

SGRD-UE-EMA

21 April 1993

MEMORANDUM FOR Commander, USARIEM

SUBJECT: Amendment to Protocol #APMD-92001-AP001, Effects of Autologous Erythrocyte Infusion in Sea-Level Residents Rapidly Transported to High Altitude (approved 12 April 92).

1. Due to changes in a scheduled deployment date for 10th Special Forces volunteers on the above study, it has become necessary to alter the date of the second blood withdrawal date from six weeks after the first blood withdrawal to four weeks. LTC R. Burr, medical advisor to the Commander, has concurred that this shortened time interval between blood withdrawal presents no additional risk to volunteers. Prior to the one-unit blood withdrawal, hemoglobin and hematocrit values will be obtained to ensure that no subject is anemic (hemoglobin value less than 12.5 gm%). Approval to continue will also be obtained from the medical monitor.
2. The test subject volunteer agreement has been revised to incorporate this change and is attached for review.
3. Request approval for the above change to the research protocol and the consent form.
4. Due to the urgency of this request, this memorandum originates with the undersigned instead of Dr. Andrew Young, the principal investigator of record.



Allen Cymerman, Ph.D.
Chief
Altitude Physiology & Medicine
Division

21 APR 93

VOLUNTEER AGREEMENT AFFIDAVIT

This form complies with AR 70-25 and AR 40-38; the proponent agency is OTSG.

PRIVACY ACT OF 1974

Authority: 10 USC 3013, 44 USC 3101, and 10 USC 1071-1087

Principal Purpose: To document voluntary participation in the Clinical Investigation and Research Program. SSN and home address will be used for identification and locating purposes.

Routine Uses: The SSN and home address will be used for identification and locating purposes. Information derived from the study will be used to document the study; implementation of medical programs; adjudication of claims; and for the mandatory reporting of medical conditions as required by law. Information may be furnished to Federal, State, and local agencies.

Disclosure: The furnishing of your SSN and home address is mandatory and necessary to provide identification and to contact you if future information indicates that your health may be adversely affected. Failure to provide the information may preclude your voluntary participation in this investigational study.

PART A — VOLUNTEER AFFIDAVIT

Volunteer Subjects in Approved Department of the Army Research Studies

Volunteers under the provisions of AR 40-38 and AR 70-25 are authorized all necessary medical care for injury or disease which is the proximate result of their participation in such studies.

I, _____ SSN _____,
 having full capacity to consent and having attained my _____ birthday, do hereby volunteer
 to participate in Effects of Autologous Erythrocyte Infusion in Sea-Level Residents Rapidly Transported
 to High Altitude

under the direction of Andrew J. Young, Ph.D.

conducted at US Army Research Institute of Environmental Medicine, Natick, MA and Pikes Peak, CO
(Name of Institution)

The implications of my voluntary participation; duration and purpose of the research study; the methods and means by which it is to be conducted; and the inconveniences and hazards that may reasonably be expected have been explained to me by

Contact telephone(s): Andrew J. Young (Tel: 508-651-5141)

I have been given an opportunity to ask questions concerning this investigational study. Any such questions were answered to my full and complete satisfaction. Should any further questions arise concerning my rights or study-related injury, I may contact

Office of Chief Counsel (Tel: 508-651-4322)

at US Army Natick Research, Development, and Engineering Center (508) 651-4322
(Name, Address and Phone number — include Area Code)

I understand that I may at any time during the course of the study revoke my consent and withdraw from the study without further penalty or loss of benefits; however I may be required (military volunteer) or requested (civilian volunteer) to undergo certain examinations if, in the opinion of the attending physician, such examinations are necessary for my health and well-being. My refusal to participate will involve no penalty or loss of benefits to which I am otherwise entitled.

