of Medicine and Surgery; (2) The discussion on the immediately available replacement fluids procedures was initiated by Dr. Robert Cade from the University of Florida in Gainesville, Florida; (3) The scenarios for small operational mission groups was introduced by LCDR John Dewar, MSC, USN from the First Marine Expeditionary Force, Camp Pendleton, California; (4) The possible collaborative efforts to deliver hyperhydration procedures was shared by Dr. Michael Sawka from the Army Research Institute of Environmental Medicine and Dr. Victor Convertino from the Kennedy Space Center; and (5) The role of the Naval Health Research Center in coordinating short- and long-term studies was shared by Jay Heaney and Dr. Robert Pozos, both from the Naval Health Research Center.

On behalf of the Bureau of Medicine and Surgery, the conference was sponsored by the Naval Medical Research and Development Command, Bethesda, Maryland and was hosted by the Naval Health Research Center, San Diego, California. The assistance of GEO-CENTERS, Inc., Fort Washington, Maryland and Dr. Monty Herron, Mrs. Nancy Kobus, and Ms. Cynthia Bechtel of GEO-CENTERS, Inc. is gratefully acknowledged.

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Introduction

LYN YAFFE: I would like to express my appreciation to everyone on behalf of the Navy Bureau of Medicine and Surgery for adjusting their schedules in order to come here on very short notice. My name is Lyn Yaffe, and I'm with the Bureau of Medicine and Surgery in Washington D.C., under the Surgeon General of the Navy, Admiral Zimble, in the area of Fleet Readiness and Support, which is run by Admiral Buckendorf.

Fleet Readiness and Support has the responsibility for Navy medical research and development, with an emphasis on operational needs and caring for combat casualties, including areas of research in submarine medicine, aviation medicine, casualty care, infectious diseases, and human performance. These research areas are directed by the Naval Medical Research and Development Command (NMRDC) in Bethesda, Maryland.

When the Persian Gulf situation arose and troops were sent, NMRDC looked for possible protocols for the troops in the Persian Gulf, particularly Special Operations and Marine Corps Special Forces hyperhydration needs. NMRDC's Director of Research and Planning, CAPT Tony Melaragno, made this meeting possible. The meeting is hosted by one of NMRDC's labs, the Naval Health Research Center (NHRC) in San Diego, California. I'm sure many of you are familiar with the lab and are, in fact, from that facility. I'd like to start off by introducing CDR Guy Banta, who is the Acting Commanding Officer at NHRC, to welcome you all. Afterwards, we'll take care of some administrative details, and then we can actually begin.

GUY BANTA: Welcome. CDR Yaffe gave you a good history of how we got here, so I won't expand on that other than to wave the flag for NHRC. I know a number of you, and I'm glad to have you here in our backyard so we can have an opportunity to show you around, if not this time, then the next time. As CDR Yaffe indicated, NHRC is a laboratory under the Naval Medical Research and

Development Command, and we have the good fortune of being extensively involved with all the Navy line communities in this area. We are right next door to Top Gun, Camp Pendleton, the submarine base, and 32nd Street for surface vessels, so we have the opportunity to respond quickly to the Navy's needs in areas such as sustained operations.

Our laboratory has two main areas: health sciences and human performance. Health sciences focuses on epidemiology and health information, nonbattle disease information, and battle injury information. The human performance side of the house concentrates on naval special warfare, landbase, aviation, submarines, and what we're looking at, heat stress and heat strain. As a laboratory, we've recently had the opportunity to go to the Persian Gulf three times. Also, there is a laboratory in-country.

We are very pleased to have members from the other services and members of the academic community here to help identify where we can best serve the Fleet's needs, especially in the area of hyperhydration. I want to thank you once again for being here.

LYN YAFFE: Thank you very much. Just a couple of administrative things. Most of you received travel voucher packets, a Navy, self-addressed, stamped envelope, and instructions for filling out travel forms for reimbursement. Once you get back to your home base, if you have any problems or questions, feel free to call Jane Hoover (301-295-1557) or me (202-653-1333). I'm going to pass around a sheet. Please list your name, organization, and phone number. We're recording everything that's said here, and I think in ten days to two weeks we'll have a transcript, which really is just for internal use, but I am going to make that available to each participant.

Meeting Goals: Hyperhydration Mission

The Navy would like to consider options for hyperhydration. Hyperhydration might have different meanings to different people. That can be part of the discussion: exactly what are people's concepts of hyperhydration. From the Navy research and development perspective, in a simplistic way, I put together a couple of viewgraphs. This is not to indicate what is feasible, but it raises a couple of questions, and it's part of the discussion. I would like everyone to feel free to make any and all comments that might impact on what's happening in the Persian Gulf.

There have been studies done with glycerol, glucose polymers, and other techniques to give an individual a loading dose of fluid, then give excess fluid and supposedly move the excess fluid into an extravascular space. That fluid is called on in the next few hours during sweating or activity. The questions for the Navy are:

1. Is that a realistic scenario?
2. Is there a protocol that is safe and meaningful in the short term?
3. Are there significant questions that need to be answered in the laboratory first, before something can be attempted in the field?
4. Are we talking about immediate, near-term, or long-term?
5. What would one have to determine in order to utilize this scenario of hyperhydration and a window of reduced fluid requirements?
6. What happens to thermoregulation?
7. Is there increased sweating?
8. Is elevation in core temperature really delayed?
9. Is there a beneficial aspect there?
10. What really happens with heavy operational exercise?
11. Is there any decrement in performance?
12. Does hyperhydration have any advantages for an individual wearing chemical protective gear in hot weather?
13. Will it increase sweating and evaporation of fluid through the skin?

For the next two days, we want to deal with the current realities. What is available near-term, long-term, and what are the essential questions? This is very informal, and I would like people to feel free to interrupt and ask questions. Sometimes I'm accused of compressing a five minute introduction into two hours, so I'm going to stop right now. Let's go around the room and have each person introduce himself. I would like to recognize those people who are not laboratory people, but who are operationally oriented and who have been in the Persian Gulf. I think they have something very important to add so our investigators can get a feeling of what the realities are when they address hyperhydration issues.

Melvin Fregley, University of Florida
Alan Markowitz, Naval Research Laboratory
Alan Ryan, University of Iowa
Marvin Riedesel, University of New Mexico
Tim Lyons, University of New Mexico
Warren Lockette, Wayne State University and the University of Michigan
Bob Hesslink, Naval Health Research Center
Jim Hodgdon, Naval Health Research Center
John Greenleaf, NASA Ames Research Center
Victor Convertino, Kennedy Space Center, NASA
Michael Sawka, Army Research Institute of Environmental Medicine
John Smaldino, First Marine Expeditionary Force, Camp Pendleton
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Hyperhydration: Participants' Discussion

LYN YAFFE: Now let's hear what people think about hyperhydration.

MELVIN FREGLEY: It would be beneficial to all of us to define the problem in Saudi Arabia more completely and then speak to the issue of how hyperhydration might be useful. As someone who gets his information only from the newspapers, I would really like to know what the problems are and what we should be thinking about.

STEVE LEWIS: May I make a few comments about that? Basically, it's not a dry heat, it's a humid heat. The Navy has on floppy disk, soon to be on CD RAM, the high and low temperatures for any 24-hour period with a 25-year window, plus the wind velocity, direction, and humidity profile. For the month of December, they are looking at a high of 83°F and a low of 63°F at Dahran. At the Navy Forward Lab, which is comparable to Kuwait City, they are talking about humidity as high as 80% and as low as 40% for the month of December, with winds as high as 93 miles per hour. This creates dust clouds that can go up to 18,000 feet.

Diarrhea has been the number one problem. There is literally an epidemic of gastrointestinal disorders. I think that it's getting contained at this point, so antibiotic resistance and sensitivity is a problem. Diarrhea is another way to lose precious fluids.

Upper respiratory problems have been the second major problem, probably viral in etiology, but again, a depredating factor, so people are spreading that problem fairly rapidly.

Another problem is skin diseases. This leads to staph infection, and the resistance organisms are prominent there. Most antibiotics used in the United States are controlled by prescription/physician intervention, but over there, antibiotics are purchased over the counter. So you have to be considerate of the antibiotic sensitivity of the organism, such that fairly sophisticated antibiotics have to be in-theater to take care of skin, oral flora, sinuses and the ENT side, lower respiratory for the chest, and then the GI track issues. There are sexually transmitted diseases requiring sophisticated antibiotics.

LYN YAFFE: Do you have detailed knowledge about the actual fluid requirements?

STEVE LEWIS: The Army soldiers have to drink a liter per hour for 24 hours when they are out in the field doing their regular routine. The heat starts in May and lasts through the end of September. That is the window of heat in excess of 105°F common to that area.

LYN YAFFE: When I spoke to Marine Headquarters in Washington D.C., that condition requires them to carry that amount of water with them for any number of hours they are on a mission. So one can ask, then, can you reduce the amount of fluid that they have to carry by hyperhydrating them for a certain period of time, as long as that hyperhydration doesn't produce any decrement in performance? Do some of the other operational people have any comments?

JOHN SMALDINO: I was there, and another problem concerning diarrhea was the vegetables imported from Pakistan. That stopped. There were no fresh vegetables served while I was there; everything was canned or frozen. The humidity, you are right about that. Along the coast, the humidity is very high, but inland it is very dry, like our desert. Dust is a big problem. People are going to drink more water, and the equipment is going to fail more. The clothes the Marines/Army/Air Force are wearing are too heavy for the desert. There is plenty of water available. The Saudis are providing cases of one-liter bottles, so we had plenty of water, except if the ROPUS (reverse osmosis purification units) were used. There were many of those there. Sea water is purified and served to the troops. It's really lousy tasting. We were adding lemonade and different additives to give it some taste.

I didn't see anyone drinking a liter an hour. If they were really working hard in the desert, they might drink that much. But they only carry two canteens on their belts, and if they're out in the boondocks somewhere running around, that's all they have, unless they get back to a water source.

The troops didn't carry their NBC suits at all. Everywhere they went, they carried their gas masks, whether they were jogging, sleeping, or eating, but not the suit itself. The suits were available, but it would take minutes or longer to find them and put them on.

ROBERT CADE: What is the volume of a canteen?

JOHN SMALDINO: One quart. Two quarts is all they carry.

MALE VOICE: They also have two-liter canteens, don't they? At least the Army does.

JOHN SMALDINO: Do they? I know each man carries two canteens.

GUY BANTA: Over the last year, I have spent six months over there with a research team looking at heat stress. Most of it was aboard ship. To give you a little insight as to some of the heat loads, I was there during the summer months as well as the fall months. It wasn't uncommon aboard ship to have dry bulb temperatures of 120°F to 125°F with radiant heat loads and globe temperatures, especially in the engine rooms as well as on the decks, up to 150°F to 155°F. Humidity would range from 40% to 90% topside, and in the engine rooms, 54% was about average, with partial vapor pressure around 30 mm mercury.

The helicopter community is exposed to added heat stress when operations involve hovering over ships. They have to worry about the combination of ambient heat with the heat and fumes associated with a ship's stark when hovering over that ship while it is under power. The wind from the down wash of the rotor blades is being forced into the fuselage and represents a combination of heat from the environment, exhaust heat from the aircraft, and ship's stack gas. We were measuring globe temperatures of 160°F within the fuselage of a helicopter during such overs. The pilots were wearing about 65 pounds of flight gear, semipermeable, similar to some chemical defense ensembles. They wore the fire retardant NOMEX flight suit with cotton underwear for fire protection, survival gear, helmets, turtleneck sweaters, and gloves. Not only do they wear that for protection against fire, but because the heat load within the fuselage is so bad that if the plastic zippers on the flight suits touched the skin, the skin would instantly blister.

For fire protection aboard ship, engine room crews are not suppose to work in a shirt sleeve environment. They wear long-sleeve dungaree shirts and pants. However, you usually find that about half the troops down there take their shirts off or work in t-shirts with bandannas tied around their heads.

The engine room is pretty much a moderate working environment. Shipboard topside is not a high metabolic workload either. Helicopter flight is different for the aircrew in the back of the aircraft versus the pilots. The metabolic workload for flying the aircraft is one thing, the aircrew in the back could be hoisting things up and down during hover; therefore, it's a little higher workload.

A number of helicopters are designed with air conditioning, but in a combat environment, they've learned to take the doors off the aircraft because once you start sticking those 50 mm cannons outside the doors, you can't have a door there. So air conditioning systems designed for the aircraft are not feasible.

Having spent some time in Vietnam 20 years ago, I remember that knowing to drink water was not well pursued or pushed by the leading NCOs. I've seen a change in the troops today as far as hydration. They know about drinking; water coolers are frequently in the engine rooms. Probably the ones at fault as far as hydration habits are the old chiefs and boatswain mates who have been in the Navy for 20 or 30 years. They drink a lot, but it isn't water, it's coffee. So you know what issue is there: dehydration. The education is there, it's just a matter of making sure it is available. If something can be provided in conjunction, be it hyperhydration or some other element of dehydration prevention, it's certainly needed.

There is a completely different environment when you look at the troops in the desert, out on patrol in chem-defense ensemble. Most of us have worked with that gear in laboratories and have a good appreciation of how long performance lasts in that kind of environment, even with hydration.

MELVIN FREGLEY: Do the men who are out on patrol carry only their two canteens? How long does a typical patrol last? What I'm really asking is, how dehydrated might one expect those out on patrol to become? Would they have a four-hour patrol?

JOHN SMALDINO: There are a lot of night patrols. The troops went out at night and returned in the morning. However, there are some forward areas where they had tents set up and the water buffaloes along side. So they did have water if they were out for extended periods. But many of the patrols went out at night and came back in the morning, especially the reconnaissance and surveillance.

MARVIN RIEDESEL: What is the night temperature?

JOHN SMALDINO: The night temperature dropped to the 80s two or three weeks ago. Now it's colder, as someone mentioned, probably in the 60s.

MICHAEL SAWKA: For the Army, the soldiers carry up to four liters of water, and water has been available. No one has been in isolated positions where they have been away from water. Obviously there has been no combat. We have received intermittent information as to heat casualties. Looking at some of the epidemiological data that has come back, although they haven't been described as heat casualties, we feel that there are some heat-related casualties due to dehydration. Historically, if you look at the military activities of soldiers out in the field, you normally see in noncombat situations levels of dehydration of 3%, 4%, and 5%, and, of course, with combat, much greater levels, up to 7%.

