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RCS MEDDH-288 (RI)

U S ARMY MEDICAL RESEARCH AND DEVELOPMENT TECHNICAL REPORT

ANNUAL PROGRESS REPORT, FISCAL YEAR 1971

U S ARMY RESEARCH INSTITUTE OF ENVIRONMENTAL MEDICINE

Natick, Massachusetts

PUBLISHED JULY 1971

UNITED STATES ARMY
MEDICAL RESEARCH & DEVELOPMENT COMMAND

172

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Natick, Massachusetts 01760

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11. SUPPLEMENTARY NOTES

12. SPONSORING MILITARY ACTIVITY
U.S. Army Medical Research and Development Command
Washington, D.C. 20314

13. ABSTRACT
The research projects reported in this Annual Progress Report are as follows:

Project: Military Environmental Medicine (3A062110A827)

Work Units: Medical Problems in Military Arctic Operations
Prediction of the Biological Limits of Military Performance as a Function of Environment, Clothing and Equipment
Effects of Environmental Stressors on Military Performance: Interactions with Extended Operations, Unusual Activity-Rest Cycles
Biomedical Impact of Military Clothing and Equipment Design Including the Selection of Crew Compartment Environments
Prevention and Treatment of Disabilities Associated with Military Operations in the Cold
Prevention and Treatment of Disabilities Associated with Military Operations in the Heat
Prevention and Treatment of Disabilities Associated with Military Operations at High Terrestrial Elevation

DD FORM 1 NOV 68 1473 REPLACES DD FORM 1473, 1 JAN 64, WHICH IS OBSOLETE FOR ARMY USE.

Unclassified

Security Classification

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14. KEY WORDS	LINK A		LINK B		LINK C	
	ROLE	WT	ROLE	WT	ROLE	WT

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DOCUMENT CONTROL DATA - R & D

(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1. ORIGINATING ACTIVITY *(Corporate author)*

2a. REPORT SECURITY CLASSIFICATION

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7a. TOTAL NO. OF PAGES

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9a. ORIGINATOR'S REPORT NUMBER(S)

9b. OTHER REPORT NO(S) *(Any other numbers that may be assigned this report)*

10. DISTRIBUTION STATEMENT

11. SUPPLEMENTARY NOTES

12. SPONSORING MILITARY ACTIVITY

13. ABSTRACT

Project: Research in Biomedical Sciences (3A061102B71R)

Work Units: Disease Susceptibility of Soldiers in Harsh Environments
Biological Processes that Limit Military Performance under Environmental Stress
Development of Cold Injury Models and Characterization of Frostbite, Non-Freezing Cold Injuries and Whole Body Heat Loss Common to the Soldier
Development of Measures to Assess the Impact of Environmental Stresses on Critical Military Performance
Biological Processes that Limit Heavy Physical Work Ability of the Soldier
Development and Characterization of Models of Heat Injuries and Disabilities and Other Heat Responses of the Soldier
Development and Characterization of Models to Study Acute Mountain Sickness and High Altitude Pulmonary Edema in Military Operations

DD FORM 1 NOV 68 1473 REPLACES DD FORM 1473, 1 JAN 64, WHICH IS OBSOLETE FOR ARMY USE.

14. KEY WORDS	LINK A		LINK B		LINK C	
	ROLE	WT	ROLE	WT	ROLE	WT

Unclassified

Security Classification

DOCUMENT CONTROL DATA - R & D

(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1. ORIGINATING ACTIVITY *(Corporate author)*	2a. REPORT SECURITY CLASSIFICATION
	2b. GROUP
3. REPORT TITLE	
4. DESCRIPTIVE NOTES *(Type of report and inclusive dates)*	
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10. DISTRIBUTION STATEMENT	
11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY

13. ABSTRACT

Project: In-House Laboratory, Independent Research (3A061101A91C)

Work Units: Factors Limiting Military Performance at Sea Level and High Altitude and their Modification by Acclimatization and Adaptation
Historical Analysis, Development and Distribution of Military Environmental Medical Information
Effects of Multiple Environmental Stress on Military Personnel
Development of a Non-Sedating Analgesic for Military Use

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Unclassified

Security Classification

14. KEY WORDS		LINK A		LINK B		LINK C	
		ROLE	WT	ROLE	WT	ROLE	WT
Acclimatization	Microcirculation						
Activity-Rest Cycles	Military Clothing						
Altitude	Military Disabilities						
Analgesia	Military Environmental Medicine						
Arctic Military Operations	Military Heat Stress						
Atropine	Military Information						
Behavior	Military Operations						
Biochemistry	Military Performance						
Biophysics	Military Tactics						
Blood Flow	Motor Performance						
Body Temperature	Motor Skills						
Carbon Monoxide	Mountain Sickness						
Cardiovascular	Multiple Stresses						
Clinical Testing	Muscle Metabolism						
Cognition	Pathology Model						
Cold	Perception						
Cold Injury	Performance						
Combat Casualties	Performance Decrement						
Combat Effectiveness	Performance Limits						
Continuous and Sustained Operations	Pharmacology						
Cryobiology	Physiology						
Defense Mechanisms	Protection						
Disabilities	Protein Metabolism						
Disease	Psychological Stress						
Drugs	Psychomotor Skills						
Endurance	Pulmonary Edema						
Energy Metabolism	Sensory Processes						
Environmental Extremes	Sleep Loss						
Environmental Stress	Stress						
Environmental Tolerance	Temperature						
Exercise	Therapeutic Techniques & Equipment						
Fatigue	Thermoregulation						
Fatigue, Mental	Tolerance						
Frostbite	Training						
Heat	Trenchfoot						
Heat Disabilities	Vision						
Heat Stress	Wind						
Heat Tolerance	Work						
High Altitude							
High Altitude Natives							
Hypothermia							
Hypoxia							
Immune Response							