PART B — TO BE COMPLETED BY INVESTIGATOR

INSTRUCTIONS FOR ELEMENTS OF INFORMED CONSENT: *(Provide a detailed explanation in accordance with Appendix C, AR 40-38 or AR 70-25.)*

You are being asked to volunteer as a subject for a study of how autologous erythrocyte infusion affects you at high altitude. Autologous erythrocyte infusion is also called blood doping. It involves removing some of your blood, storing it in a blood bank while your body makes new blood to replace the loss, and then returning the stored blood to you at a later time. As a result, the number of red blood cells in your body is temporarily increased. Red blood cells carry oxygen from the lungs to the muscles. Increasing the number of red blood cells in your body can help the muscles to work better, and can greatly increase your ability to perform strenuous exercise and work.

Blood doping has never been tested at high altitude. At high altitude, blood doping might have an even bigger effect on physical work capacity than at sea level, since the ability to perform strenuous work and exercise is less at altitude than at sea level due to the lack of oxygen in the thin air. Soldiers rapidly deployed to high altitude must complete their mission despite the lack of oxygen, so blood doping might help sustain their performance capacity. On the other hand, it is possible that the beneficial effects of blood doping might be cancelled out as the body acclimatizes to high altitude, since some of the body's adjustments during altitude acclimatization could offset the effects of blood doping.

After you are medically cleared to participate in this study, a pint of your blood will be removed. The procedure is the same as when you donate blood to a hospital or the Red Cross, except that special precautions will be taken to ensure that the blood is clearly labeled as yours. The red blood cells will be separated from this blood, and then frozen and stored using standard blood banking procedures. A second pint of blood will be removed from you four weeks after the first unit is removed. The four week period is sufficient for your body to make enough blood to replace that re-

I do do not *(check one & initial)* consent to the inclusion of this form in my outpatient medical treatment record.

SIGNATURE OF VOLUNTEER		DATE	
PERMANENT ADDRESS OF VOLUNTEER	TYPED NAME OF WITNESS		
	SIGNATURE OF WITNESS	DATE	

REVERSE OF NATICK FORM 1487

1 MAR 93

moved. After another four-week recovery period, the experimental portion of the research project will begin. The experimental portion of the project will consist of two consecutive phases, each lasting about 15 days, and a final test will be completed on the day following the end of the second phase. The overall test schedule is summarized in the chart attached to this consent form. The exact dates of the study are not yet decided, but we anticipate the first day of the sea-level phase will be sometime in mid to late June, with the entire study being completed before Labor Day weekend.

The first phase will be performed at sea level, primarily in laboratories at the US Army Research Institute of Environmental Medicine located in Natick, MA which is very close to sea level. On the last morning of the first phase of the study, you will be infused with the red blood cells which were collected during the two blood withdrawals. On the first day of the second phase of the study, you will travel (commercial airlines and automobile) to Pikes Peak, CO. The research laboratory located at the summit of Pikes Peak is at an altitude of 14,110 ft. During the sea level phase, you will be billeted in Massachusetts while throughout the high altitude phase you will live in a dormitory that is part of the Pikes Peak laboratory.

§ BODY FAT MEASUREMENT

The amount of your body weight which is fat will be calculated from the difference between your body weight measured on dry land and your body weight measured while you are underwater. While you are being weighed underwater you will breathe through a snorkle. For several breaths, the snorkle will be attached to a bag containing 100% oxygen. At no time during the underwater weighing procedure is there anything which keeps you from raising your head out of the water, but if you do, it may be necessary to repeat the measurements. This test will be done only once, at the beginning of the sea-level phase. The test requires about half an hour of your time.