MELVIN FREGLEY: Right now, we might expect about 3% or 4% in heat casualties?

MICHAEL SAWKA: I would expect that probably for soldiers doing strenuous work without forced hydration, it's not unusual at the end of the day to see a 4% body weight reduction.

LYN YAFFE: There is also the concern about combat. Talking with the Marines in particular, they were interested in the concept of hyperhydration in order to give small groups the edge if they become cut off from their water supply, or if they go on some combat mission and are unable to get back when anticipated and have only taken a limited amount of water.

MIKE CURRAN: Does anybody here have knowledge of what we've learned from an historical perspective, such as from the British SAS and Royal Marines in Oman? The Pakistanis and Royal Marines have been in Yemen for a period of time. There have been a number of similar environments where there should have been some experience gained. Do we have anyone who knows the experience base of other nations in similar environments?

GUY SANTA: I did notice when I was over there last summer, just reading the local paper in Bahrain, heat casualties (death from heat stroke) were being identified daily among the Pakistani workers. In that part of the world, most of the day-to-day hard laborers, working 15 hours a day (digging ditches, laying bricks, working on the streets), were people brought in-country from Pakistan, and they were succumbing to the heat loads. The civilian community was constantly reporting heat injuries in the local newspaper. But I don't know what the history of military operations is in those countries.

MIKE CURRAN: Does anybody else know?

JOHN GREENLEAF: The English have a long history in that part of the world. There is a large literature on this. All the comments that we have been hearing have all been reemphasized many times, and they've spent a lot of time looking at this problem. They have always come to the same problem we have now: how to get the liquid into the troops. There is a kind of natural mechanism that somewhat inhibits intake. If intake is voluntary, it's not going to be equal to the outgo. Probably half of us here have been looking at this particular problem, and we have got comments on it.

JOHN SMALDINO: At Twenty-Nine Palms, they've been doing this for years, and their climate is almost the same as Saudi Arabia. All we would have to do is go to our troops there and look at the reports of what they have done over the past years, and the problems they've had would be similar.

MICHAEL SAWKA: Our institute does have that information. We have data on the Persian Gulf and the incidence of heat casualties. But again, as I stated, we believe much of that information is tainted, and what they are describing as heat casualties, we don't feel is inclusive. They are not including things such as stragglers. We are not getting a good handle on the total impact. There is a great deal of laboratory data collected by Dr. Adolph during World War II, and that information is available.

LYN YAFFE: In general, I think the problem is one of getting sufficient fluid into people so that they might have an operational window that is different from what they have now. Theoretically, if a boot carries 15 liters of fluid on his belt, and he is going out for 10 or 15 hours, he is fine. But in the Marine Corps, when they go out on reconnaissance missions, they hate to have that fluid sloshing around. They would much rather go out as light as possible. Can you put fluid inside of them that would give them a two- to six-hour window? Is there something that needs to be checked in the next couple of months that would make it doable? Even if we were to just focus on one scenario, where it's a dozen soldiers going out for four to six hours to work hard in the field at night or during the day, and they want to go prepared for an unexpected delay in returning to their operational center. They don't want to take 30 liters of fluid per man. Is it conceivable to give them a window of opportunity for improved hydration and performance through hyperhydration, or is that a concept that is just a dream and a laboratory observation?

MELVIN FREGLEY: It would be worthwhile to define what dehydration is and what the limiting factors in the sequence of events are that would be expected.

JOHN GREENLEAF: One can speak about hyperhydration, hypohydration, and dehydration; sometimes they're used interchangeably. We have a normal level of hydration, euhydration is one of the terms for it, and, of course, it has an oscillation. You are dehydrated a little bit when you get up in the morning, and you consume various amounts of liquid during the day, depending on the energy level.

The process of losing the liquid might be termed dehydration. One can be hyperhydrated and lose liquid, and one would use the term dehydration. When you have a consistent lower level of hydration, then one might call it hypohydration, which means you come to perhaps a lower level, and you hold it there for awhile, hours, maybe even days, when you are in the desert. If I remember correctly, psychological performance begins to deteriorate with 3% to 4% of total body weight loss. It has been considered that there is a 0.1°C increase in core temperature with exercise with each 1% of body weight lost. So with 5% to 6% loss, we have a 0.5°C to 0.6°C increase in internal temperature, and that can become debilitating. At 6%, we begin to run into heat exhaustion casualties. As probably all of you know, the mechanisms of voluntary intake do not keep up with the rate of loss. So if troops are rather uninitiated in this whole area, they will not consume enough to equal the outgo, and they will become progressively dehydrated. That can lead to problems if they do not recover overnight and begin to exercise the following day. The troops will progressively dehydrate.

I think it was in 1979 that the Marine Corps changed its operating policy of one canteen per man per day. The commanders in the hot environments began emphasizing that intake has to be higher than normal take. Education on the subject has increased, and it has helped. I was at Twenty-Nine Palms a number of years ago for a two week exercise. It was in the summer, and I was working in the hospital. We were trying to help with the heat casualties. There was an old colonel there, probably from the Guadalcanal days, saying, "You guys are still fooling around with all this liquid. In my day, it was one canteen per man per day." Well, needless to say, we had an opportunity to educate. We had only about 18 heat casualties over that period of time, and the previous average was something in the hundreds. I think the attitude is there; as somebody brought up, the young troops are more cognizant of the liquid, they are looking for the liquid. The Army is after some kind of rehydration drink for the troops because when they have access, they will buy Gatorade. So I think the attitude is there.

MICHAEL SAWKA: As an institute, we have thought a lot about hydration over the last ten years; we've had a containment program. We have thought about hyperhydration; in fact, we have experiments planned for the summer. We have also thought about special operations and a way to intervene. If you want to see some slides, I can take you very briefly through what I feel are the issues, what is or isn't doable.

JOHN SMALDINO: Mike, whatever happened to salt tablets? Do people take them anymore?

MICHAEL SAWKA: It depends on whether you are acclimated or not. You really don't lose that much. As I'll show you here, you probably want to avoid salt. When you think of dehydration, people tend to think of only looking at volume depletion. There is also the change in tonicity, which is of equal importance, and perhaps for some military situations, more important. Many of the slides I have are based on experiments from people in this room, so feel free to interrupt, make any comments, or disagree.

The first point I want to make is that any time you are looking at a military situation, it is different than an athletic situation. People here from the sports medicine community think of an athlete doing a pure aerobic task where he has musculoskeletal compactivity. He doesn't have to wear any clothes, and in those situations, it is difficult to predict performance. In the military, it's a lot more complex. You have clothing systems involved and you have very complex tasks; not every soldier is marching or running. Most of them are actually lifting and grasping, which changes cardiovascular responses. Over the years, as an institute, we have tried to identify the factors a soldier brings into a particular mission. What does the mission require? What environment will the individual encounter? How do these factors interact to affect thermoregulation and performance?

Today we're talking about hydration. We, as an institute, believe hydration is the most important factor influencing performance, but how does it do this? It's going to depend on the mission. As Drs. Convertino and Greenleaf questioned, what are the mission requirements, how hard are the troops working, and what clothing are they wearing? If the individual has certain clothing systems, where they have CW protective clothing or armor, they are going to have a greater reliance on dry heat exchange, which is going to change the ability to work under tolerances of hyperhydration and syncope. The Navy is in the high humidity coastal regions, not requiring sweating rates. The water requirements are much lower, and as I'll show you later, they have different mechanisms of performance reduction due to hydration than in the desert.

We know that an individual runs, but a soldier in the field changing tank treads or a person aboard ship is doing more arm work. There is a higher blood pressure response with arm work, and individuals do not get the venous return from the legs. This results in more incidences of syncope and more susceptibility to dehydration casualties. So when you ask what the scenario is, it's very difficult to say. When you look at specific scenarios, you may see that hyperhydration may or may not have advantages.

Someone said that the water requirement is seven or eight liters a day. That is true for a soldier working in a desert environment doing continuous activity. What we can provide is very specific water requirements depending on work rate and clothing. But they are not precise. Here is a slide taken from laboratory data from Dave Costa's labs and our lab. We tried to have somebody doing something simple, like running, at different speeds. Look at the range of sweating rates due to environment and the effects of acclimation. The only point I want to make here is that when individuals are taking about seven or eight liters of water a day, you are talking about a mean value for a specific type of activity. There is going to be great variability between individuals because sweating rates vary.

Let's talk about dehydration first. There's two ways dehydration influences performance. Adolph popularized the idea that dehydration primarily acts through reduction in blood volume, which causes a failure in the thermoregulatory system. Most people in sports medicine believe that this is the driving mechanisms for dehydration-induced heat casualties. Another theory, advanced by Hertzman and Ferguson, is that dehydration results in regulated changes in the temperature regulatory system. What I'm going to show you is that, in fact, both of these statements are true. That in some situations, such as a soldier out in a desert where he can thermoregulate, hydration is going to have an important influence, and dehydration is going to react to the changes in tonicity in blood volume by altering steady-state thermoregulation. In these situations, I don't believe that hyperhydration has a lot of impact. On the other hand, in situations where an individual is in protective clothing, or fire control gear aboard a ship, where the individual has very high sweat rates, the only way to thermoregulate is dry heat exchange, but he can't because of the barrier. But the most important thing is, the individual has a lot of blood and skin in addition to being dehydrated. Under those situations, the individual is very susceptible to syncope. So for short periods of work in protective clothing, such as fire control aboard ship, I believe hyperhydration may have a lot of application in that it may not improve the ability to thermoregulate. If it does, it really doesn't matter because the person can't thermoregulate, but the expansion of the volume may help the individual avoid syncope.

So what is known? This slide reviews what has been done in the literature on the effects of hyperhydration and thermoregulatory responses. You can see there has been a number of studies over the years. These are the studies. These are the treatments, how they did hyperhydration. These are the conditions, what they found in terms of core temperature compared to control sweating and blood flow. These are the studies that looked at different ways of hyperhydrating.

When you first look at the slide, it looks like most studies do, showing an improvement in thermoregulation with hyperhydration. However, if you go and actually examine the studies, most are not done very well. A study by Bass et al. found a lowering of core temperature. But if you read the report, they never compared hyperhydration to euhydration, which is the correct control. They had individuals dehydrated during the experiments, so they are comparing euhydration and dehydration. Obviously, you would expect a higher temperature with dehydration. They did not have an adequate control.

The next study was done by Nelson and is the most widely referenced for showing improved thermoregulation. First, there were no statistics. Second, they never defined their control groups, but probably the control group was aggressive dehydration. They were not comparing euhydration to hyperhydration, they were just looking at hyperhydration, which is really euhydration to some level of dehydration.

The two studies that really did a good job controlling were done by John Greenleaf and Ethan Nadel and Gary Mack and his lab. Both studies did very precise controls of euhydration, and neither found a significant difference. A recent study by Lyons et al. fed the individuals glycerol so they could increase the total body water. They reported fairly large improvements of hyperhydration with glycerol feeding. I might add, in that study, they had fairly low-fit people. They probably were heat acclimated, but it is not known, and they found a fairly large improvement. If you look at the literature, probably just drinking water or some sort of beverage has no advantage in terms of improved thermoregulation. It may be that ingesting glycerol does have an advantage.

VICTOR CONVERTINO: From an operational standpoint, wouldn't the comparison be more appropriate between the hyperhydration state and the dehydration state?

MICHAEL SAWKA: I'm not sure. From an operations point of view, you would be better off comparing euhydration in terms of maintenance of adequate fluids. It depends what your question is. If you are comparing hyperhydration with progressive dehydration to euhydration with progressive dehydration, that is operationally what you would see.

VICTOR CONVERTINO: By the time the soldiers go out into the field, the hyperhydration state in this operational scenario may be something that is helping maintain euhydration, rather than going out and being in a dehydration state. I'm wondering whether or not, although these are interesting data, a comparison between hyperhydration and euhydration really is the appropriate comparison.

MICHAEL SAWKA: That is a good question, you are leading into the next point I was going to make. What can you get out of hyperhydration? What would be the possible advantages? One would be, as I pointed out, an improved ability to thermoregulate, higher sweating rates, higher peripheral blood flow, lower core temperature. The second benefit might be just a delaying of the dehydration. It would take longer to get to a level of dehydration. A third benefit might be, regardless of any thermoregulatory effect, an improved performance through stability of blood volume. An interesting point from this paper by Lyons is that they reported a large increase in sweating rate of 200 mls when hyperhydrating beforehand.

TIM LYONS: It was a little bit more than that actually.

MICHAEL SAWKA: 200 mls per hour. If you do have a large increase in sweating rate operationally, and you allow a person to go out and dehydrate, you have to also look at the tradeoffs. Experiments done by Jim Agnew from our institute looked at individuals who were acclimated and unacclimated to the heat. With heat acclimation, the sweating rate increased the same as with glycerol ingestion. They then had individuals perform work in a standard exercise heat task with a progressive dehydration. What they found was that in the acclimated state, individuals with progressive dehydration, by virtue of their higher sweat rates, actually had a greater progressive dehydration and ended up doing the same or worse. Whether or not you would get that with this, I don't know.

LYN YAFFE: Obviously, it is an important point that activity becomes a major factor in how much sweating occurs.

STEVE LEWIS: Mike, how would you define, operationally, hyperhydration? Would you say a 4% gain in weight due to fluid?

MICHAEL SAWKA: No, you are probably talking about a liter, a liter and a half. It depends on if you put it in the vascular space.

LYN YAFFE: Can it be pushed beyond that, assuming there is some advantage to hyperhydration? Theoretically, how much fluid could you put on board?

MARVIN RIEDESEL: I don't know, it has never been done. It is true that what we are expanding with the glycerol is the extravascular volume, and I don't know of any system that regulates the extravascular fluid in terms of physiological control of extravascular volume. It is true that in comparative physiology, studies have been done that demonstrated deterioration because of water toxicity, and this is not something you run into very often in humans. There are some studies on water toxicity. I think these are people in a neutral environment drinking 24 liters a day and not putting out the sweat; this is a psychological problem.

TIM LYONS: I would like to make a point along those lines. I don't know how many of you attended the ACSM meeting in Salt Lake City, but there were several discussions on water toxicity. Many had to do with people exercising. Some examples given were ultraendurance runs or triathlon-type events where people actually were over drinking. They were drinking more than they were putting out, and they were reporting quite a few incidences of water toxicity.