U S ARMY RESEARCH AND DEVELOPMENT

TECHNICAL REPORT

RCS-MEDDH-288 (R1)

U S ARMY RESEARCH INSTITUTE OF ENVIRONMENTAL MEDICINE

NATICK, MASSACHUSETTS

ANNUAL PROGRESS REPORT

1 July 1970 - 30 June 1971

**Approved for public release;
distribution unlimited.**

UNITED STATES ARMY

MEDICAL RESEARCH & DEVELOPMENT COMMAND

FOREWORD

1. This has been another year of progress. The civilian and military scientists of USARIEM at the bench are the producers and interpreters of new data. Dr. David E. Bass, Deputy Scientific Director; Colonel James D. Grindell, Executive Officer and Chief, Support Office; the directors of our eight laboratories, LTC William H. Doolittle, Dr. E. Ralph Dusek, LTC Wayne O. Evans, Dr. Ralph F. Goldman, LTC L. Howard Hartley, MAJ David K. Hysell, Dr. Milton Landowne, Dr. Milton Mager, the Support Office managers, Mr. Frank W. Botsch, Mrs. Josephine B. Donnelly, CPT Fred D. McKellar, CPT Joseph H. Miller, 2LT George R. Moore and Mrs. June L. Zolner; and many other members of USARIEM's staff have contributed abundantly to the preparation of this report and the work summarized therein.

2. This work was authorized under the following DA Technical Projects: In-House Laboratory Independent Research (3A061101A91C); Research in Biomedical Sciences (3A061102B71R); and Military Environmental Medicine (3A062110A827). These three DA Technical Projects are divided into a total of 18 Work Units, each of which is relevant to finding solutions to the problems imposed upon the soldier who must work under hostile terrestrial environmental conditions.

3. In conducting the research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animal, Resources, National Academy of Sciences-National Research Council.

4. We express special appreciation to General Richard R. Taylor, Commanding General, US Army Medical Research and Development Command and his staff; to General Dean Van Lydegraf, Commanding General, US Army Natick Laboratories and his staff; and to the several civilian scientists who serve as consultants to USARIEM.

5. In July 1971, Colonel LeeRoy G. Jones, MC, will assume the responsibilities of Commander/Scientific Director, and LTC Norman E. Clyde, MSC, those of Executive Officer and Chief, Support Office. Colonel Grindell and I leave our coworkers with appreciation for their friendship and past accomplishments and best wishes for their personal and professional plans and projects.

James E. Hansen

JAMES E. HANSEN, M.D.
Colonel, MC
Commanding

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Page No.

Project No: 3A062110A827

Title: Military Environmental Medicine

(83101)

RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY

1. AGENCY ACCESSION	2. DATE OF SUMMARY	REPORT CONTROL SYMBOL
DA OA 6120	71 07 01	DD-DR&E(AR)636

3. DATE PREV SUMRY	4. KIND OF SUMMARY	5. SUMMARY SCTY	6. WORK SECURITY	7. REGRADING	8. GROUP MARK	8a. SPECIFIC DATA-CONTRACTOR ACCESS	9. LEVEL OF SUM
70 12 31	D. Change	U	U	N/A	N/A	☒ YES ☐ NO	A. WORK UNIT

10. NO./CODES:	PROGRAM ELEMENT	PROJECT NUMBER	TASK AREA NUMBER	WORK UNIT NUMBER
a. PRIMARY	6.21.10.A	3A062110A827	00	045
b. CONTRIBUTING				
c. [redacted]	CDOG 141 (2a)			

11. TITLE (Precede with Security Classification Code)

(U) Medical Problems in Military Arctic Operations (02)

12. SCIENTIFIC AND TECHNOLOGICAL AREAS

003500 Clinical Medicine; 005900 Environmental Biology; 016200 Stress Physiology

13. START DATE	14. ESTIMATED COMPLETION DATE	15. FUNDING AGENCY	16. PERFORMANCE METHOD
65 07		DA	C. In-House

17. CONTRACT/GRANT

a. DATES/EFFECTIVE: N/A EXPIRATION:

b. NUMBER:

c. TYPE: d. AMOUNT:

e. KIND OF AWARD: f. CUM. AMT.