MAXIMAL EXERCISE TESTS

Once during the sea-level phase, you will complete a maximal exercise test. For this test, electrodes will be placed on your body which will allow the function of your heart to be monitored, and your blood pressure will be measured periodically. After resting measurements of your breathing are made while you sit quietly listening to music through earphones, you will complete a 10-min warm-up walk. After a brief rest, you will then begin running with the treadmill set on a flat angle. Every 90 sec, the grade will be increased. You will run until you achieve your maximum capacity. You will occasionally be asked to describe your feelings of exertion using a chart we will show you. You will

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breathe through a mouthpiece like that used by SCUBA divers. Air from the room enters one side of mouthpiece for you to breathe in, and the air you breathe out is carried by a hose to a special machine for analysis to determine how much oxygen your body is using. Three times during this test, the change in grade will be slightly delayed to allow time for an additional measurement that will require you to breathe in and out several times from a bag containing a small amount of carbon dioxide mixed with oxygen. The maximal exercise test will be completed two more times at high altitude, on the first and ninth day you are living at Pikes Peak. This test requires about an hour of preparation and resting measurements, 15 to 30 minutes of exercise, and about an hour of on-site recovery after the test.

During the maximal tests, a number of blood samples will be obtained while you run. Some blood will be drawn from a catheter (a sterile plastic tube) inserted into an artery in your arm before the test and also while you are running. The rest of the blood will be drawn before you begin to run (or when you first wake up in the morning) and just after you reach your maximum capacity. These blood samples will be obtained by inserting a hypodermic needle into a vein in your arm. The amount of blood to be removed during each maximal exercise test is 64 ml, which is about 2 ounces.

WALKING TEST

Once during the sea-level phase, you will complete a two-hour walk. You will walk at 4 miles per hour and the grade of the treadmill will be set at an angle so as to make the work require about one half of your maximal capacity. All the measurements described for the maximal exercise test will be performed during the walking test. You will repeat this walking test two times at high altitude, on the second and tenth day you are living at Pikes Peak. Blood samples will be taken during one of the sea-level walking tests and two of the walking tests at high altitude, but only the arterial catheter blood samples will be needed, so less blood will be drawn during the walking test than the maximal exercise test. The amount of blood to be drawn during each walking test is 16 ml which is about one half of an ounce. This test will require about an hour of preparation before the test, and about an hour of preparation before and an hour of on-site recovery after the test.

2-MILE RUN TEST

Two times during the sea-level phase and two times at high altitude, you will complete a timed two-mile run. The run will be performed on a measured course laid out on black-top roads around the military post in Natick, and along the dirt road which circles the summit of Pikes Peak. As in your regular PT test, the object is to achieve your fastest time. The tests will be separated by about

CONTINUATION PAGE FOR NATICK FORM 1487

Witness's initials	Volunteer's initials
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a week. At the end of the run, your pulse and blood pressure will be measured.

QUESTIONNAIRE

When you wake up in the morning on days that the maximal tests, the walks, and the 2-mile runs are scheduled, you will fill out a 67-item questionnaire. The questionnaire asks you to rate how you are feeling with respect to a number of symptoms, and takes five to ten minutes to fill out.

LUNG FUNCTION TESTS

On one day at sea level and two days at high altitude you will complete a series of breathing tests to determine how well your lungs are functioning. These tests will be done while you rest on a lounge chair listening to music through headphones. You will be breathing through a mouthpiece and hose attached to a bag containing different air mixtures. The mixtures are all gases contained normally in the atmosphere, but for these tests the amounts of the gases will sometimes be varied. During one test, you will breathe gas containing the normal amount of oxygen at first, but since you will be rebreathing the same gas in and out of a bag, the amount of oxygen will slowly fall as you use it up. The carbon dioxide you exhale will be cleaned from the air. You will rebreathe from the bag for about 4 minutes, after which you will return to breathing room air. You will repeat this maneuver several times. In another test, the bag will contain slightly more carbon dioxide than you usually breathe, and very much more oxygen. You will rebreathe this gas for about 4 minutes, after which you will return to breathing normal room air. You will repeat this test several times. For the last lung function test you will sit upright. You will be asked to breathe room air in and out normally and then maximally, and during one test a very small amount of carbon monoxide will be added to the air you inhale for one breath. About an hour is required to complete this series of tests.