ROBERT CADE: Sixty percent of the people admitted to aid tents at the Iron Man Marathon in Hawaii had hyponatremia to convulsions as a manifestation of it.

TIM LYONS: They are thinking this hyponatremia is due to water toxicity, drinking too much water, not losing much salt.

ROBERT CADE: Well, they are doing both. I have data that I brought along, and part of it bears on giving glycerol as part of a replacement solution during exercise.

WARREN LOCKETTE: As a clinical endocrinologist, we see disorders of fluid regulation all the time. The question becomes, if you do hyperhydrate someone, how much can you hydrate them safely? We routinely give three or four liters to an individual with no untoward consequence. The other thing is, and this is giving more of an isotonic solution, if you calculate the volume of distribution of sodium in the extracellular water, taking a 70 kg man with an extracellular body volume of 20%, that is 14 liters of volume distribution. If someone has serum sodium concentration that averages 140 meqs/l, he can take in a good deal of free water without significantly altering the sodium concentration, inducing hyponatremia. If you can get him to take sodium with that, all the better, because it is more fluid that you can introduce, such as Gatorade.

ROBERT CADE: Water isn't distributed just in the extracellular space. Better than 60% goes to the intracellular. When you talk about change in sodium, you have to talk about the total body water because only that part that stays in the extracellular fluid is going to dilute your sodium. So two liters, something like two thirds, is going to go into the intracellular space.

WARREN LOCKETTE: We are saying the same thing. There is a tremendous volume you can give an individual.

MICHAEL SAWKA: It is glycerol that would go into the intracellular space. But with just water, it is unclear how much.

ROBERT CADE: This slide shows a series of experiments we have been doing the last several years. These people are all athletes. They were all riding a bike at somewhere around 70% to 75% of their $VO_{2\ max}$ in a thermoneutral environment. The temperature was kept at about 23°C. There were seven subjects, and each one of them made each of these bike rides. They would drink our laboratory designated solution containing glycerol pyruvate (Thirst Quencher II TQII)], Gatorade (TQI), water, or nothing exercising. They fasted for 12 hours before the ride began. When they started riding, there was a very marked drop in blood volume. This was due to at least three factors. The first is blood flowing in muscles through preferential channels. The area of epithelium exposed is relatively low. When they started exercising, the true capillaries opened up, and most of the blood went through them. At rest, these are opening and closing, but they are opened only a small amount of the time. During exercise, when it is up in the 75% $VO_{2\ max}$ range, they are open all of the time. They are leaking rather rapidly, with fluid slowly being returned to the vascular space. Part of the initial drop in blood volume is due to that redistribution out of the vascular space into the interstitial space.

A second component is the fluid going into the intracellular space. With the contraction of a muscle, sodium goes into the cell, potassium leaks out, and water goes into the cell. As sodium goes into the cell with rapid, repetitive contractions, there is not enough time for the potassium to be reaccumulated and for the sodium to be extruded from the cell. So there is a rise in intracellular volume at the expense of the extracellular space, or if you will, vascular space goes back.

The third thing that happens with exercise is a breakdown of glycogen in the cell. Glycogen is osmotically inactive, but when you break it down and have glucose, fructose, and carbon fragments, they are osmotically active, and water will go into the cell because of that osmotic force. This drop in blood volume occurs early. In this experiment, we were drawing blood first at 30 minutes, so it doesn't show. But at 15 minutes, a major part of this drop is occurring. After that, blood volume will continue to fall, and it falls at a rate that is proportional to sweating.

WARREN LOCKETTE: Can you be more specific in saying what percentage of intracellular volume increase occurs in the response to exercise? Your comments indicate that action potential increases the sodium uptake in the cell. First, given the membrane conductance and potential for sodium, you only need one or two ions to get into the cell to cause depolarizing change in the membrane potential. Secondly, how much is the intracellular vascular volume really changed?

ROBERT CADE: I don't know. I can tell you that if you measure a working muscle and calculate the frustum of a cone, the volume of the muscle will go up. For the nonmathematicians, if you take a cone and slice it off at any angle, it is a truncated cone. If you slice it off through a level parallel to the base of the cone, it is the frustum of the cone, and you can calculate the volume of the muscle.

WARREN LOCKETTE: Is that intracellular? We know the blood volume is going to be greater.

ROBERT CADE: I think a major part of it is intracellular simply because the volume changes are enough that it almost has to be. But I don't know the answer to your question.

GARY MACK: Is the movement of the fluid through the intracellular and extracellular space basically due to osmotic gradients?

ROBERT CADE: Absolutely. That is what that second slide basically shows, except the old scheme that Stalling drew up. It is only partially true. It is modified by the situation that you have different vessels open for different amounts of time.

GARY MACK: During the scenario you are talking about, the increase in plasma osmolality is primarily 60% of the increased osmolality in the plasma.

ROBERT CADE: There is an appreciable amount of water moving out of the vascular space in the working muscle, and a significant amount of that goes into the cell. I don't know how much. A significant amount of water moves into the cell with exercise.

HAL GOFORTH: I am really impressed with the difference in percent of volume change in the blood. I am going to ask a question about method. Did you use hematocrit hemoglobin or did you use Evan's blue dye?

ROBERT CADE: This is hematocrit and hemoglobin. We have done all of our early experiments with Evan's blue dye before and after the period of exercise. There is a problem with that during the exercise, though, because it takes about 30 minutes with Evan's blue dye, and much of this shift in volume has come back into the vascular space by that time. If you measure Evan's blue before and after, what you get is the loss that occurred with sweating. If you measure Evan's blue here and exercise for 15 minutes, you get a drop in volume calculated by hemoglobin and hematocrit, but you don't get a major drop in volume measured with Evan's blue or radio-labelled iodine because that change is basically how much you have lost by sweating.

HAL GOFORTH: Would there also be a change in the cell volume with glycerol versus the others? These solutions don't all equally enter the red cell, so that would affect your plasma volume.

ROBERT CADE: The change in red cell hemoglobin concentration with glycerin is almost nonexistent. We cannot tell if there is one, at least early on, so that glycerin has not entered the red cell and expanded it markedly. Anyway, this is volume distribution change, and we can talk about the components of it, but there is a significant drop in blood volume. As they continued, blood volume continued to fall, and it fell in relationship to how much they were sweating. When they were drinking water or NPO throughout the experiment, by 60 minutes, they were down to 8% vascular volume depletion; by 90 minutes, a little bit more than that. None of them went farther than that. I think the principal reason, and I'll show you why in a minute, was their vascular volume had gone down significantly.

Drinking water, they did a little better, but water does not replace the loss in extracellular volume because that is, in part, salt. So when they drank water, it goes into the cell and is only moderately effective in keeping the extracellular space and its component, the vascular space, expanded. When drinking Gatorade with 25 meqs of sodium, they did a little better. Vascular volume continues to fall slowly throughout the period of exercise. This is when drinking TQII with 1% glycerol in it. This initial drop in blood volume is completely prevented, and vascular volume remained high throughout the period of exercise.

LYN YAFFE: As Dr. Sawka asked, is there any increased sweating with TQII?

ROBERT CADE: No, the opposite. We will get to that in just a minute. This is cardiac output. I have not shown the control values, all of which were down between three and four liters per minute. When exercise began, cardiac output went way up. With NPO, it was down at 60 minutes and still falling. These people stopped because cardiac output had fallen; the changes that go along with that we'll talk about in a minute. With water, they are still doing fairly well at 60 minutes, at 90 minutes, and 120 minutes, way down. With Gatorade up, and they remained pretty good. Here, with TQII, they are significantly higher at 30 minutes and throughout than with Gatorade. This difference correlates with the volume changes that occurred. The 4% volume depletion that occurred in here is the difference in cardiac output. Volume has a profound effect on cardiac output, and it does it with a fall in stroke volume. As they become more volume depleted, they increase their rate in an attempt to keep cardiac output up. As pressure goes into the right side of the heart, the increase in rate causes a further decline in the stroke volume. Volume depletion lowers effective return to the heart, decreases filling of the right atrium and ventricle, and decreases stroke volume and cardiac output.

LYN YAFFE: What is the workload again?

ROBERT CADE: Between 75% and 80% of their $VO_{2\ max}$.

MICHAEL SAWKA: What was the oxygen uptake then?

ROBERT CADE: It's up around 2,500 to 2,600 mls per minute.

MICHAEL SAWKA: Two and a half liters of oxygen uptake.

ROBERT CADE: And some of them are higher than that.

MALE VOICE: Volume of fluid?

ROBERT CADE: They are taking in water, Gatorade, or TQII at 200 cc every 20 minutes. By and large, they drank all of it.

MALE VOICE: Did they start drinking immediately?

ROBERT CADE: They started drinking 15 minutes before exercising.

MICHAEL SAWKA: What was the ambient temperature?

ROBERT CADE: The ambient temperature was 23°F, and relative humidity was about 50%.

STEVE LEWIS: Dr. Cade, what is in TQII again? You said pyruvate and glycerol?

ROBERT CADE: It is a modified Gatorade; the glucose has been cut down, the sodium phosphate and potassium phosphate have been changed, the sodium citrate is down a little, and then glycerin and pyruvate are added.

MALE VOICE: What percent glycerin and pyruvate?

ROBERT CADE: A half a gram per deciliter.

MALE VOICE: Per deciliter, 0.5%.

LYN YAFFE: Don't you think the observations are primarily due to the glycerol?

ROBERT CADE: This set of experiments was done without pyruvate in it. This is just glycerin. Changes in glucose occur with exercise also. They are not all that striking, but almost the same then, up a bit, and then way up. It goes up with carbohydrate-containing drinks. If you have someone who has fasted for only six hours, generally their serum glucose will go up when exercise begins. If they have fasted for 12 hours, it doesn't go up. If they have fasted for 24 hours, and I'll show you some of those in a minute, it goes down a whole lot more.

STEVE LEWIS: Does endurance decline as glucose falls after 24 hours of fasting?

ROBERT CADE: Yes, after 24 hours of fasting, the principal reason they stop is they have run out of substrates for energy. In these experiments, the principal reason for stopping is blood volume. There is a rate of rise in rectal temperature and sweat loss during the exercise period. They went up a little more than 0.03°C per minute when they were NPO; they went up somewhat slower than that drinking water; less than that drinking Gatorade; and lower than that, about 0.014°C per minute, when they were drinking TQII.

This is the rate of sweating. When they have to drink water, and the rate of sweating with water is higher than it is with NPO or in experiments where they have previously been volume depleted and are now given water, the rate of sweating goes up. I think this is in part due to the changes in ADH. In renal patients who are anephric, there is a marked change in rate of water loss according to the presence or absence of ADH. Here, with water, they sweat more than they did NPO; with Gatorade they sweat less; with TQII they sweat least. I think the reason this occurs is perfusion of the skin. In measuring skin blood flows, the skin blood flow varies with the cardiac output.

ROBERT POZOS: Looking at the rectal temperature changes, maybe I misheard you, but are those significantly different?

ROBERT CADE: Yes, they are different.

ROBERT POZOS: But for me, from a functional point of view, those are not really impressive.

ROBERT CADE: That is rate of rise. In 60 minutes, they are up above 39°C.

HAL GOFORTH: There must be an enhancement of heat release. What technique are they losing their heat through. It obviously isn't evaporative cooling.

ROBERT CADE: It is evaporative cooling; just a minute, I'll show you why.

MALE VOICE: Are your errors on sweat rate standard deviations?

ROBERT CADE: Yes, that is standard deviation. If you watch runners at the end of a mile race, about half come in sort of a ghastly, greenish gray color. Those people are no longer perfusing their skin. With their very high rate of work, their redistribution of fluid goes up to 10%, 12%, and 15%, and their cardiac output is already down at the end of a half mile or a mile run. If you watch an athlete running a five- or ten-thousand meter race in a fairly warm climate, color pictures show their skin gets red, and then somewhere out toward the end of the race it will become this greenish gray color. At that point they are no longer running, they are jogging, but they are effectively out of the race. They are no longer perfusing their skin, and their rectal temperature has gone up to the point that they stop.

VICTOR CONVERTINO: Bob, if this is the argument for an apparent advantage of your TQII, how effective do you think the advantage would be, if any, if the soldiers are in an environment of 100°F to 120°F?

ROBERT CADE: I can't say at 120°; I can tell you about 90°F with a humidity of 50%, and it makes a big difference.

MICHAEL SAWKA: I think my slides later will pick that up. It's nice that you showed that because we are going to be in agreement on that later.

STEVE LEWIS: Two questions, Dr. Cade, with regard to your measurements. What would happen if you used one of these capsules and had the athlete/subject swallow it and instead of getting a rectal core, which I have particular difficulties with, you get the temperature of the right atrium? Or using the capsule, get the temperature of the GI tract, which would be relatively noninvasive? The other question concerns infrared spectral analysis. Through infrared pictures, could you quantify the fact that the guy who is really in fine condition is augmenting his evaporative loss and his skin blood flow and segregate those who are in fit condition versus those who have turned green and have lost the race and are not fit?

ROBERT CADE: I think you could if you have the equipment to do it.

LYN YAFFE: If I could just recap for my own understanding from the standpoint of what you have shown, is my interpretation correct that the possible use of appropriate amounts of glycerol for keeping vascular volume adequate, and even the possibility of using this or some modified approach for hyperhydration, alive and well?

ROBERT CADE: Well, I think yes, in a way.

MALE VOICE: What about performance?

ROBERT CADE: How far they went was the measure of performance.

WARREN LOCKETTE: I have a fundamental question, my motivation for asking it will become obvious later. The basic reason why you think the TQII works better than Gatorade, plain water, whatever, is what? Do you have a hypothesis?

ROBERT CADE: I think it keeps the vascular space expanded. When the vascular space is expanded, the filling of the heart is better and cardiac output is significantly greater at any work level. With cardiac output sustained, perfusion of the skin is sustained.

WARREN LOCKETTE: Is everyone who uses glycerol in agreement that if the plasma volume is maintained, you will see this efficacious kind of response? There are other molecules that freely distribute the way glycerol does. A lot of carbohydrate-type rapanose that are not easily metabolized stay and distribute much in the way that glycerol does. Is there any reason why it was chosen over these other freely diffusible molecules?