18. RESOURCES ESTIMATE	a. PROFESSIONAL MAN YRS	b. FUNDS (In Thousands)
FISCAL YEAR — PREVIOUS 71	5.0	210
FISCAL YEAR — CURRENT 72	6.0	210

19. RESPONSIBLE DOD ORGANIZATION

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NAME: Doolittle, William H. LTC

TELEPHONE: 317-353-9157

SOCIAL SECURITY ACCOUNT NUMBER:

ASSOCIATE INVESTIGATORS

NAME: Gregory, Roger T. MAJ

NAME: Marshall, Henry Dr. DA

21. GENERAL USE

Foregin Intelligence Not Considered

22. KEYWORDS (Precede each with Security Classification Code)

(U)Cold; (U)Cold Injury; (U)Trenchfoot;(U)Military Environmental Medicine;(U)Acclimatization;(U)Therapeutic Techniques &Equipment (U)Hypothermia

23. TECHNICAL OBJECTIVE. 24. APPROACH. 25. PROGRESS (Furnish individual paragraphs identified by number. Precede text of each with Security Classification Code.)

23.(U)To identify and quantitate detrimental local and systemic physiologic changes induced by cold in experimental animals and military personnel and to generate and evaluate effective methods of treatment or prevention of these changes.

24.(U)I.Combined clinical and experimental programs to (a) perform epidemiologic studies in cold injury in military population; (b) assess various methods of treatment of cold injury;(c)evaluate Xe-133 blood flow measurement as a tool to predict outcome of cold injury;(d)evaluate methods of resuscitation in accidental hypothermia. II.Measure changes in human performance in the cold by(a)quantitating pulmonary function; endocrine function, and threshold of anaerobic metabolism before and after exercise in the cold; and (b)by measuring digital dexterity and correlating it with objective determination of nerve conduction after a variety of physical and cold stresses.

25.(U)70 07-71 06 Data from 298 cases of cold injury and 3,993 controls have been punched on IBM cards and are being analyzed to identify risk factors for cold injury among Alaskan troop units. Soldiers evaluated before and after a 10-day field exercise in mild cold temperatures showed improvement in physical condition, but a decrement was demonstrated in finger nerve conduction time and block stringing test of digital dexterity. Cold exposure at -2°C resulted in complete suppression of nerve response in the fingers of a number of subjects tested. Blood flow, as measured by Xe-133 has proved a reliable method for prediction of tissue loss in experimental cold injury. One new case was added to the dextran protocol. Pilot studies using a fibrinolytic drug (Urokinase) in experimental freezing injury suggest some benefit from this agent. Cardiovascular function of dogs who were cooled and rewarmed by either peritoneal dialysis or a heated blanket was more effectively restored to normal by the former (i.e. peritoneal dialysis) technique. Cold was found to have an adverse effect on vibration sense in peripheral nerves. With cold injury, degeneration of nerve fibers begins at the site of injury and progresses toward the body.

* Available to contractors upon originator's approval

DD FORM 1 MAR 66 1498 PREVIOUS EDITIONS OF THIS FORM ARE OBSOLETE. DD FORMS 1498A 1 NOV 65 AND 1498-1 1 MAR 66 (FOR ARMY USE) ARE OBSOLETE

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Title of Study: Epidemiology of frostbite in a garrison situation

Investigator: Roger T. Gregory, MAJ, MC

Eighty-nine new cases of frostbite were treated by AMRLA personnel during the winter 1970-71. Of these, 75 were military and 14 were civilian. There were 52 first degree, 20 second degree, 1 third degree, and 1 fourth degree injury. The fourth degree injury was in an Alaskan Native. This one case of fourth degree injury was added to the dextran protocol. The case eventuated in amputation but the circumstances included physical injury other than cold and clearly modified the potential for restoration of circulation of the part. The data is being reduced to IBM cards and compared to earlier years' studies. In the future, it is anticipated that accumulation of epidemiologic data will continue to be used as a reflection of level of training and efficiency of protective systems for troops in the field. This past year, the number of injuries was surprisingly small when compared to the 1968-69 winter in which 191 cases were accumulated in a much more mild winter. We feel this change in attack rate despite comparable levels of exposure of field units is a reflection of improved training and supervision.

We continue to be involved in the orientation of troops to cold weather protection. The cold weather orientation program generated here has been distributed widely over the command and to some other installations (Base Ops, Malmstrom AFB; Eielson AFB).

Title of Study: Effect of cold exposure and exercise on physical condition

Investigator: William H. Hulbregtse, Ph.D.

The hypothesis that the combination of physical exercise and cold exposure might bring about a decrement in physical fitness as has been previously suggested by other investigators, was tested during a cross country snow trek involving three investigators from AMRLA and twelve volunteers from the 171st Infantry Brigade. The unit was 100% foot mobile on snowshoes and pulling ahkios with tentage and organizational equipment. Although the original program proposed a 20 day trip, hopefully to cover 200 miles of Interior Alaskan terrain, the trip lasted only from 17-27 January. The unusually rigorous weather during that period with recorded temperatures to -65°F and the highest temperature recorded during the trek of -35°F, placed such a burden on supporting facilities, specifically air, that it was felt discreet to abort the trek in the interest of safety of these supporting personnel. Interestingly, the test subjects and investigators on the ground did remarkably well and all were disappointed at the early cancellation. The distance covered was approximately 60 miles. In addition to the basic physiologic assessment, other accomplishments during the trek included the evaluation of a communications network using a man-transportable single side band radio (PRC/74), two experimental, light-weight, five-man tents, and fortuitously a variety of foot wear from native mukluks and Air Force mukluks to the conventional cold dry VB boot. Evaluations of these items are contained in a separate report. The exercise further emphasized the grave difficulties encountered by Army air when operating in extremes of temperatures. Close support of men on the ground is virtually impossible under these circumstances and the risks to aircrews with current survival equipment was inordinately high.