MORNING, FASTING BLOOD SAMPLES AND BODY WATER MEASUREMENTS

Besides the blood samples to be drawn during the maximal exercise test and walking test, blood will be drawn on a few other occasions. One morning at sea level and two mornings at high altitude, you will not rise from bed after you awaken until after a blood sample is taken from you. This will be done very early in the morning using the same procedures normally employed by medical personnel when you have a physical. The amount of blood to be drawn will be 23 ml which is a little more than half of an ounce.

When this is done at sea level and on the last day you are at Pikes Peak, you will be asked to provide a sample of your saliva

CONTINUATION PAGE FOR NATICK FORM 1487

Witness's initials	Volunteer's initials
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and urine after the blood is drawn. After that, you will be given water to drink which contains two naturally occurring safe substances (deuterium and sodium bromide) which we use as tracers to measure the amount of water in your body. Another small blood sample will be taken, 1 ml (less than eighth of a teaspoon), two and three hours after you drink the tracers, using the same method as before. You will provide another saliva sample at three and four hours after you drink the tracers. You will be asked not to eat, drink, smoke or chew anything after midnight before these tests until they are completed.

On the mornings of days at high altitude that do not have any testing scheduled which involves blood samples, a small fingerprick blood sample will be drawn to allow us to determine if your blood is becoming too thick.

UPRIGHT TILT TEST

On two days at sea level and three days at high altitude you will complete a procedure called the upright tilt test. Electrodes will be attached to your body to allow the function of your heart to be monitored during this test, and periodically your blood pressure will be measured. You will lie upon a special padded table for about twenty minutes while measurements are made. After warning you, the table will be rapidly moved to an upright position, while you are still on it. Safety restraining straps around your torso will secure you to the table (your hands will be free) to ensure that you do not fall off the table. Measurements will be made for another 15 minutes, after which your finger will be pricked to allow us to collect a drop of blood. The upright tilt test is safe, although it is possible that you might feel faint when you are moved to the upright position. This test takes about 30 to 40 minutes to complete.

DIETARY CONTROL PERIODS

During the thirty-six to forty-hour period preceding each maximal exercise test, your food and fluid consumption will be closely monitored. Your diet will consist solely of a pre-mixed, lactose-free liquid nutrient beverage obtained commercially (two such beverages that are commonly available are Sustacal and Ensure). This beverage, available in several flavors, will provide 2500 to 4000 calories per day (50% carbohydrate, 30% protein and 20% fat), depending on how much you choose to consume. During the sea-level phase you will be asked to consume at least 2500 calories per day, and you will be allowed to consume up to 4000 calories per day. During the two high altitude dietary control periods, you will be asked to consume the same amount of the beverage as you did during the sea-level phase. All other RDA requirements (vitamins, minerals, etc.) will be satisfied using this diet. Also during

CONTINUATION PAGE FOR NATICK FORM 1487

Witness's initials	Volunteer's initials
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these days, all of the urine your body produces will be collected, and you will be asked to provide urine samples at certain specific times. You will be provided appropriate containers and instructions concerning their use.

BLOOD VOLUME MEASUREMENTS

During the first week of sea-level testing, on the day you leave to go to Pikes Peak and on the day you return from Pikes Peak, the amount of blood in your body will be measured by scientists at the Naval Blood Research Laboratory at Boston University Medical Center, Boston, MA. A small sample of blood will be taken from your arm vein. A minute amount of radioactive chromium and iodine will be added, and the blood will then be reinjected. Blood samples will be collected twice following the injection. The total volume of blood removed for this test is about 20 ml, which is little more than half an ounce. The amount of radioactivity you will be exposed to is small, less than that in a single chest x-ray. One half of the radioactivity will be gone from your body in 30 to 60 days. Each of these tests will take 2 to 3 hours to complete.

HAZARDS

Exercise, especially maximal exercise, may uncover or aggravate pre-existing heart problems, possibly leading to a heart attack or disrupting the normal rhythm of the heart beat. In young healthy men, these occurrences are rare, and the incidence of these occurrences is no greater at high altitude than at sea level. However, your electrocardiogram will be closely monitored during all treadmill exercise tests for signs of heart irregularities. You could fall and injure yourself on the treadmill, so a staff member will stand near you while you exercise to provide assistance if needed.