ROBERT CADE: It is also a carbohydrate source, basically. It is three alcohols on pyruvate. The alcohol groups are split off in the liver. Now you have pyruvate which can go to make glucose, or it can be burned directly in the cell. That is only the liver reaction.

WARREN LOCKETTE: I would hate to measure triglycerides in these folks. They don't get picked up as triglycerides?

ROBERT CADE: It does.

LYN YAFFE: It may be too early to ask this question, but how would you mesh this with the mission concept of hyperhydration where you could limit the intake of fluid during a four- or five-hour period?

ROBERT CADE: If you are perfusing the skin well, your fluid requirement is going to be less. Because it isn't how much you sweat that is important, it is how much you evaporate. How much you evaporate depends on the temperature of the skin, which is the function of the perfusion of the skin.

LYN YAFFE: So by maintaining blood volume and putting some extra fluid extravascularly on board in a hyperhydration concept, if you are losing heat other than sweating and thereby reducing fluid requirements, you might have a four-hour window where two canteens would be sufficient?

ROBERT CADE: They are liter canteens.

JOHN GREENLEAF: But if you have relative humidity of over 80%, you're not going to have that.

ROBERT CADE: I can show you data from a marathon that was run in high humidity.

LYN YAFFE: When you say high humidity, what percentage are we talking about?

ROBERT CADE: It depends on the temperature, but when the temperature was 60°F, the humidity was about 85%. As the day went on, the temperature rose and the humidity fell. By the end of the day, the temperature was up around 80°F and the humidity was still above 40%.

LYN YAFFE: We shall take a five or ten minute break.

BREAK

GARY MACK: I wanted to show a slide to support Dr. Cade's comments. Here is an example of exercise in an individual where we impose lower body negative pressure during exercise. Lower body negative pressure reduces preload and therefore reduces cardiac output 1 to 1-1/2 liters per minute. This slide shows the esophageal temperature in which the probe is placed about heart level, very fast responding. Then here we have a forearm blood flow which is Whitney Strain Gage venus occlusion. What I want to emphasize is this response of maintaining blood volume or filling pressure to the heart during exercise. We can see that, here is the levels of LBNP, this represents no suction, normal exercise, and blood flow is around 18 or 20 mls per minute for 100 mls of tissue, and that's a pretty good blood flow. When we apply -40 mm/mercury LBNP, this is equivalent to going from about supine to standing. You can see that the blood flow drops markedly in this subject, to below 5 mls/minute.

If you watch core temperature, you can see that with that sort of insult, core temperature rises very rapidly. Part of that rise is due to vasoconstriction in the skin, and some of it is due to a redistribution of blood flow in other places in the body. Then if we turn it off, we can see that esophageal temperature starts to recover a little bit.

The point is to show that definite changes in preload to the heart really affects skin blood flow. If skin blood flow is important in the heat dissipation mechanisms involved, depending on the environment you are in and the conditions, then maintaining blood volume and plasma volume are very important. In fact, that is the work Ethan and I have done over the last four or five years.

I just want to support the fact that blood volume expansion and maintaining cardiac preload are important in the skin blood flow effect. If that is going to be an important factor in temperature regulation or circulatory control during any mission, then that is a good consideration.

ROBERT CADE: This slide shows the same guys who rode in the earlier experiment, but this is an experiment in which they fasted for 24 hours before they started exercising. This shows blood glucose and the fluids they drank during exercise (water, Gatorade, or TQII with pyruvate). Blood glucose values all start off low before exercising. When they drank water, it went down very quickly. When it was down in the mid-70s, they stopped exercising. When they drank Gatorade, it went up. When they drank TQII, it went up even more and stayed up.

FRANK TOPPO: Did these people preload with water and TQII?

ROBERT CADE: They started fifteen minutes before drinking 200 cc of one of the three solutions.

JOHN SILVA: Did the 24-hour fast include water?

ROBERT CADE: Yes. They were allowed water and that was all.

JOHN SILVA: They were allowed water, there was no control over that?

ROBERT CADE: No.

MALE VOICE: What accounts for that drop?

ROBERT CADE: I don't know. That is at 90 minutes.

BOB HESSLINK: Are these groups or repeated measures for the same individuals?

ROBERT CADE: They are the same individuals who rode the bikes on three occasions.

JIM HODGDON: Is this an individual or means from the group?

ROBERT CADE: These are the means from seven people. Each one had ridden three times and so on.

ROBERT CADE: This slide shows lactate and pyruvate measures from the same set of experiments. When they start exercising, pyruvate goes up in everyone, then it parallels the rise in lactate. The ratio is a little bit different than it was at rest, but both have gone up. In our earlier experiments, we were looking at pyruvate and lactate, and it always went down to half of the resting value. They start accumulating a whole bunch of acetoacetic acid. That is why we did these experiments. You can see with water, up and down very sharply; with Gatorade, up and coming down; with a solution containing half a gram of pyruvate per 100 mls, it goes up and stays up; lactate, up and stays up, and so on. The pyruvate level stays higher when you give someone a pyruvate solution. The thing we were interested in was acetoacetic acid and betahydroxylation or betametabolism of fat.

You produce two carbon fragments which go to acetyl-co-a. Then acetyl-co-a enters the Krebs cycle by combining with oxaloacetate. The presence of oxaloacetate is necessary for the acetyl-co-a to get into the Krebs cycle. If it cannot get into the Krebs cycle, it will condense to form acetoacetic acid and betahydroxic gluterate. Betahydroxic gluterate does the same thing as acetoacetic acid.

When they were drinking water, acetoacetic acid went up very sharply, a little bit of a drop here, started to rise again, and then stopped. When they drank TQII with pyruvate in it, their acetoacetic acid went down and stayed down, allowing the two carbon fragments from fat metabolism to get into the Krebs cycle. The reason for this, we think, is that pyruvate can go either of two ways. It can lose a carbon and go to acetyl-co-a, or it can accept the bicarbonate and go to oxaloacetic acid. The beauty of this system is that pyruvate can make the oxaloacetic acid accept the acetyl-co-a. All the other fragments that come in from protein, or particularly from fat, have to come in as acetyl-co-a. So that pyruvate has a central role in metabolism, particularly during early exercise. By going to oxaloacetate, it provides the acceptance mechanism for acetyl-co-a to enter the Krebs cycle.

VICTOR CONVERTINO: On this subject, I got the impression you implied that the limitation to exercise in these groups, as you go from your "no drinking" through your scenario down to TQII, was cardiovascular limitation.

ROBERT CADE: I think it depends on how you set the experiment up. These people are fasting for 24 hours, so they are now depleted of glycogen in both muscle and liver.

VICTOR CONVERTINO: Could that really have been the limiting factor here in the exercise rather than cardiovascular-related thermoregulatory problem?

ROBERT CADE: In the ones who fasted only 12 hours, their blood sugars were still okay when they stopped, and their pyruvates were, by and large, okay. They don't have an astronomical level of acetoacetic or betahydroxic gluterate. In those people, volume cardiac output and cooling were important. In these people, they stopped, their cardiac output was down, but their body temperature was not up to 39°C or 40°C either. It is still around 38°C.

MICHAEL SAWKA: On this slide, you have a difference in plasma volume between the TQII and the control of about 6% to 8%; now you have about a 6% to 8% lower value. Is this corrected for the changes in volume?

ROBERT CADE: No.

MICHAEL SAWKA: So this could all be accounted for by the large volume because you have an 8% larger volume and you have an 8% lower value. Of course, it is relative to the others.

ROBERT CADE: But you have acetoacetate accumulating at a very rapid rate here.

MICHAEL SAWKA: That is with the water. You also had the opposite, the volume going down during that time. And with this, you had the volume being the same or higher. It seems to me that, proportionately, it is about the same.

ROBERT CADE: I don't know.

VICTOR CONVERTINO: From a physiological standpoint, the reactions are going to be based on concentration, so that is a moot argument. In fact, it may be a greater argument for volume expansion and maintaining the particular levels.

FRANK TOPPO: Did you do insulin levels?

ROBERT CADE: In these, we didn't, but we have done insulin levels in riders before. When they are drinking Gatorade or TQII, their insulin levels go down, but they are about double what they are if the riders are drinking water or drink nothing.

FRANK TOPPO: They were fasting also, so when they went from 70 to 120 there was not a real significant change?

ROBERT CADE: No. I could show you insulin levels throughout a marathon race and how they change.

WARREN LOCKETTE: But these folks, even with prolonged exercise, never really dropped their glucose levels below 7 mg%.

ROBERT CADE: That is true, and we think that is very significant. The quotient goes down as their blood sugar goes down. I'm not sure what the normal blood sugar is, but in people at rest, it is something like 90 $\pm$ 4. I've looked in some of the textbooks, and some people say blood sugar is 70.

WARREN LOCKETTE: Standard error for blood sugar would be two standard errors, which is 95% confidence level, taking you as low as 60.

ROBERT CADE: I think there is a big difference between sitting here with a blood sugar of 80 and trying to run at 5 miles an hour with a blood sugar of 80. The requirements for substrate are greater when you are running. And a blood sugar of 70 does not surprise me.

WARREN LOCKETTE: Let me be speculative because the 70 may be protective. From a clinical standpoint, the most common cause of hypothermia is hypoglycemia.

Everyone is assuming that the body temperature regulation is occurring because of changes in plasma volume. Everyone is showing the correlation of plasma volume and temperature regulation. It may be protective to have a lower blood sugar from a temperature regulation standpoint. But if you give metabolic inhibitors of glucose uptake, like 2-d-oxyglucose, you induce profound hypothermia. In fact, in the 1940s, when they used insulin shots for depression, the major morbidity was associated with hypothermia.

The second issue in terms of these intermediary metabolites is that the lactate was elevated. Since the concentration of lactate is elevated, given the equilibrium association constant, lactic acid levels are going to be higher. I am not an exercise physiologist, so I don't know whether lactic acid really decreases muscle performance or not, but could that cause a decrement in performance by an increase in lactate or by raising blood glucose? That would be a good study to do. Look at temperature regulation at different levels, of what is generally considered to be euglycemic between 60 and 120, to determine what the optimum glucose levels are.

ROBERT CADE: I have never seen a normal individual with a blood sugar of 60, unless they have been starving for three or four days. I do not like the mean ± twice the standard deviation as the definition of normal. I think that has nothing to do with what is normal; it is just a laboratory device we use.

WARREN LOCKETTE: What is "optimal" would be a better term to use, rather than what is normal.

GARY MACK: In our laboratory, about three years ago, we got involved in a project about human-powered flight which required prolonged cycling for six hours. We did a great deal of testing with blood glucose, and there were some people, even when we kept the blood glucose up, who eventually stopped. So simply maintaining blood glucose does not keep you going entirely. We did find that if we maintained blood glucose up around 90 to 100, they were fine. We never integrated the glucose problem with temperature regulation.

WARREN LOCKETTE: I will tell you that one of the most potent regulators of skeletal muscle flow is insulin; it directly vasodilates. When blood glucose levels are high, insulin levels are higher. Does that increase perfusion of the skeletal muscles decrease the effect of plasma volume blood pressure? Are there a number of studies? I guess part of the meeting is to determine what kinds of studies we need to look at. I don't know if these are germane or not.

MELVIN FREGLEY: That is germane because hypoglycemia may, in one sense, be protective, but in the other sense, it may affect performance. So we have a double-edged sword.

WARREN LOCKETTE: In endocrinology, we frequently do insulin experiments, and the whole purpose and thrust is to maintain blood sugar at an exact point and then measure the amount of insulin or the amount of glucose that is given. It is very easy to look at changes in blood sugar and change in temperature regulation. You can do an insulin experiment in a heat chamber or a cold chamber.

JOHN GREENLEAF: To add one comment to that. My colleagues in Poland exercise in temperature using dogs. When you exercise, you get a certain increase in core temperature, depending upon the load. If you give an IV infusion of glucose, it increases maybe half a degree. It looks like it has some aspect.

WARREN LOCKETTE: Guy Banta and I did a study that we published this year on gravity-induced loss of consciousness in pilots. We used a drug that raised plasma insulin levels but didn't change glucose, and it caused dramatic increase in peripheral blood flow. We are following up on that now, but this has not been published before. I can't explain it; maybe the insulin increases were doing it. Now we want to repeat the study in subjects who are diabetic and do not have insulin onboard, type 1 diabetics, and see if the same changes in flow occur.

ROBERT CADE: This slide shows free fatty acids. They go along with what we have been saying. In the starving individual, free fatty acids are higher for exercise, drinking water, or a very marked rise when drinking Gatorade, an initial drop, and that is what we generally see. If they are not starving, a secondary rise and so on. But as they run out of fuel, or as they deplete the fuel, free fatty acids are mobilized, broken down to the two carbon fragments, and so on.

MELVIN FREGLEY: Do you want to say again what the differences in performances were when you gave the various treatments, how much better was TQII than Gatorade, and so on?

ROBERT CADE: On this slide are the mean times they were on the bike for each of those rides; so endurance in this context is proportionate to performance. With NPO they stopped. They did a little bit better with water, a little bit better with Gatorade, and with TQII they were all still going at 180 minutes. But we did a perceived exertion thing. They will go along steadily for a little bit, and then perceived exertion starts going up. They get to 18 or 19, 20 is the top, and they stop. These people are still down in the 13 and 14 range. So they're saying this is moderate; their perceived exertion is still moderate. I don't know how long they would go, but clearly longer than 180 minutes.

BOB HESSLINK: Is the increase in performance due to the maintenance of the blood volume or due to the substrate?

ROBERT CADE: I think it depends on the condition you're in.

BOB HESSLINK: So this is a combination of maintaining the substrate along with maintaining the blood volume?

ROBERT CADE: It depends on many things. If you are exercising in a hot room, then volume is going to limit your performance. If you are in a relatively cool environment and you are dissipating heat well, you will still stop when you run out of substrate. Years ago, we tried to get Stokely Van Camp to make winter Gatorade and summer Gatorade. The summer Gatorade would have a higher sodium content and lower glucose; and the winter Gatorade the reverse, higher glucose content and lower sodium. In studies in our lab, it made a significant difference in performance. So it depends on what condition you are trying to evaluate.

BOB HESSLINK: So these guys are getting Gatorade or TQII every 20 minutes?

ROBERT CADE: Yes, they're getting 200 cc every 20 minutes.

JOHN GREENLEAF: And they have to drink it all?