Assessment of physical fitness was made by measurement of maximal oxygen uptake on a bicycle ergometer. In every case there was improvement in physical fitness. Although it could be argued that this relatively short period of stress was not comparable to that reported in previous studies in which a decrement in physical fitness was observed, for purposes of military operations it seems that this period of time under the conditions encountered was representative and that a longer expedition, while of academic value, would less closely simulate actual missions.

Title of Study: Clinical use of xenon to predict tissue loss in cold injury

Investigator: William H. Doolittle, LTC, MC

A major impediment to progress in evaluating new methods of therapy in frostbite has been the inability to early and reliably identify those cases at risk of tissue loss. Studies here in experimental freezing injury have shown the efficiency of Xe-133 blood flow measurements in predicting the survival of a frozen part. Clinical studies performed at Cook County Hospital by Dr. David Sumner have been completed and data analyzed (D. S. Sumner, et al. "Prediction of Tissue Loss in Human Frostbite with Xenon-133" Surgery - in press). The technique using 20 severely frostbitten patients improved on the clinical accuracy of prognosticating in cold injury, and if used only to predict viability of the part, was 97% accurate. Modification of the technique of administering the isotope in terms of site selection must be made. Plans are made for continuing to use this technique in Bassett AH in the coming year. AEC licensure application is being processed. In addition, efforts are underway to form a collaborative study with Cook County Hospital, Colorado General Hospital in Denver, and Dr. William Mills in Anchorage, Alaska, to expand the program so as to use xenon in the assessment of the therapeutic agents in a larger patient population.

Title of Study: Assessment of human peripheral nerve conduction and psychomotor performance during a subarctic field exercise

Investigator: Henry C. Marshall, Ph.D.

Approved protocol AMRLA 70-6 "Assessment of human peripheral nerve conduction and psychomotor performance during a subarctic field exercise" has been completed and approved for publication as of 3 May 1971. It is to be published under the title "The Effects of Cold Exposure and Exercise Upon Peripheral Function."

Title of Study: Evaluation of various rewarming techniques following induced hypothermia

Investigator: John F. Patton, CPT, MSC

In view of Alaska's climatic conditions, expanding trans-Alaskan travel, increased industrial and economic activity and changing military tactics which involve sustained operation of small units, the likelihood of accidental hypothermia and the requirement for effective, readily available therapy is apparent.

In a brief survey of 179 cases of treated accidental hypothermia over the past fifteen years in England, a surprisingly high (63%) mortality rate was found when surface methods of resuscitation were employed. Furthermore, in a recent survey conducted by this Laboratory of Alaskan physicians, 61 cases of accidental hypothermia have been seen during the past fifteen years. Because of the high mortality attending this injury when current methods of treatment are employed, studies are presently being conducted to evaluate peritoneal dialysis as a method of core rewarming following induced hypothermia. Initial experiments have been centered upon assessing cardiovascular function in dogs rewarmed by peritoneal dialysis compared to those rewarmed externally by means of an omnitherm hypothermic blanket. The cardiovascular parameters of interest include the arterial blood pressure, central venous pressure, heart rate, cardiac output, and the electrocardiogram. Preliminary results suggest that following three hours of hypothermia at a core temperature of 25°C, animals rewarmed by peritoneal dialysis exhibit a more complete recovery of the cardiovascular system as determined by the cardiac output, heart rate, and arterial blood pressure. In addition, the electrocardiogram of the peritoneally dialyzed animals returns toward normal at a much earlier period than those animals treated by external means.

These experiments as well as compilation and analysis of the data on this initial part of the study will soon be completed.

Renal function has been found to be impaired by induced hypothermia. Therefore, additional studies comparing peritoneal dialysis to external rewarming on renal function will be undertaken.

Title of Study: Use of peripheral nerve response to forecast tissue loss in frostbite injury

Investigator: Henry C. Marshall, Ph.D.

In experimentally frozen animals, attempts to forecast tissue loss by means of electromyographic studies in association with analysis of a nerve response has indicated thus far that we have been able to accurately anticipate the level at which the tissue will prove non-viable.

Evaluation of a series of clinical cases has shown that in most cases of frostbite injury, which have been clinically evaluated as first or second degree, the nerve conduction decrement has been of long term or of a semi-permanent nature. In one case of a Korean war veteran, second degree frostbite injury has resulted in a nerve conduction decrement of 20 years duration. Another indication is that evaluation of the peripheral nerve response may result in a more accurate diagnosis of the degree of injury than the subjective clinical evaluation. In one case diagnosed as second degree frostbite, the peripheral nerve response returned to normal within a period of two weeks, indicating that the damage was considerably less than that normally associated with second degree injury.

Measurements of nerve conduction velocity in frostbitten fingers is normally made from the distal phalanx to the base of the finger. The actual injury, however, usually involved the distal pad or tip of the finger. This indicates that nerve fibers are degenerating from the site of the injury proximally, and there is further indication that cold injury selectively damages the faster, larger fibers. A paper reflecting these findings entitled "Additional Information on the Pathophysiological Effects of Cold Injury" is now in the rough draft stage and will be submitted for clearance soon.