There are some hazards associated with the blood doping procedure. With all transfusions, there is the possibility of transmitting infectious disease. In this case, however, you will be receiving your own blood back in the transfusion, so there is little chance of any disease being transmitted to you. It is possible that your blood could be contaminated while in storage, but careful procedures are used to ensure the chance of this happening is very low. Large blood transfusions can sometimes cause fluid accumulation in your lungs, but the amount of blood you will be receiving is small enough that this is very unlikely to happen, and you will be closely checked by a physician during and after the transfusion for any signs that this is occurring. It is possible that the infusion of red blood cells could cause your blood to become too thick, especially at high altitude. If this happens, the blood flow to certain regions of the body could become restricted, blood clots could form, and, more seriously, a stroke

CONTINUATION PAGE FOR NATICK FORM 1487

Witness's initials	Volunteer's initials
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could occur. We (the scientists in charge of this research) don't believe that your blood will become this thick, but to allow us to monitor for this effect, we will, as already described, be checking your blood every day you are at Pikes Peak. If it becomes too thick, you will be brought down from the mountain, and remain in Colorado Springs until it is safe for you to return to the summit.

Placing the catheter in the artery in your arm can be somewhat painful. This procedure will be performed by an experienced physician who will administer a local anaesthetic (a "pain-killer" like dentists use when drilling teeth) to the spot on your arm where the catheter is to be placed in order to minimize discomfort. Drawing blood from your veins with a hypodermic needle may sting sometimes, and occasionally causes a bruise to form. There is a slight chance of infection following both of these, so sterile procedures will be used. Other complications that can result from arterial catheters are clot formation and bleeding around the site during or after the procedure. Although these complications are rare, they are serious and require immediate medical attention so you will be closely monitored following the procedure for any signs of complications.

During most tests you will be breathing room air, but some of the tests require you to breathe gases normally found in room air, but in very different amounts than normally inspired. At sea level, you will sometimes breathe air containing enough helium to temporarily make your voice sound strange (like Donald Duck), but otherwise helium is harmless to breathe. Some of the tests require you to breathe higher amounts of carbon dioxide than usually found in room air. Although harmless, this can cause your throat to burn somewhat until you return to breathing room air. One test requires a very small amount of carbon monoxide be added to one of your breaths, but the amount of carbon monoxide you will breathe is less than that contained in one puff from a cigarette. During any of these tests, you may experience a sensation of breathlessness or an urge to breathe faster. All of these tests are safe, and at no time are you restricted from removing the mouthpiece and breathing room air (although if you do this before instructed to, the test is invalid and must be repeated).

There are some risks and hazards associated with living in the Pikes Peak facility. The building is heated, but it is often cold outdoors, especially at night. Snow and hail storms can occur, even in the summer. The summit of Pikes Peak is about 3000 feet above the tree line, and the Peak (and the research facility itself) is sometimes struck by lightning. The building's safety features protect occupants, but whenever a thunderstorm is imminent you must come indoors. Recreational activities are very limited on the summit of Pikes Peak, and are generally limited to activities such as reading, card and board games, correspondence courses, television and video tapes. The thin air at high altitude can make

CONTINUATION PAGE FOR NATICK FORM 1487

Witness's initials	Volunteer's initials
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you feel out of breath and can cause a headache. Some people experience symptoms similar to the flu, such as nausea, loss of appetite and vomiting. These symptoms are usually worst during the first day or two at altitude, and then disappear as you acclimatize. These symptoms, although uncomfortable, are not usually cause for concern. However, it is possible that while you are at high altitude you could experience buildup of water in your lungs, or even more seriously, in the brain. This is life-threatening, if not treated. Therefore, you will be frequently checked by a physician for any signs that this is occurring. If this condition develops, treatment involves breathing oxygen and moving you to low altitude. Usually these treatments result in complete and rapid recovery, but occasionally hospital treatment is necessary.