ROBERT CADE: No, if their stomach was getting full they could stop.

JOHN GREENLEAF: So then, perhaps, they've not had all of it?

ROBERT CADE: No, the TQII and Gatorade, they got 200 cc every 20 minutes and they drank it all. Occasionally, some of them would drink more than that. Several of them asked for more. With water, 200 cc every 20 minutes, the majority of them stopped drinking that much after 80 or 90 minutes. If we gave them 200, they would drink 100 and hand it back to you. They said their stomach was full, it's sloshing around in their stomach, it does not feel good, and so on. But with Gatorade and TQII, they would drink 200 cc every 20 minutes all the way through.

HAL GOFORTH: You mentioned earlier that under exercise conditions, possibly a higher glucose level in the blood would be required. But if you look at that 103 or wherever these guys were quitting at, would you normally think that would be a hypoglycemic condition?

ROBERT CADE: No.

HAL GOFORTH: So in answer to Hesslink's question, it would be more cardiovascular rather than substrate because you are looking at blood glucose as the substrate. Only 15% of the energy requirement for exercise comes from blood glucose for muscle uptake?

ROBERT CADE: Almost all of it is produced in the Krebs cycle. Acetyl-co-a entering that is mostly from fat. Once you really get going, probably all of it is either from fat or protein because the pyruvate is going to oxaloacetate. The conversion of pyruvate to acetyl-co-a is inhibited as a concentration of acetyl-co-a in whatever fluid goes up, so you start with pyruvate going both ways. When acetyl-co-a goes up, then that pathway, the pyruvate carboxylase, is inhibited, and everything from pyruvate goes into oxaloacetate.

HAL GOFORTH: My point was that blood glucose as a substrate for an exercising muscle is a relatively small percentage of the total energy required to maintain an exercise level of 75%. It is mostly for the brain tissue that we want to maintain high blood glucose.

MICHAEL SAWKA: Eddie Coyles has published studies where depletion of muscle glycogen is associated with fatigue and discontinuation of work. And there are studies by Coyles where he has given glucose drinks that have maintained blood glucose and extended performance. But the studies also show the person goes to exhaustion. The studies also show blood muscle glycogen levels are maintained. The drinks have a glycogen sparing effect, if you preferentially metabolize some of the glucose that you ingest. So that would be the mechanism of extending it to protect the muscle glycogen.

LYN YAFFE: Do people have comments on this as it relates to an operational scenario or temperature situations in the Persian Gulf?

ROBERT CADE: In answer to the question on glucose, this is the same seven guys, but they were riding at between 60% and 65% of $VO_{2\ max}$. With that, seven of them started out on each ride. When they drank Gatorade, they all got to 180 minutes. Some of them were up to 15, 16, or 17 on perceived exertion, while others were still down at 13 and 14. When they drank nothing, four of them got up to just under 150 minutes. When they drank water, as shown here, they got farther than when they drank NPO. At the blood sugar level, they are stopping out. Their blood volume was down and their cardiac output was down, but not tremendously reduced as it was in some of the others. With a lower work rate, they are still ending up stopping with blood sugars that are okay, but others are getting down to a really low rate.

ALAN MARKOWITZ: There were a lot of parameters mentioned. How would you assess the relative importance of all of the parameters in a combat situation? For example, it seems to me from the data that you have shown that the single most important thing was the blood volume. If you lose that, everything else goes to hell rapidly. Whereas, if you maintain blood volume, then if the actual chemical balance slowly got out of whack, it was a relatively secondary effect. Is that a correct assessment? Perhaps you would like to comment on the relative significance of the various parameters?

ROBERT CADE: I think either one of them could stop you. In the situation we are talking about, I would think volume is going to be paramount. I do not think anyone is going to be able to maintain volume long enough to become hypoglycemic. In a marathon run, there are a lot of people who stop because of hypoglycemia or stop because of low blood sugars. Their blood volumes are still reasonably good, their rectal temperatures are not terrible, but they stop because of lack of sugar as a substrate. Gordon and the cardiology guys in the 1920s, looked at the Boston Marathon of 1924 and 1925 and assessed people as they finished the race. They drew blood sugars on them, and the ones with blood sugars down to 70 and 60 were in terrible shape; they didn't run as fast. The same runners were given Tang the next time, and every one of them improved their time significantly, they finished looking good, and so on. Those were two marathons that were done with temperatures in the 50s. If you look at the time of the winner of the Boston Marathon every year, there is an almost linear correlation between the ambient temperature and the time. When the temperature is in the upper 40s or low 50s, the times are low. When the temperature starts getting up in the 60s, the times are 5, 10, 12, and 15 minutes slower. Again, go below 48° or 49°, the times get slower as it gets colder. But in the desert where the ambient temperature is 100° or more, I don't think anyone is going to be able to work long enough to become hypoglycemic.

MELVIN FREGLEY: With what you have presented so far, glycerol might help in improving performance, in maintaining certain physiological effects, but you have to give a solution every 20 minutes. I think what limits the problem is the question of whether you could hyperhydrate and maintain this for a long period of time. We don't know what the limitation is here, at least I don't, of carrying some extra hydrating solution. The two canteens are what the soldiers are allowed, is that right?

LYN YAFFE: That is what they carry on them. Depending on where they are, they have access to other fluids.

MELVIN FREGLEY: If they cannot be hyperhydrated initially to last a four-hour mission, they will have to be hydrated with stops in-between. The first question that we need to answer here, if Dr. Riedesel could tell us, is about the hyperhydration, and how long could we go?

JOHN SMALDINO: Let me ask one quick question. You have been doing studies and reports for more than ten years on this. This is not a new problem, yet the only thing new that I have seen since the Vietnam days is how much water you drink a day. Why don't they have Gatorade and stuff like that sent out with the military?

MICHAEL SAWKA: They do.

JOHN SMALDINO: We didn't have it.

MICHAEL SAWKA: The Army has a replacement beverage with meals. That may or may not provide an advantage.

JOHN SMALDINO: What provisions are being made to take TQII out there and try it. In fact, I would like to volunteer to have the Marines try it.

LYN YAFFE: It is possibly one option. I think Dr. Fregley brought up the appropriate point that we should not forget that hyperhydration is part of the issue. Obviously, the troops are going to carry two canteens on a mission. What is the best fluid? Water, Gatorade, a glycerol mix of something for that little bit of fluid that they are going to be drinking subsequent to hyperhydration?

Hopefully we will come up with some possibilities for immediate protocol, perhaps to try in the field over the next 30 days, or some protocol guidance by the end of tomorrow for some longer term studies if there are some essential questions that need to be answered before we would feel safe with providing new options to operational personnel.

HAL GOFORTH: Don't we also have to keep in mind that the exercise work level that we are seeing here may not equate to the military's application? We are looking at 75% $VO_{2\ max}$, and we are not talking anything even close to that for the Fleet and the Marines.

LYN YAFFE: I think tomorrow we would at least want to pick one or two very clear operational scenarios and see if we have an answer for that level of heat, humidity, and activity that would give the troops a hyperhydration window requiring less fluid. I'm sure we could list 50 different scenarios that may require different protocol strategies. Some of them we might be able to meet within 30 days or less; some of them will require two years of research. Once we get information presented that we can address, we can go away from this with a clear direction based on the expertise that is here.

MARVIN RIEDESEL: This slide shows a study that was conducted this past summer on students at the University of New Mexico. We had an n value of 7, and the students were not heat acclimated or trained individuals but were active students who were not the type who never exercised. Also, the extent to which they were heat acclimated is a question mark. We had them go through a routine of taking in glycerol at specific times; we used orange juice to make the glycerol a little more palatable. They took in a large volume of water early in the day. One of the key things might be that they took in the water prior to eating breakfast. This has been a routine that we have gone through: a large volume of water in the morning right after the glycerol, or 20 to 30 minutes after the glycerol, and then relatively reasonable or small amounts of water throughout the rest of the day. The subjects went through this routine three times. The first, we called the pilot study, to get the subjects down to the routine of drinking at specific times, keeping track of their urine output, and reporting to the laboratory at specific times. Some of the subjects went with the glycerol solution the second time, and then the third time they just had water without the glycerol.

LYN YAFFE: They all tolerated the glycerol?

MARVIN RIEDESEL: Yes. This was set up with our control. The plasma osmolality data are relatively high for what we usually have. We usually had means of around 295 or 290. With all this water intake, I don't know why these ran high except I think it is a matter of the technician and the instrumentation being consistent. The days they had the glycerol did not result in an increase in plasma osmolality. During the first day of this routine, the glycerol dropped off by 4:00 in the afternoon, and by evening it was down very low. The second day of the routine, the glycerol was not as high in the serum. In the next transparency, this is a plot of their fluid intake, which was constant on both days. This is their urine output without the glycerol, and this is their urine output with the glycerol. There was a significant retention of water over the 48 hours.

MALE VOICE: Was this one load?

MARVIN RIEDESEL: One load of water each morning.

MALE VOICE: Similar loads?

MARVIN RIEDESEL: Yes. 21.4 ml/kg.

MIKE CURRAN: Is this an average over the days?

MARVIN RIEDESEL: Yes. That is accumulated urine output.

JOHN SILVA: Do you have any feel for the quantity of other fluid losses over the same period of time?

TIM LYONS: We are assuming they are similar between the two. We are assuming that any of the losses due to respiration, etc. are similar between the control and glycerol. We maintained the weight every day and weighed the students periodically throughout the day.

JOHN SILVA: I'm not sure it would be a good assumption to say that it would be the same.

TIM LYONS: I'm not sure, but in the past we haven't seen any changes.

WARREN LOCKETTE: If you don't take glycerol or you take glycerol, how much does the plasma osmolality change?

MARVIN RIEDESEL: I don't know why it's high except to say it's in the summertime. It is high in our control as well.

WARREN LOCKETTE: The difference in osmolality goes from 285 to 300, which in terms of osmol regulation is a tremendous concentration. What is the mechanism by which the urine output is decreased, given the fact that the osmolality in that person is so high?

MARVIN RIEDESEL: I don't have an answer.

WARREN LOCKETTE: The reason I bring this up is because most of the discussion I have seen in the glycerol loading studies, the reason that urine output decreases, is because there is redistribution of the water with the active glycerol into the extracellular space. This suggests that there is a decrease in free water excretion rate.

TIM LYONS: We did do a study and measured vasopressin, but we did not see a relation between the vasopressin and the urine reduction. We did not see vasopressin levels being elevated at the time we were having urine reduction.

WARREN LOCKETTE: At say 60 or 80 minutes, where there is a maximum difference between 285 and 300, what would be the plasma levels of vasopressin?

MARVIN RIEDESEL: I don't have those numbers with me. The only comment I have to that is that the vasopressin response is very rapid and of short duration. We are overhydrating people for initially 48 hours with one single dose of glycerol. What has happened is that the glycerol has moved into cellular or, at least, interstitial spaces.

WARREN LOCKETTE: The vasopressin will stay high as long as the osmolality is high.

MARVIN RIEDESEL: But it comes down within 2.5 hours.

WARREN LOCKETTE: But isn't most of your urine volume saved within the first two hours?

MARVIN RIEDESEL: Yes. This is what he's referring to.

WARREN LOCKETTE: Well, that's four hours.

ROBERT CADE: Poken did a micropuncture study in kidneys and showed that flow through the proximal tubule went way down.

WARREN LOCKETTE: If there was a vasodilator, you are going to get increased afferent perfusion pressure, and blood flow is going to go up.

ROBERT CADE: Perfusion pressure is a function of afferent and efferent tone, and efferent dilation occurred as the afferent dilation. He didn't measure glomerular capillary pressures, so I have no idea what the perfusion or filtration pressure was. The second thing happens and there is perfusion equilibrium. If you start off with a high osmotic pressure, as you filter water out at the same glomerulus, the osmotic pressure goes up still more so that GFR will drop, and in effect, instead of filtering across the entire capillary loop, you reached filtration perfusion equilibrium.

WARREN LOCKETTE: The flow from glomerulus to feedback filtration will decrease, but he is also dumping a lot of glycerol. I'm willing to bet urine excretion and glycerol is relatively tight.

ROBERT CADE: Well, he showed that.

WARREN LOCKETTE: I agree, but he is also dumping a lot of glycerol. I'm willing to bet urine excretion of glycerol is relatively high. The osmolality of that urine is going to be high.

TIM LYONS: We have analyzed urine, sodium, potassium things like that, and none of those have changed with the glycerol with the water.

WARREN LOCKETTE: The reason why it becomes more than just an interesting question as to what the mechanism of the antidiuresis is, is because Guy and I have data that illustrates that you can give vasopressin and block the excretion of free water, and then you can use anything you want to expand plasma volume. I made the statement earlier, is everyone in agreement that it is the plasma volume regulation that is important in determining hyperhydration? In other words, if you can expand the plasma volume, you can solve this crisis of volume regulation.

I hear a lot of thrust in terms of whether we should expand intravascular and extracellular fluid with glycerol. We have data to show that if you give vasopressin to block free water excretion you can probably expand the volume with anything you want. The advantage is, since it has a long biological half-life, at least the analog that we used, you can hyperhydrate somebody four or five hours in advance and send them out into the field.

MARVIN RIEDESEL: I would argue against the use of a hormone or hormone analog on the basis of what are you doing to the receptors and the sensitivity to the hormone when you are throwing it off.

WARREN LOCKETTE: The chemical half-life is about 75 minutes, the biological half-life is about six to eight hours.

ROBERT CADE: Is this sniffing it in the nose?

WARREN LOCKETTE: Yes. I actually have a sample.

ROBERT CADE: You have problems if you start asking 200,000 soldiers to sniff ADH.

WARREN LOCKETTE: Why is that a logistical problem?

ROBERT CADE: Teaching them how to do it.

MARVIN RIEDESEL: Haven't there been some studies done with mentally ill people using vasopressin?

WARREN LOCKETTE: I can't find any; I was told this morning there was one from the Pierce Laboratory.

LYN YAFFE: We don't need to get into that, but it is an important point about what can be done logistically. We should certainly concentrate on whether hyperhydration can be made a reality, with glycerol, with TQII, with vasopressin. Quite honestly, one would want to be concerned if you haven't sufficiently convinced yourself that there is safety in regard to all possible scenario changes on vasopressin. It is not something to do in the next two weeks. But it may be a legitimate option to pursue over the next few months for utilizing nonhormonally-based mechanisms of hyperhydrating and reducing the need for fluid over a four-hour interval. I don't think it is a matter of necessarily choosing one over the other near-term, but it may be a matter of looking at what option is best if we are talking about delivering something in a 30-day time frame.