Limited experience with burn injury has indicated that although burn and cold injury appear subjectively similar, there may be a difference between these injuries with the respect to the amount of nerve damage involved. Burn injury appears to result in a much more rapid recovery of normal nerve response than does cold injury, however, more burn injuries are required to substantiate this evaluation.

Pursuance of these studies has resulted in the acquisition of considerable experience in the evaluation of human nerve response. The results of this experience have been summarized in a paper entitled "Possible Pitfalls in the Clinical Measurement of Nerve Conduction Velocity" which is in its final draft stage and will soon be submitted for publication clearance.

Title of Study: Significance of cold induced decrement in peripheral nerve function

Investigator: Henry C. Marshall, Ph.D.

This study has been broken into phases.

Phase I, in which peripheral nerve function is being analyzed with respect to discrete fiber function, is temporarily held in abeyance pending completion of a screened room. The screened room is required to assure accuracy of results by eliminating external interference. All materials for this structure are presently on hand and await only the passing of the current anticipation of spring flood before assembly. Progress in pursuing this phase, however, may be outlined as follows:

1. The evaluation of the effects of cold on the vibration sense has shown that this sense is significantly affected by moderate cold exposure.

2. Investigation of the disappearance of distal action potential phases have indicated that this is due to a selective cold block upon these lower amplitude fibers.

Phase II involves collateral studies designed to measure alterations in peripheral nerve function in response to (among other things) emotional stress. It has been found that emotional stress, in this case fear, is indeed reflected in peripheral function, at least in rabbits. This phase has been completed and a paper entitled the "Effects of Emotional Stress on Peripheral Nerve Conduction Velocity" is currently in a rough draft stage and will be submitted for clearance soon.

Phase III is designed to investigate possible alterations in distal nerve tissue in response to varying degrees of cold injury and cold exposure. Initial electron micrographs taken of graded cold injuries have clearly indicated that there is a progressive damage to the myelin sheath with respect to degree of cold injury. Tighter controls, however, are required to assure the degree of cold injury and its repeatability and the positive identification, in each animal subject, of the nerve tissue involved. Controls in the first instance

involve the following experimental animals over a period of 30-60 days. Controls in the second instance involve utilizing a selective stain that can be used *in vivo* that will stain only nervous tissue, and this has presented a temporary problem. Work on this phase continues.

(83102)

RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY

1. AGENCY ACCESSION	2. DATE OF SUMMARY	REPORT CONTROL SYMBOL
DA OB 6122	71 07 01	DD-DR&E(AR)636

3. DATE PREV SUMRY	4. KIND OF SUMMARY	5. SUMMARY SCTY	6. RSRCH SECURITY	7. REASSIGNED	8a. GRAPH INSTR'N	8b. SPECIFIC DATA: CONTRACTOR ACCESS	9. LEVEL OF SUM
70 12 31	D. Change	U	U	N/A	N/L	☐ YES ☐ NO	A. WORK UNIT

10. NO./CODES:	PROGRAM ELEMENT	PROJECT NUMBER	TASK AREA NUMBER	WORK UNIT NUMBER
a. PRIMARY	6.21.10.A	3A062110A827	00	046
b. CONTRIBUTING				
c. CONTRIBUTING	CDOG 141 (2a)			

11. TITLE (Precede with Security Classification Code): (U) Prediction of the Biological Limits of Military Performance as a Function of Environment, Clothing and Equipment (22)

12. SCIENTIFIC AND TECHNOLOGICAL AREAS: 016200 Stress Physiology; 013400 Psychology; 011700 Operations Research

13. START DATE	14. ESTIMATED COMPLETION DATE	15. FUNDING AGENCY	16. PERFORMING ORGS
70 07		DA	C. In-House

17. CONTRACT/GRANT
a. DATES/EFFECTIVE: N/A EXPIRATION:
b. NUMBER:
c. TYPE: d. AMOUNT:
e. KIND OF AWARD: f. CUM. AMT.

18. RESOURCES ESTIMATE

FISCAL YEAR	a. PROFESSIONAL MAN YRS	b. FUNDS (In Thousands)
PREVIOUS 71	3.0	182
CURRENT 72	2.0	145

19a. RESPONSIBLE DOD ORGANIZATION
NAME: USA Rsch Inst Env Med
ADDRESS: Natick, Massachusetts 01760

RESPONSIBLE INDIVIDUAL
NAME: Jones, LeeRoy G. COL
TELEPHONE: 955-2811

19b. PERFORMING ORGANIZATION
NAME: USA Rsch Inst Env Med
ADDRESS: Natick, Massachusetts 01760

PRINCIPAL INVESTIGATOR (Provide Name if U.S. Academic Institution)
NAME: Goldman, Ralph F. Dr.
TELEPHONE: 955-2831
SOCIAL SECURITY ACCOUNT NUMBER:

ASSOCIATE INVESTIGATORS
NAME: Breckenridge, John R. Mr.
NAME: DA

20. GENERAL USE
Foreign Intelligence Considered

21. KEYWORDS (Provide Key Technical Terms and Security Classification Code)
(U) Environmental Tolerance; (U) Performance Limits; (U) Heat Stress; (U) Cold Injury; (U) Military Tactics

22. TECHNICAL OBJECTIVE, 23. APPROACH, 24. PROGRESS (Provide individual paragraphs identified by number. Precede text of each with Security Classification Code.)