RESTRICTIONS

Throughout this study, you must abstain from alcohol during the 24 hours before any exercise test or blood sample. There will also be periods before certain of the tests that you will be asked to fast and/or refrain from smoking. These periods will usually be overnight for tests first thing in the morning, or for 3-4 hours before tests conducted later in the day. Starting two weeks before the first tests and continuing throughout the entire study, you will be asked to stop taking any medications, over-the-counter drugs included, unless they have been approved by the senior physician monitoring your health during this study. This physician will be identified to you at the beginning of the study.

There is little direct benefit to you for your participation. You will find out your percent body fat and physical fitness level, and you will experience the effects of high altitude on your body, which may be of benefit to you if you ever are deployed to a high altitude region. All data and medical information obtained about you as an individual will be considered privileged and held in confidence; you will not be personally identified in any presentation of the results of this study. At any time, you may ask the investigators to explain the tests, procedures and measurements they are making. Complete confidentiality cannot be promised to military personnel, because information bearing on your health may be required to be reported to appropriate medical or command authorities, and applicable regulations note the possibility that the U.S. Army Medical Research and Development Command authorities may inspect the records. You will be provided with a copy of this consent form for your records.

At any time during this study, you are free to withdraw from participation.

CONTINUATION PAGE FOR NATICK FORM 1487

Witness's initials	Volunteer's initials
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Experimental test schedule.

SL ₀ (diet)	SL ₁ (diet)	SL ₂ tbw*, max*, vent, AM Blood (diet)	SL ₃ walk*	SL ₄ tilt	SL ₅ 2 mile run,bv	SL ₆
SL ₇	SL ₈ PFT, HOVR, HCVR, tilt	SL ₉ %fat	SL ₁₀ makeup	SL ₁₁ 2 mile run	SL ₁₂	SL ₁₃
SL ₁₄	SL ₁₅ infusio n (diet)	HA ₀ bv, depart, tilt (diet)	HA ₁ max*, vent, am blood, (diet)	HA ₂ walk*	HA ₃ 2 mile run, tilt, HOVR, HCVR, PFT	HA ₄
HA ₅	HA ₆	HA ₇ (diet)	HA ₈ (diet)	HA ₉ tbw*, max*, vent, am blood (diet)	HA ₁₀ walk*	HA ₁₁ 2 mile run
HA ₁₂ tilt, HOVR, HCVR, PFT	HA ₁₃ return, bv	SL max				

%fat = underwater weighing test
max, vent = maximal exercise test, preceded by resting breathing tests
walk = 2 hour walking test
tilt = upright tilt test
bv = blood volume measurements at Naval Blood Research Laboratory
tbw = body water involving drinking deuterium and sodium bromide
am blood = blood samples collected by venipuncture following overnight fast
2-mile run = timed 2-mile run
HOVR, HCVR and PFT = lung function test
infusion = red blood cells or placebo administered at Naval Blood Laboratory
depart = leave Natick travel to Pikes Peak
return = leave Pikes Peak travel to Natick
rest = subject rest, recovery time
asterisk* indicates test involving arterial catheterizations

CONTINUATION PAGE FOR NATICK FORM 1487

Witness's initials	Volunteer's initials
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SGRD-UE-ZA

15 March 1993

MEMORANDUM THRU Dr. Sawka

FOR Dr. Young

SUBJECT: Amendment to Approved Protocol

It has been determined that the requested amendment does not increase the risk to participating subjects, and seems justified for practical reasons. Therefore, amendment to protocol, (APMD92001-AP001-H001) "Effects of Autologous Erythrocyte Infusion in Sea-Level Residents Rapidly Transported to High Altitude" is approved.

for G. P. Krueger
GERALD P. KRUEGER
Colonel, MS
Commanding

CF:
SGRD-HR