WARREN LOCKETTE: I think what Lyn is saying is, we need to have different scenarios because there is no one panacea from a physiological standpoint.

LYN YAFFE: If we can get all of these various options on the table, then tomorrow we can focus on some specific scenarios and what might be best immediately or 60 days from now for that scenario, as long as we are certain we are not going beyond what is safe.

MELVIN FREGLEY: Bud did answer, at least partially, the question that I asked, which was whether you could hyperhydrate over a long period of time. Was that one gram of glycerol per kilogram of body weight?

MARVIN RIEDESEL: Yes, to start with.

MELVIN FREGLEY: That sounds like it's feasible. But you didn't do any measures of performance, did you?

TIM LYONS: No, not in that study.

MALE VOICE: But the sweating rates improved, didn't they?

MARVIN RIEDESEL: That was another study.

MELVIN FREGLEY: With the same dose, the body temperature remains lower, is that right?

MARVIN RIEDESEL: Yes.

LYN YAFFE: Did your study show that due to increased sweating rate?

TIM LYONS: Yes.

LYN YAFFE: Which is different from Dr. Cade's data, with his 1% glycerol. Is that possibly related to the ambient temperatures and humidities that you were using?

TIM LYONS: We had very high ambient temperatures and low humidity. Twenty-five percent humidity, temperatures were about 105°F.

MELVIN FREGLEY: But this brings up a point I was going to make, some idea of dose has to be struggled with. Consideration will have to be given to the length of time that you can hyperhydrate and the dose that is going to be used.

LYN YAFFE: It's like saying, give us a six-hour window where you would put 2.5 or 3 liters of a particular fluid onboard Taking two canteens, what should they drink other than water to sustain them for that six hours?

TIM LYONS: We have done some work using different dosages and concentrations of glycerol and have showed that the one gm/kg was optimal. We went below that, down to a half gram/kg, and we did not get the retention that we did with the one. Then we went to 1.5, and retention did not significantly increase over the one gm. Then we tried using more diluted solution versus more concentrated solution. Again, we showed greater retention taking a single concentrated dosage (about 20%), followed by the high volume of water as opposed to having a large dilute solution.

MICHAEL SAWKA: If you look at the glycerol experiments with very high increase in sweating rate, is there some action besides the changes in volume or tonicity or whatever and is there some impact glycerol is having on thermoregulation? Because of the controls, where they drank the water, volume would be about the same. There was no real difference in tonicity, and there was a tremendous increase in sweating normally not seen.

MARVIN RIEDESEL: There is evidence that glycerol does have a vasodilatory effect on smooth muscle, so that is a possibility. It might increase blood flow.

MICHAEL SAWKA: But it's the sweating.

TIM LYONS: I think, as you mentioned, that perhaps it is having some type of effect directly on the sweat mechanism.

WARREN LOCKETTE: Is it clear why the absorption is seemingly in question? If you have an osmotically active particle that is not 100% absorbed, the likelihood of diarrhea is great. If your subjects say they do not have diarrhea, I'm willing to bet it is 100% reabsorbed.

TIM LYONS: We have been looking at the appearance and disappearance of serum, that is about the only way we have really had any sign of absorption rates.

FRANK TOPPO: Maybe it holds the fluid for a period of time?

TIM LYONS: Serum glycerol is elevated quickly.

HAL GOFORTH: We gave a 1.2 dose, and we had diarrhea and nausea in our group. But we didn't give the bolus, we gave it in a two-liter solution. Eighty gms of glycerol were mixed in one large solution, and the ten subjects had 30 minutes to drink it. One had diarrhea, one was vomiting, and a couple had a little visual disorientation. But we used 1.2, which is a little above the one you are using.

ROBERT CADE: We had four of our bike riders drink a 3% glycerin solution, and they all got cramps in their belly and headaches, and several of them felt nauseated. How much could nausea have to do with increased sweat rate?

LYN YAFFE: These comments are different from the idea that if you give the appropriate amount of glycerol as a bolus, followed by fluid, then you do not get the nausea or diarrhea problems. Is that correct? There is a right way of giving glycerol and a wrong way? If you give it the right way, you don't see these side effects?

TIM LYONS: We have run close to 100 subjects over four to five years, and we have had only one incidence of nausea and no problems with diarrhea that I'm aware of.

LYN YAFFE: Have you repeated other studies where you have changed the way you administer it?

HAL GOFORTH: No, we have only had it as a mixture because of our scenario. We have not tried other dosages.

ROBERT CADE: In 1930, Johnson gave glycerol in a fashion similar to the way Dr. Riedesel has, and he did not report any diarrhea. They kept track of stool volume, frequency of stool, and so on. There apparently was a little bit of loosening of the stool, but no one developed diarrhea. I don't think any of them complained of abdominal cramping pain. They gave amounts of glycerol that were even greater than Dr. Riedesel's for a period of 50 days.

LYN YAFFE: That is an interesting commer . The Marines did mention to me that they would be concerned about procedures that, if interrupted for any reason, put the people in jeopardy because they could not finish the protocol. The idea being, if you inhaled vasopressin or took a bolus of glycerol and for some reason could not follow through with appropriate hydration procedures, you wouldn't want those people to be in any sort of jeopardy, to go out and face combat when they were not able to put the appropriate amount of fluid onboard that was anticipated.

In an operational setting, one has to be concerned about that. You have to provide a procedure they can follow and not feel there is going to be an interruption. If you give them a procedure to use at some forward echelon, it is something that they realistically have to be concerned about. Interruption in some 30- or 90-minute procedure that we might be asking them to follow would put them in jeopardy; we cannot have that occur. If there is a protocol for glycerol hyperhydration, you want to give the glycerol in the fluid incrementally side by side, not a bolus, and then have the 90 minutes for hyperhydration interrupted.

MIKE CURRAN: Lyn, before we place too much importance on that, we still have not heard from the operational side as to their definition of what the scenarios would be. We have had reports from people in Washington D.C. and from us "experts." I hope we can hear from the Navy Special Forces and the Marine Corps. We have heard about the operational environment, but we have not heard one possible scenario discussed. And I don't see how you can focus a discussion beyond this point until we hear what general scenarios are, in an unclassified setting.

LYN YAFFE: I agree. It is nice to know exactly what the mission is or some sort of mission scenario for the investigators to focus their attention on.

MICHAEL SAWKA: We showed you what was done with hyperhydration. Other people have tried to do things invasively to simulate hyperhydration, to artificially expand blood volume or alter tonicity. What have those invasive studies shown? I'm not proposing that you do something invasive to extend performance, but again, it allows you to look at the mechanisms for improved fluid regulation. There have been a number of studies with different approaches in attempts to expand blood volume and have individuals work in heat. Studies that you looked at, primarily sweating and dry heat exchange, usually use about a 30° environment. They pick an environment to get dry heat exchange. In studies that look at sweating, they use something like a 40° environment to accentuate evaporative exchange. But if you look at the studies, it's not real clearcut. Within a given laboratory, or between laboratories, you see different results.

Here you looked at blood infusion and albumin saline. Fortney showed, with cycligometer exercise in a 30° environment where he expanded blood volume, there was a slight thermoregulatory advantage. On the other hand, we had people walking in a 45° desert, hot, dry environment, and we found no effect. I might add that in this study we had them work to exhaustion, so there was a performance measurement, and there was no influence on performance. There was a fairly good substantial increase in plasma volume by about 8%. What we were trying to do was simulate the expansion that occurs with acclimation to see if that was a mechanism of acclimation.

We have done a number of studies with blood infusion and, depending on the conditions, we either found a thermoregulatory effect or we didn't. Again, Fortney's lab is doing albumin, actually infusing during the experiment so that they were expanding and infusing while they were working; both he and Deschamps and showed effects. So the picture is mixed, looking at a variety of different environmental conditions and measurements. If you actually expand blood volume, you might see a small thermoregulatory benefit or you might not.

Now what we have attempted to do in the next couple of slides is to try to collapse those studies together and look at how volume expansion or tonicity might affect thermoregulatory responses. Not to make anything complicated, but when we looked at the other slides, and I showed you steady-state core temperatures, steady-state sweating, and steady-state blood flow, that response is dependent on the core temperature because it is an effecter response to regulate body temperature. Some people believe this is centrally mediated, some believe this is peripheral; you can argue either way. It is probably both, it is not important. So if you pull together the studies from the literature that have looked at altering tonicity and volume, and then looked at these responses, what you are going to see are threshold and sensitivity changes.

Essentially when I say threshold, I'm saying it is the onset of sweating or blood flow to go up or down with changes of volume or tonicity. If you had a decrease in threshold, that means you would be starting the effector response earlier. That's good. If you had an increase in threshold, that means you are turning on with greater drive. That's bad. That means you are sweating less, or have less blood flow, so you store more heat. When you pull it all together, it's pretty interesting.

First, let's look at the effector responses of sweating. What becomes clear is that sweating is very dependent upon tonicity changes; that if you decrease tonicity from euhydration levels, you'll have a reduction in threshold, you turn on earlier; if you increase tonicity, you'll have a delay in the onset of sweating. The sensitivity is not affective to tonicity, just the threshold, when it turns on and off. If you lower blood volume, like when you are dehydrated, you can delay the time in terms of the onset of sweating. If you increase the blood volume, make it greater, it has no effect on the threshold for sweating. Likewise, if you reduce the blood volume, like with dehydration, you decrease the sensitivity for sweating, but it has no effect increasing the blood volume on the sensitivity for sweating. So, sweating seems to be very dependent on tonicity. It is clear that if you decrease the blood volume you will change the skin blood flow response by also altering the sensitivity. Looking at dry heat exchange in terms of skin blood flow, if you lower tonicity, you don't really have any effect. But on the other hand, if you become dehydrated and your plasma tonicity goes up, you will increase the threshold, so it is a disadvantage. Skin blood flow sensitivity is not affected at all by tonicity.

Looking at blood volume changes, if blood volume goes down, the threshold for skin blood flow goes up, so it delays it. If you expand blood volume, it really does not affect skin blood flow, but the skin blood flow sensitivity response is affected by increases and decreases in blood flow. The bottom line is, depending on the thermoregulatory effector response, whether it is an environment where you need dry heat exchange or an evaporative heat exchange, you need to know that because whether you expand blood volume or alter tonicity, there is going to be different side effects.

If I were going to look at this and interpret it, I would say that for a soldier working in a desert environment, it is very important to maintain tonicity. I don't feel that it is very important to maintain blood volume beyond normal levels because you want to maintain sweating, or perhaps in some situations, enhance it. But if you are in a situation where you have to depend on dry heat exchange, and that could be operations in a hot coastal region where it was 37°, 38°, or more realistically, operationally, if you had to do things like fire control or some high intensity work in protective clothing, then it becomes an advantage to increase blood volume. You may get some ability to thermoregulate, but if you are in protective clothing, as Dr. Cade showed earlier, you probably could maintain cardiovascular stability a little better, and last a little longer.

I might add that we, at our institute, have experiments planned for this summer on hyperhydration, although we may change after listening today. We were going to do two controls, one euhydration, the other one progressive dehydration. We were then going to do a hyperhydration with predrinking of some glucose electrolyte, drinking of water, and do a proglycerol-type of situation.

LYN YAFFE: You almost need to assign a couple different scenarios to cover the sweating versus dry heat.

MICHAEL SAWKA: We will be doing just the hot, dry environment.

ALAN MARKOWITZ: Does this mean that what you want to achieve for this immediate situation, where you are not looking to increase or decrease sweating, is to remain exactly the way it is right now, just maintain a larger amount of fluid in the body?

MICHAEL SAWKA: You may not go longer. In one study I showed you, volume was very much expanded and the people went to exhaustion, but they did not go longer. You could go longer if you had an expansion, but that is not really clearcut.

LYN YAFFE: It depends somewhat on the environment that you are in, whether you would reduce your need for fluid during a six-hour period.

MICHAEL SAWKA: Dehydration will mediate exhaustion from heat strain via two mechanisms. One is the decrease in blood volume from sweating. Second, if you are in an environment and you can't thermoregulate, say it's a hot, dry environment and your sweating decreases, your body temperature is going to rise, and the net effect is that you are going to get greater cutaneous vasodilation so you have a displacement of central blood volume to the periphery. As your skin warms, it becomes more compliant. You put the blood in the skin and you cannot get it out. Some people, like Ethan Nadel, believe that is perhaps more important than reduction in blood volume.

So you have two things working together. One is the maintenance of blood volume and the second is the maintenance of factors such as sweating so you can keep a cool skin and you don't displace this blood volume to the skin.

ALAN MARKOWITZ: Is there any situation that you can think of where an increase in blood volume is detrimental as long as you are not changing their sweating capabilities?

MICHAEL SAWKA: No, I don't think it would be detrimental at all.

ALAN MARKOWITZ: But in most cases it would be beneficial because it could be rapidly dehydrated.

MICHAEL SAWKA: I'm not sure I agree. I'm not saying it would not be beneficial, in some cases it might be beneficial.

ALAN MARKOWITZ: The reason I'm asking this is that I think it is important not to lose sight of a certain perspective. There is really essentially two things I see that are critical to the conference. One is to answer the question, what can be done immediately? And the second question is, what would be valuable to do in terms of the short term research effort, or even as long as a year or two, looking into this entire question? All of the talk presented this morning was essentially dealing with the research aspects of the problem. Almost everything I heard presented makes questions that are going to take at least several months, if not a year or two, to resolve.

The other question, is there a Gatorade or an enhanced Gatorade-type fluid that can be put together quickly that would be of benefit to people in this hot combat environment without any detrimental effects? That is a question where the data that you presented, Mike, is actually very helpful. If there is no difference other than to maintain a hydration level higher than what would otherwise occur, that could be of significant benefit. I'm not looking at a specific scenario which would be related to the research question. The general question is, what is the best combination of fluid to put together for a particular individual? The combat soldier who is going to be drinking water, can we give that person something other than water, like Gatorade, so that it doesn't change anything? All the soldier drinks is Gatorade instead of water and goes about everything else normally. But should he wind up in an emergency situation and where he finds he cannot drink water, or he is in a chemical/biological warfare environment where he cannot take off gear, then the fact that he has been drinking this enhanced Gatorade will buy him a couple of hours and might make a lifesaving difference, whereas before he would just dehydrate in a short period of time. The key thing is to keep the distinction between the two questions in mind. One would be an immediate capability that we could suggest and, if we could get funded and get some mechanics in place, actually save someone's life with a zero risk situation. In addition, as an offshoot from that, we could go on to a rapid prototype program that might take several months or a year, even two years, to do the studies for the particular scenarios with the particular research as appropriate.