23. (U) Develop mathematical equations and computer programs to synthesize available information on military task requirements with the interaction between the man and his clothing, equipment and environment, to predict mission performance capability and identify areas where additional information is necessary.

24. (U) Factors which affect the soldier's thermal exchanges with his environment and relevant military clothing and equipment characteristics, environmental parameters, physiological factors and mission requirements will be reviewed and tabulated. Predictive models of heat production and loss and limiting criteria, in terms of maximum work capacity as well as with reference to comfortable, tolerable or unsafe extremes of body heat storage or debt will be selected. A system for predicting individual and/or unit mission performance decrements or tolerance times will be developed from these models. These predictions of military performance limits will be validated by controlled physiological chamber and small scale field studies as well as by participation in appropriate field maneuvers. The results will guide military clothing design, suggest tactical doctrine and indicate potential environmental casualties.

25. (U) 70 07 - 71 06 Energy cost prediction equations have been extensively validated in controlled chamber studies, and terrain coefficients to fit swamp, sand, brush or other terrains have been developed. Formulation of very accurate prediction of rectal temperature response to work and rest in different environments, with varied clothing, now allows sound guidelines for necessary rest breaks to avoid heat exhaustion. Time shared computer terminal has been obtained and programming is being initiated. Adjust-

* Available to contractors only if contract security requirements for extended operations are being studied.

DD FORM 1 MAR 66 1498 PREVIOUS EDITIONS OF THIS FORM ARE OBSOLETE. DD FORMS 1498A, 1 NOV 68 AND 1498-1, 1 MAR 68 (FOR ARMY USE) ARE OBSOLETE

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Title of Study: Prediction of energy costs for the soldier

Investigators: R. F. Goldman, Ph.D., R. Soule, Ph.D. and B. Givoni, Ph.D.

The predictive equation presented last year, which predicts the caloric cost of marching, with or without well balanced loads at any speed, on any grade on a treadmill has been validated in further studies, on terrains other than treadmills. The suggested modifications for varying terrains indicated that the energy costs are increased by approximately 75% in a swamp, 50% in heavy brush, 25% in light brush and 10% on a dirt road, over energy costs on a treadmill. These terrain coefficients were found to be essentially independent of load weight, something that had not been anticipated. Furthermore, contrary to earlier published reports in the literature and a 1955 study from this laboratory, the energy cost for marching on a blacktop road was found to be essentially the same as that of walking on a treadmill. This apparent contradiction with earlier work was the subject of several additional independent studies which confirmed that in fact treadmill walking and blacktop walking produced essentially the same energy cost at a given speed.

Separate studies were carried out on the effect of multi-layer clothing on energy cost, since it had been suggested that there is a hobbling effect of clothing, which will increase energy cost beyond the cost increase demanded by the increased weight of such clothing per se. A seven-layer Arctic uniform was found to increase energy cost by 16% above the cost of carrying the equivalent weight on a waist belt. This finding was further validated in a subsequent study where subjects were asked to walk across a blacktop road, wearing the seven-layer system at two speeds which had previously been studied on the treadmill. It was found that using a blacktop terrain coefficient of 1.0 in the prediction equation, and adding 16% for the hobbling effect of the seven-layer clothing, as predicted from the chamber treadmill studies, predicted energy costs which were essentially identical with the measured values were obtained during this field study.

Future plans include a field study this summer to assess the validity of using the 425 kcal/hr ± 10% estimate for the self-paced energy expenditure at which a man will voluntarily work, in combination with these terrain coefficients, to predict the time it will take soldiers to cover a given distance across a specified terrain. Topographic maps will be studied to select one to three mile segments of each type

of terrain; using the predictive equations with the appropriate terrain coefficient, the energy cost of 425 kcal/hr will be used to predict the march rates which will be voluntarily adopted across each of these terrains. If successful, the predicted times to traverse each terrain should correspond closely with the actual times measured in this field study.

Title of Study: Voluntary march rate during extended operations

Investigators: R. Soule, Ph.D. and R. F. Goldman, Ph.D.

We have demonstrated that the soldier will tend to adjust his march rate for load and/or terrain condition so that his energy expenditure averages 425 kcal/hr ± 10%. However, such an energy expenditure has only been demonstrated to be valid as a limit for march rate when the man is relatively fresh. The question arises that during extended operations, the soldier may very well not continue to march at this 425 kcal/hr level. Accordingly, a chamber study has been designed to examine the validity of this voluntarily adopted 425 kcal/hr ± 10% energy cost of self-paced work concept when the men are fatigued. Subjects will be kept awake during a 36 hour period, and asked to march for a three mile distance once every six hours. The energy cost and the adopted march rate will be measured to assess the effect of extended operation.

Title of Study: Circadian rhythms of sweating and exercise

Investigator: L. F. Cipriano, Ph.D.

Studies on human tolerance in response to environmental stress have usually been conducted in the morning or early afternoon. Little information is available on the day-night differences of physiological responses to imposed environmental stresses. Data was collected in a staggered regimen that provided the subject's response to a heat stress challenge every three hours. Furthermore, the design allowed data pooling for four subjects during each of the 24 hours of the day. Oxygen consumption, sweat production, sweat rate and skin and rectal temperature measurements were taken both at rest and during the heat stress. Initial data analysis has revealed considerable variability in individual responses. Despite a general feeling that additional data collecting should be attempted before definitive conclusions are drawn, there appears to be no major variation in sweat production over a 24 hour period.

It appears that any minor changes that may subsequently prove to be statistically significant can nearly be explained by the underlying circadian body temperature rhythm. The circadian periodicity of sweat production, which may eventually be statistically validated, will have at most negligible effects on military task performance.

(83103)

RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY	1. AGENCY ACCESSION: DA OA 6145	2. DATE OF SUMMARY: 71 07 01	REPORT CONTROL SYMBOL: DD-DR&E(AR)636

3. DATE PREV SUM'RY	4. KIND OF SUMMARY	5. SUMMARY SCTY	6. WORK SECURITY	7. REGRADING	8. DISB'N INSTR'N	8a. SPECIFIC DATA-CONTRACTOR ACCESS	9. LEVEL OF SUM
70 12 31	D. Change	U	U	N/A	N/L	[X] YES [ ] NO	A. WORK UNIT

10. NO./CODES:	PROGRAM ELEMENT	PROJECT NUMBER	TASK AREA NUMBER	WORK UNIT NUMBER
a. PRIMARY	6.21.10.A	3A062110A827	00	047
b. CONTRIBUTING				
c. CONTRIBUTING	CDOG 141 (2a)			

11. TITLE (Precede with Security Classification Code) (U) Effects of Environmental Stressors on Military Performance: Interactions with Extended Operations, Unusual Activity-Rest Cycles (22)

12. SCIENTIFIC AND TECHNOLOGICAL AREAS: 002300 Biochemistry; 012900 Physiology; 013400 Psychology; 005900 Environmental Biology

13. START DATE	14. ESTIMATED COMPLETION DATE	15. FUNDING AGENCY	16. PERFORMANCE METHOD
70 07		DA	C. In-House

17. CONTRACT/GRANT
a. DATES/EFFECTIVE: N/A EXPIRATION:
b. NUMBER:
c. TYPE: d. AMOUNT:
e. KIND OF AWARD: f. CUM. AMT.

18. RESOURCES ESTIMATE		a. PROFESSIONAL MAN YRS	b. FUNDS (In thousands)
FISCAL YEAR	PRECEDING 71	4.3	226
	CURRENT 72	3.5	193

19. RESPONSIBLE DOD ORGANIZATION
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TELEPHONE: 955-2879
SOCIAL SECURITY ACCOUNT NUMBER
ASSOCIATE INVESTIGATORS
NAME: Shershow, John C. MAJ
NAME: Cahoon, Richard D. Dr. DA

21. GENERAL USE
Foreign Intelligence Not Considered

22. KEYWORDS (Precede EACH with Security Classification Code) (U) Continuous and sustained operations; (U) Activity-rest cycles; (U) Heat; (U) Cold; (U) Altitude; (U) Motor performance; (U) Fatigue, mental

23. TECHNICAL OBJECTIVE, 24. APPROACH, 25. PROGRESS (Furnish individual paragraphs identified by number. Precede text of each with Security Classification Code.)

23. (U) Rapid deployment of troops to desert, jungle, arctic or mountain areas may require simultaneous adjustment to the adverse climate as well as to unusual activity-rest cycles or periods of sustained sleep loss. Such combined stressors may limit combat effectiveness and cause performance decrements. Research will characterize these human limitations at biochemical, physiological and behavioral levels, and investigate methods of attenuating the effects on military personnel.

24. (U) Thus, the effects of these environmental stresses will be assessed at three levels: a. metabolic (amino acid metabolism and circadian periodicities); b. physiological (reflexes, motor performance and maximal physical work capacity); c. behavioral (sustained alertness, cognitive function, complex decision making, group interactions).

25. (U) 70 07 - 71 06 SLEEP DEPRIVATION: In mice prolonged sleep deprivation disrupted the periodicity of the important liver enzymes, tryptophan oxygenase and tyrosine aminotransferase. Plasma corticosterone levels indicated that sleep deprivation, particularly after 72 and 96 hours, evoked an intense adrenal response resulting in extremely high plasma hormone levels. Studies on the plasma amino acids, tyrosine and tryptophan, revealed that the aforementioned increases in enzyme activity may be limiting the availability of these amino acids for protein, hormone, and catecholamine synthesis. COLD EXPOSURE: Six human volunteer subjects were acutely exposed to cold for 2 days after a 5 day stabilization period. Blood and urine samples were collected serially to determine the effects of this stressor on amino acid metabolism. Results indicate that acute cold exposure disrupts the diurnal rhythmicity of plasma and urinary cortisol, plasma amino acids and plasma tyrosine. PSYCHOLOGICAL STRESS: An interdisciplinary study on performance in a stress situation and its relationship to catecholamine metabolism is in progress. Measurements of urinary metanephrine, normetanephrine, and other important central nervous system metabolites are now being made. This study will be transferred to ILIR funding work unit 023 in FY72

*Available to contractors upon originator's approval

DD FORM 1498, MAR 68 PREVIOUS EDITIONS OF THIS FORM ARE OBSOLETE. DD FORMS 1498A, 1 NOV 65 AND 1498-1, 1 MAR 68 (FOR ARMY USE) ARE OBSOLETE

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Title of Study: The Effects of Acute Cold Exposure on Circadian Periodicity in Man as Monitored by Alterations in Tryptophan Metabolism

Investigators: Ralph Francesconi, Ph.D., Aubrey E. Boyd, MAJ, M.D., Milton Mager, Ph.D.