LYN YAFFE: I think that said it very well.

MELVIN FREGLEY: I think you are asking the most important questions, and as a scientist I'm not used to answering the most important questions first. I have to think about all of the possibilities that enter into it to come up with the best possible scenario.

LYN YAFFE: I think this group can do it.

MELVIN FREGLEY: I think we will have that answer or something approximating that answer anyway by the time this conference is over. Maybe right now we cannot do it.

STEVE LEWIS: If this group can't come up with an answer to that, then there will not be an answer.

LYN YAFFE: Let's break for lunch now and we will reconvene in the El Pueblo meeting room at 1400. Thank you for a very productive morning session.

LUNCH

WARREN LOCKETTE: I have worked on problems of dehydration, not with desert environments, but with Navy divers. When you are placed in a water environment, the ambient pressure of the water on the lower extremities causes an increase in venous return on the heart. This increase in venous return is sensed by volume receptors and pressure receptors in the artery and blood vessels and causes a marked diuresis. That is where vasopressin starts to work and causes us to urinate. Vasopressin is the hormone that causes you to reabsorb water in the kidney and actually decreases your urine output.

We got volunteers at the Navy SEAL training base on Coronado. We then placed them in a thermoneutral water tank. Before they went into the tank, they got vasopressin in a meter-dosed nasal spray (0.2 micrograms). We used the underwater egress trainer at Miramar where we could study six subjects at one time. We pulled them up each hour to do a routine venipuncture and urine sample. The subjects put out about 700 mls of fluid in about three hours of partial water submersion. Aldosterone levels fell. Aldosterone is the most potent hormone in the control of the secretion of salt. These individuals all increased in atrial peptides and decreased in aldosterone level. The use of vasopressin along with a glycerol-containing liquid will jointly help to keep the body hydrated.

LYN YAFFE: What about the impact of all this on the requirement to maintain core temperature, cooling, and sweating?

WARREN LOCKETTE: We will be doing additional studies in the next three to four weeks, but we don't expect problems in thermal regulation. So there may be direct feasibility to the live community.

VICTOR CONVERTINO: Do you have any evidence where the volume is, is it in the vascular space?

WARREN LOCKETTE: It is most likely free water that is going to freely distribute between the intravascular and extravascular compartment.

VICTOR CONVERTINO: What kind of volume did you find in the two groups, and what might that mean in the actual plasma volume?

WARREN LOCKETTE: It is totally a function of how much fluid you take in.

ALAN MARKOWITZ: This looks more like a secretion inhibitor.

WARREN LOCKETTE: It will not decrease secretion below what you can maximally do.

MELVIN FREGLEY: It will be critical to your studies to determine what happens to extrarenal volume. Would it be a good idea to have an even more potent analog than vasopressin?

WARREN LOCKETTE: I don't think there is any problem with vasopressin working well in a hot and humid environment. We still have to see how it works in a hot and dry climate.

HAL GOFORTH: Is there a problem of overdose?

WARREN LOCKETTE: If one is urinating comfortably and it has been 12 hours since the last dosage, then another dose of vasopressin would be safe.

LYN YAFFE: How would this interact with drugs available in the Middle East that are to be used in conjunction with the threat of chemical warfare?

WARREN LOCKETTE: I'm not advocating this on a daily rate. If you have a particular mission that might occur once a month, then that could be an option. I have also read that vasopressin is being used for bedwetters. They can now go 12 hours without urinating.

LYN YAFFE: Have you heard of any marathon runners using vasopressin?

WARREN LOCKETTE: I have never heard of them using it.

CARL ENGLUND: Warren, what is the possible interaction with atropine or puristignine?

WARREN LOCKETTE: I don't know. I have looked at the literature on topic gases. I just don't know.

GARY MACK: I see the two protocols being complimentary. The one protocol, you load the body with fluid. My problem with this is they will unload it as urine. You show that with the glycerol the difference in urine output is not that much different, only about 500 mls at the end. I think the worst thing we can do to Marines is load them and then send them off on a mission and the first thing they have to do is find a tree.

WARREN LOCKETTE: I think that loading with glycerol and perhaps vasopressin can avoid that during a combat scenario.

JOHN GREENLEAF: When are we going to hear more about these scenarios?

LYN YAFFE: If we base our environment on hot and humid and hot and dry with what you described, is there any contraindication on using the protocol you just described?

GARY MACK: I'm not sure. Warren, what were the plasma volumes?

WARREN LOCKETTE: We didn't actually measure it. We only recently got our ADT assay working.

VICTOR CONVERTINO: Warren, if you put volume into an individual and not reduce the vasopressin, could you hypothesize based on your data?

WARREN LOCKETTE: That is what I think we are doing.

LYN YAFFE: Any additional comments? Is there someone who has some additional data that impacts on our task?

JOHN GREENLEAF: As you know, a couple of hours before reentry, the astronauts take salt tablets and water. They are dehydrated according to earth standards. Astronauts are like a lot of us, if they do not want to take them they don't. Now almost all do take it because they found it helps. We have tried to develop a fluid that has the same consistency as isotonic saline. We have mixed aspertame with a variety of different fluids. Sodium is about 9.5%.

About one hour before reentry, they drink about 800 mls of liquid. We did it in 100 ml doses. It took about five minutes to drink it all. The results show that for the astronauts, the isotonic saline plus aspertame seems to hydrate them best. Now we did this over again and added exercise. When they exercised loaded with water they complained of aches and pains. They complained because they were simply "out of gas." I don't know what all of this means, but I think one has to be careful not to hydrate so early that performance decreases just when you need it.

MALE VOICE: What you are saying is, do not do anything before you expand the blood volume. Make certain you wait long enough.

JOHN GREENLEAF: Correct.

JAY HEANEY: How many subjects does that represent?

JOHN GREENLEAF: Five, and they were all in the same condition.

WARREN LOCKETTE: John, what is power surge?

JOHN GREENLEAF: Commercial dehydration drinks. They are not significantly different from Gatorade-like drinks.

VICTOR CONVERTINO: I would like to show you this slide. In our first study, we take the plasma volume measurement by blue dye technique one hour after the solution was given to our subjects, about 800-1000 mls over an hour. We found similar results to John's study reported earlier. Two years later we conducted another experiment and, because of the baroreceptor analysis, we took our plasma volume measurement about three hours later, and it was at the same level as our earlier study. It certainly seems then that simple isotonic saline solution taken orally can expand the plasma volume on the order that helps. There were also no changes in the plasma osmolality, sodium, potassium, protein, and no changes in the hormones we associate with electrolytes like vasopressin. It does not seem to change the physiology in terms of the electrolyte values.

MALE VOICE: My impression of the scenario is, the problem is that these people are stationed in a hot and humid environment and are already hypohydrated. Are we concentrating on rehydrating people who are dehydrated?

JOHN GREENLEAF: They don't actually get dehydrated. It is only when there is excessive exercise.

MALE VOICE: Aren't these people working in the heat? Do you expect them to be dehydrated at all?

JOHN GREENLEAF: Not if they are eating right. We aren't dealing with dehydrated people, not to any significant extent.

MALE VOICE: What is the normal salt intake for these people in the desert?

HAL GOFORTH: MREs have about 18 to 20.

JOHN GREENLEAF: We must be careful not to confuse what the person is taking in and what the person needs.

MALE VOICE: I'm trying to establish that we are not dealing with a dehydrated population prior to setting up a hyperhydration scenario. There is the classic finding that Adolf reported in the desert. Soldiers remained relatively dehydrated while in the desert and rarely made up their water deficiency at the time they ate.

LYN YAFFE: Could someone describe the rations the Marines have in the desert.

HAL GOFORTH: The meals that they take are MREs. Their noontime meal is an MRE. They are like C-rations. Some are dehydrated and some are ready to eat.

LYN YAFFE: The ones I have tasted were salty, at least to my taste.

HAL GOFORTH: If they eat all three meals as MREs, they will consume about 8 to 9 grams of salt. If they eat it all, they will get 1,500 calories per meal. The average daily intake will be about 4,500 calories. Plus they get calories from Gatorade. The average MRE includes 40% to 45% fat. They are not very high in carbohydrates.

LYN YAFFE: Any questions or comments? If not, let's take a 10 to 15 minute break.

BREAK

LYN YAFFE: Maybe we can establish some specific scenarios based on our knowledge of the Persian Gulf. We encourage and invite those here from the operational commands to comment on this subject. I think we are talking about a small group going out for six hours, maybe an extreme case of eight hours. We want to reduce their need to carry an excessive amount of fluid. We must assume hot/dry or hot/humid weather. Let's assume they are going to be engaged in some sort of exercise, walking or running in the desert. We are not necessarily interested in hyperhydration or vasopressin.

JOHN DEWAR: During the break, we discussed MOPP gear. Has everyone here seen MOPP gear? A six-hour ambush is not going to cause a serious problem. This MOPP gear is the problem. I will be glad to bring it in.

JOE JOHNSON: We have a program at NHRDC to look at a variety of NBI products. That is complimentary to what you are speaking about.

LYN YAFFE: The Navy is looking at active cooling equipment that goes with MOPP gear, but if that was not available, a water load may help.

JOHN DEWAR: You can see how hard it is to hydrate with a gas mask on. Canteens have an adaptor, but once the canteen is opened, it is contaminated. Hyperhydration will have a greater significance with MOPP gear situations.

MIKE CURRAN: What is the need? What are people doing now? What do they have on, how long do they go, and when do they come back?

JOHN DEWAR: I don't know how to paint a scenario. The troops in the field have a lot of idle time, sitting around playing cards waiting for something to happen. They have as high as 120°F weather. They may have to carry a wounded soldier across sand.

LYN YAFFE: Let's look at two to six hours, a little exercise, that would be less than running the last three miles of a marathon, 80°F to 100°F, and exercising 40 minutes out of every hour. Also, what we developed for the MOPP gear, have we helped in that case?

MELVIN FREGLEY: How do we measure? That is the essence of the problem.

LYN YAFFE: That's true. If we are going to conduct some preliminary studies, we have to have some measurement criteria.

MELVIN FREGLEY: May I suggest something? I asked John what would be the fluid loss in the desert at 100°F, 20% humidity, walking 50% $VO_{2\ max}$. That turns out to be a liter per hour, which is about what the replacement of water has been. I don't know whether this helps, but it is someplace to start. How much electrolyte do we estimate this person would loose? Let's first talk about maintaining in a normal state, say 2 to 6 hours. I don't know what fluid they need to take on. Let's start here.

MICHAEL SAWKA: Amount of water is going to vary due to a lot of things. For light tasks, 1.2 liters sticks in my mind. That is a reasonable amount for replacement. Now, when you put on protective clothing, it is a much different picture. Sweat rates in excess of two liters would be expected.

ROBERT CADE: We looked at student runners using run, walk, run, walk scenarios. When they were NOP, they lost sweat at 31 cc per minute. With saline solution, sweat was down to 27 cc per minute. With Gatorade, it was 19 cc per minute. With football players in full gear plus 90°F temperature, they were loosing 40 to 45 cc per minute.

MELVIN FREGLEY: Do we know the hydration status of our soldier in the desert? Do we know what the plasma osmolality is at the end, even if they drank their two canteens of water along the way? What kind of shape are they in?

GARY MACK: My guess is your plasma tonicity is about 280 to 290. If you go back into what has been done in storage replacement, 0.1% saline is satisfactory. If you are dehydrated and you want to replenish that fluid, the salt would have to be equal to the salt lost. Our studies showed that. Can I show a slide? People exercised at 60% of $VO_{2\ max}$, 30°C, and 30% humidity for one hour. They drank ad lib. This shows what happened in our dehydration scenario. You can't hold the fluid you drank unless you add this salt. Replacing the sodium is critical. You don't know when your sodium level is in trouble, so you have to give some people more than others.

ROBERT CADE: These slides show marathon runners. This is accumulative loss of sodium and potassium. Some were drinking Gatorade and lost a great deal of sodium, but the accumulative loss of potassium was negligible, less than 50 meqs over the course of a marathon. There is a definite correlation between the rate of sweat and the concentration of sodium in sweat. The loss of sodium in sweat is much greater during the last 18 miles of a marathon than in the first 9 miles. We have learned that after you have been running for an hour or sweating for an hour, the sodium in the interstitial fluid is much higher as a result of reabsorption. This reabsorption in the tubules is caused by the countercurrent mechanism. We have also shown that large loss of fluid can be lost from the vascular space during exercise on our own two legs.

LYN YAFFE: Can we do something about hyperhydration? Can we do something about limiting the amount of fluid that is lost in order to have some impact on what happens with chemical protective gear or some impact in a six-hour mission? Does anyone feel that we have something immediately doable as a conservative approach or not?

MELVIN FREGLEY: I think we have come to one conclusion. Water is not the best replacement fluid for people in Saudi Arabia. Is there consensus on this? Good, then we agree that some form of an isotonic solution is better. Everyone also seems to agree that glycerol in an electrolyte solution might be very helpful. What dose of glycerol do we use?

ALAN MARKOWITZ: In an initial study, we did use .1%. They had no problem with that.

LYN YAFFE: Do we have a scenario where they prehydrate with something and they are also able to take along a couple liters?

MALE VOICE: If we are losing a liter per hour at heavy work conditions, three hours would give you a 4% body loss. Potentially, if you kept going, you would loose 32% in one day. If we look at a three-hour window, based Dr. Cade's data, what kind of an initial charge is there to offset that loss?

ROBERT CADE: We had them drink 200 ccs every 20 minutes.

WARREN LOCKETTE: What is the implication of an osmotic diuresis of someone who is already bogged down?

LYN YAFFE: We must assume they are euhydrated. How do you make sure someone is hydrated before they are hyperhydrated?

WARREN LOCKETTE: We know that if they are producing urine they are at least hydrated.

GARY MACK: What is a safe limit for use of glycerol?

HAL GOFORTH: We have no problem with oral intake. Only when it is IV or subcutaneous do we find a problem.

WARREN LOCKETTE: Is that true for someone who is dehydrated?

MALE VOICE: Concerning different dosages of glycerol, we used a concentrated dose of glycerol and immediately following they began drinking 1.5 liters of water. Dosage is one gram per kilogram of body weight.

LYN YAFFE: Perhaps we should break for the day. Can we actually decide on a glycerol protocol for hyperhydration and what is the data to back that up? Should we routinely use something other than water or mix water plus some electrolytes for use during the day in case we do take the group to hyperhydration? How long can we rely on hyperhydration to be effective? I think, from what I heard today, we can put together a proposal that includes a safety margin that is better than we have now. Thank you for a most successful day.

ADJOURN FOR FIRST DAY

MORNING OF SECOND DAY

LYN YAFFE: Would Marines in each group be required to drink the same amounts of liquid?

JAY HEANEY: Yes, they would be encouraged to do that.

LYN YAFFE: Also, to keep the weight down the Marines have to carry, we should recommend replacing the canteens of water with thirst-quenching liquid first. If this helps, they would not have to carry another canteen.

ROBERT CADE: Some of his subjects have complained of nausea and headaches when asked to drink liquids with 3% glycerol and less problems with 1% solution. The problems occurred after two hours.

LYN YAFFE: Availability is important, so are we talking about Gatorade with glycerol? Gatorade is acceptable to most of our troops. So what do you think about these test categories?

1) NPO

2) H_2O

3) Electrolyte replacement with glucose

4) Electrolyte replacement with glucose and glycerol

JAY HEANEY: It would be good to serve cold drinks because Gatorade tastes best cold, but we have trouble keeping ice in the canteens.

VICTOR CONVERTINO: Another thing we could do is add sodium chloride to the plain water. At NASA, we are concerned with hydrating our astronauts before reentry and landing; if they do not like the taste, they won't drink it. Also, how fast they drink the fluid is critical to how successful the hydration process is.

MALE VOICE: I recommend replacing electrolytes at the level equal to what is lost in sweat and urine. Further, we need to be alert to the blood volume associated with electrolyte replacement. Much of our research has been with exercise on ergometers and not with marching soldiers. Fluid dilution or concentration is different for each.

ROBERT CADE: This slide shows a loss of sodium/potassium in marathon runners. Results show a large loss of sodium with sweat as high as 50 cc/min. for the first nine miles. Accumulated loss of potassium was less than 50 meq for the entire marathon. The results show that sweat is more concentrated with sodium for the last portion of the race than the first portion. He discusses the countercurrent mechanism of sodium exchange in tissue and interstitial fluid.

LYN YAFFE: This helps us to answer the question, can we do something about hyperhydration and about limiting the amount of fluid lost during a six-hour patrol scenario. Is there something immediately doable as a conservative approach?

MALE VOICE: I think we have reached one conclusion, water is not the best replacement fluid for Operation Desert Shield. We know that we want some electrolytes in our replacement fluid, but what about glycerol? With glycerol added, can we last for at least four hours?

JOE JOHNSON: We can't forget that these Marines are working hard in the heat. They are sweating a lot and working hard.

LYN YAFFE: What dose of glycerol do we use if we agree that glycerol will enhance survivability?

MELVIN FREGLEY: If 3% to 4% body weight loss in fluid causes sharp performance decrements, how much fluid must be replaced? If we lose one liter of fluid/hour at working conditions, we can only go three hours before we have reached 4% body weight loss. How much fluid must be taken ahead of the three hours to offset the fluid loss? What can we do in the short haul? We know we need something better than water that would give someone an extra half to one hour of physical activity.

VICTOR CONVERTINO: I recommend adding salt into the canteen aid. Because high concentrations of glycerol may cause headaches and nausea, we must find a way to safely administer glycerol in water with electrolytes. Simply said, adding salt to water with flavoring to make it palatable is a quick fix.

ROBERT CADE: Two hundred ccs of water with glycerol every 20 minutes causes no problem.

VICTOR CONVERTINO: We must be careful to avoid the Marines taking a bolus of the fluid with glycerol. I recommend giving the Marines 1.5 liters of fluid at five minutes, some at 15 minutes, to see if there is an adverse effect to drinking a lot in a short amount of time.

LYN YAFFE: What is the worst case scenario and test to see if the troops get into trouble with our plan to administer NPO and three forms of fluids?

ALAN MARKOWITZ: I suggest including carbohydrate in these drinks would be batter than adding salts.

ROBERT CADE: This slide compares the use of Gatorade by runners and another using water with the temperature above 85°. Gatorade showed most improvement over plain water. Fluid intake was limited to less than one liter at a time.

LYN YAFFE: Yes, but also to give our Marines something better than water. Do you know what should be in that fluid?

VICTOR CONVERTINO: I am concerned mostly about how the fluids are taken during the operational exercises.

ROBERT CADE: Let's look at this slide showing runners and the amount of fluid loss and skin temperature measurements after a variety of distances and times.

LYN YAFFE: Are we in agreement for these four items?

1) NPO
2) H2O
3) Electrolytes and carbohydrates
4) Electrolytes and carbohydrates and glycerol

JAY HEANEY: What is a typical Marine combat work load during an exercise?

JOHN GREENLEAF: Never exceed your physical capability so that you could not fight throughout the exercise.

MALE VOICE: Are we going to get enough subjects for these four scenarios?

JAY HEANEY: Yesterday, John Smaldino said he would help us with Marines, plus with NHRC's work with the Navy bases in San Diego we should be able to get enough subjects.

LYN YAFFE: We must assume that is not a problem.

JOHN GREENLEAF: I have a question. If the soldiers are eating properly, why study such a wide variety of replacement fluids? Are we assuming there is some exercise and work for them each day and these fluids will be used daily as maintenance fluids?

JAY HEANEY: That is true.

JOHN GREENLEAF: Do I understand that there will always be a selection of drinks for them?

JOHN DEWAR: That is what we expect.

LYN YAFFE: Do we know of something better than water to help maintain fluid level that would keep them in a better combat posture at the end of the exercise as well as at the beginning? That is what this first protocol is aimed at. Let's select those fluids and move on.

MALE VOICE: We have them, three levels of tests:

1) Demonstrate various fluids are not dangerous
2) Workload study
3) Hyperhydration in the field

HAL GOFORTH: I have brought one MRE food packet like the ones the Marines are consuming now in Saudi Arabia. It looks like the MRE contains a great deal of sodium, so this will assist us in electrolyte replacement.

MALE VOICE: We think many of the Marines don't eat the complete MRE so, again, we have the problem where people are consuming unequal amounts of electrolytes and fluids.

HAL GOFORTH: The candy bars they do eat along with the MRE have enough sodium to keep them at four grams of sodium chloride each day.

LYN YAFFE: OK, on to the workload portion of our study. Is four hours enough?

CARL ENGLUND: No, I think eight hours is more realistic.

ROBERT CADE: But, after that, can they get up and do it over again tomorrow? Athletes run marathons but not two days in a row.

JAY HEANEY: We recommend four hours because our previous studies have been in the lab with a thermoneutral environment.

LYN YAFFE: We must select a time that is manageable for a 30-day initial study. After that 30-day period, maybe we can extend it to six or eight hours.

MALE VOICE: The standard Marine workload is 37 Kgrams.

LYN YAFFE: The four-hour period is a good place to begin our workload study.

CARL ENGLUND: We should tell the subjects the study goes for up to six hours and then stop it at four if we choose. We must account for the ending spurt of energy.

MALE VOICE: Do you have Saudi Arabia heart rate data?

GUY BANTA: We have a lot of data onboard the ships and helos but not for ground troops.

ROBERT CADE: We should offer our subjects an unlimited supply of fluid during a first test to see how much they want. We should not limit them to two canteens.

JOHN GREENLEAF: We want to know how much and when they consumed the fluid. That is important.

LYN YAFFE: The Marines can be very resistant to us telling them to carry another six liters of weight.

JOE JOHNSON: We must do all we can to decrease the weight a Marine carries. The two canteens probably have nothing to do with how thirsty they are but how much they weigh.

BREAK

LYN YAFFE: Let's now discuss hyperhydration. Our goal is to propose a means for a group of Marines in a combat/patrol scenario to reduce their dependence on water for a few hours by loading up on fluids prior to the mission.

ROBERT POZOS: I would like to present the NHRC proposal for hyperhydration. The proposal includes two solutions including glycerol. We also have divided the effort into premission and mission phases. Performance measurements would be conducted to include both physiological and psychological assessments.

MELVIN FREGLEY: What doses of glycerol do you expect to use?

ROBERT POZOS: 0.5 in premission and 0.5 mission. Also, the workload on a treadmill is at 3.5 miles per hour. The temperature will be 115° with 10% humidity. All subjects will be acclimatized within 12 days of the experiment.

LYN YAFFE: Is 1.5 liters of fluid in the premission phase too conservative?

TIM LYONS: I recommend waiting 2 to 2.5 hours after fluid loading to begin exercise phase.

MALE VOICE: I suggest loading the subjects with the water plus glycerol prior to eating as food interferes with the amount of glycerol absorbed. I suggest NHRC also consider dosages of one gram per kilogram of body weight in the premission phase.

JOHN GREENLEAF: If you have the subjects, why not use a variety of dosages. I propose 0.25, 0.5, and 1.0 grams per one gram of body weight.

LYN YAFFE: With these dosages, is the proposed volume of 1.5 liters adequate?

TIM LYONS: 1.5 to 1.8 liters would be fine.

JOHN GREENLEAF: What about the meals? How many calories do you recommend?

HAL GOFORTH: We bring in a meal that is about 70% carbohydrate and is about 700 calories. We feed our people first, and I like what you recommend about drinking first and then eating.

MARVIN RIEDESEL: Don't rush between ending the drink and forcing them to eat and wait two hours before beginning the scenario after eating.

ROBERT POZOS: Subjects will drink two ways: one group will drink ad libitum and one group fixed interval. Two hundred ml at 20 minute intervals is a good volume.

ROBERT CADE: I recommend the premission eating and drinking be as follows: Drink the entire solution and then wait 45 minutes before eating.

JOHN GREENLEAF: What is the meal made up of?

ROBERT POZOS: Carl, you work with Marines. What do they eat on maneuvers?

CARL ENGLUND: Marines eat MREs. If they can't heat it up, they will eat it cold. I recommend we give them MREs.

JOHN SILVA: Why do they have to eat at all?

JOHN GREENLEAF: It seems important because we are interested in performance, and performance may very well depend upon eating.

ROBERT POZOS: Then we agree they will have to eat a meal. How much food should they eat?

HAL GOFORTH: Some of the MREs are very high in calories and may be too much in combination with forced drinking.

CARL ENGLUND: Pick an MRE that has an adequate amount of calories and have all of them eat the same thing and same amount.

ROBERT POZOS: OK, NHRC will select which MRE the Marines will eat.

LYN YAFFE: Let's not forget that this is an attempt to solve some problems in a quick manner and we have to deal with follow on work with Marines in MOPP gear.

MALE VOICE: I recommend we use a thirst rating scale.

ROBERT POZOS: No problem, we will include it.

LYN YAFFE: I think that concludes our goals for this meeting. I would like to thank all of you on behalf of the Surgeon General for your participation. I thank the Naval Health Research Center for hosting this meeting and know that our troops participating in Operation Desert Shield will benefit from our recommendations and the important science that will follow. Thank you and have a safe trip home.

MEETING ADJOURNMENT

Unclassified
SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

1a. REPORT SECURITY CLASSIFICATION Unclassified	1b. RESTRICTIVE MARKINGS N/A
2a. SECURITY CLASSIFICATION AUTHORITY N/A	3. DISTRIBUTION/AVAILABILITY OF REPORT Approved for public release; distribution unlimited.
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE N/A	
4. PERFORMING ORGANIZATION REPORT NUMBER(S) Report No. 91-5	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION Naval Health Research Center 6b. OFFICE SYMBOL (If applicable) Code 10	7a. NAME OF MONITORING ORGANIZATION Chief, Bureau of Medicine and Surgery
6c. ADDRESS (City, State, and ZIP Code) P. O. Box 85122 San Diego, CA 92186-5122	7b. ADDRESS (City, State, and ZIP Code) Navy Department Washington, DC 20372-5120
8a. NAME OF FUNDING/SPONSORING ORGANIZATION Naval Medical Research & Development Command 8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER
8c. ADDRESS (City, State, and ZIP Code) NNMC Bethesda, MD 20889-5044	10. SOURCE OF FUNDING NUMBERS PROGRAM ELEMENT NO. 63706N; PROJECT NO. 0095; TASK NO. 004; WORK UNIT ACCESSION NO. DN241537

11. TITLE (Include Security Classification)
(U) Proceedings, Hydration and Hyperhydration Issues Concerning Operation Desert Shield

12. PERSONAL AUTHOR(S)
D.M. Herron (Ed.)

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Final	FROM 11790 TO	1990 November 5-6	76

16. SUPPLEMENTARY NOTATION
Hydration and Hyperhydration Conference Proceedings, 5-6 November 1990

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	Dehydration; Heat; Stress; Desert Climate; Body Fluids: Thirst

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

The conference was organized to address two issues that were raised as a result of Operation Desert Shield. The first deals with a short-term study to determine if there is a more appropriate fluid than water to keep military men/women hydrated while on exercises in the desert environment. The second deals with a long-term study to determine the most effective means to hyperhydrate a soldier to provide him/her with increased performance and survivability in extended desert operations. The conference was divided into five parts: (1) Introduction and background; (2) Discussion on immediately available replacement fluids procedures; (3) Scenarios for small operational mission groups; (4) Possible collaborative efforts to deliver hyperhydration procedures; and (5) The role of the Naval Health Research Center in coordinating short- and long-term studies.

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT ☐ UNCLASSIFIED/UNLIMITED ☒ SAME AS RPT ☐ DTIC USERS	21. ABSTRACT SECURITY CLASSIFICATION Unclassified
22a. NAME OF RESPONSIBLE INDIVIDUAL R.S. Pozos	22b. TELEPHONE (Include Area Code) 619-553-8396 22c. OFFICE SYMBOL Code 10

DD FORM 1473, 84 MAR — 83 APR edition may be used until exhausted. All other editions are obsolete

Unclassified

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