Previous animal studies in this laboratory have documented the lability of selected liver enzymes, plasma amino acids and various hormones to environmental stressors, e.g. heat, cold, altitude. We have extended these studies to humans, to ascertain whether similar changes occur when man is acutely exposed to cold stress.

Six human test volunteers were maintained on a controlled liquid diet for a five day stabilization period. During the subsequent control period of two days, blood was taken prior to each meal (0700, 1200, 1700, 2200 hours), and three eight-hour urine samples (0700-1500, 1500-2300, and 2300-0700 hours) were collected daily. Following this the men were subjected to cold (56° - 57°F, shorts and stockings only) for 48 hours. The men were then returned to ambient conditions for a two-day recovery period with continued blood and urine collections. Plasma cortisol, total amino acids, tyrosine and tryptophan, and urinary cortisol, creatinine, kynurenic and xanthurenic acids, and amino acids were measured. Preliminary results indicate significant alterations in the daily AM-PM rhythmicity of plasma and urinary cortisol and plasma amino acids. Further human studies are proposed. The pivotal roles of tyrosine and tryptophan in catecholamine, serotonin, and protein synthesis, and the responsive characteristics of the factors controlling their metabolism, make these ideal for investigations involving stressors of importance to military operations, e.g. sleep deprivation, unusual activity rest cycles, and rapid transition of time zones.

Title of Study: Effects of sleeplessness, altered light-dark cycles, and multiple stresses on the daily periodicity of selected liver enzymes

Investigators: Ralph Francesconi, Ph.D., and Milton Mager, Ph.D.

Upon acute exposure to cold or altitude stress, naive mice responded with a hyperproduction of adrenal glucocorticoids which disrupted the periodicity of several liver enzymes as a result of increased protein synthesis. Within 48-72 hours after exposure, enzyme levels returned to normal and daily rhythmicities were reestablished. Thus, the effects of the stresses were maximal during the first 24 hours, and by 72 hours the finely regulated periodic oscillations were clearly evident. The metabolic importance of these enzyme-substrate systems, their extreme responsiveness, their naturally occurring daily rhythmicities, and the analogy between their control in animals and man continue to afford us an ideal tool to extend our studies of the effects of various stress situations on amino acid metabolism. In this study we have investigated the effect of sleep deprivation on the periodicity of metabolism of tryptophan and tyrosine.

Adult, male mice were deprived of sleep for up to 96 hours by isolation on corks surrounded by water. The animals were sampled at 12-hour intervals (0800-2000 hours - the minimum and maximum respectively of enzyme activity) for hepatic tyrosine aminotransferase (TAT), tryptophan oxygenase (TO), and their respective substrates tyrosine and tryptophan, in liver and plasma. Additionally, plasma corticosterone was estimated every 24 hours to ascertain the progressive degree of stress. Both enzymes demonstrated increased activities at each sampling interval. TAT maintained its daily periodicity, although with increased amplitude, through 60 hours of sleeplessness, then rose abruptly; TO levels were maximal at 12 and 96 hours, but its normal cyclicity pattern was disrupted as a result of increases in the normally low AM values. Hepatic concentrations of tryptophan decreased through 72 hours of sleep deprivation, while plasma levels increased. Alternatively hepatic concentrations of tyrosine increased while its content in the plasma was unaffected. Thus, sleep deprivation not only affects naturally occurring diurnal rhythms, but, if prolonged, effects an intensification of the generalized stress response possibly to the point of severely affecting amino acid availability.

These data should be applicable to parallel changes occurring in man while undergoing prolonged periods of sleep deprivation and/or continuous military operations.

Title of Study: Interaction of Environmental Extremes with Extended Operations, Unusual Activity - Rest Cycles

Investigators: Arlene Sampson and Stanley M. Halpin, Ph.D.

A pilot study to monitor group interaction during the study entitled, "The effects of acute cold exposure on circadian periodicity in man as monitored by alterations in tryptophan metabolism" has been completed. The effects of confinement in combination with cold stress and dietary control were expected to influence group behavior. Monitoring interactions in this situation afforded us the opportunity of testing tentative hypotheses, checking the feasibility of monitoring equipment, as well as gathering data and possibly discovering new dimensions of the confinement situation sensitive to variation.

Data was collected through unobtrusive monitoring with a remote control T.V. camera. A microphone was utilized to monitor verbal interactions. In addition subjects periodically filled out various rating scales. Apart from some minor technical problems, the T.V. monitoring yielded the desired data; the subjects had no objection to this form of monitoring. Further refinement of the activity check list and pilot work is in progress.

Title of Study: Interaction of Hypoxia and Carbon Monoxide on Human Performance

Investigators: James A. Vogel, Ph.D. and Malcolm A. Gleser, CPT, MC

Background:

Combat soldiers are often expected to perform heavy physical work under adverse situations. It has previously been shown that exposing men to high altitude (low ambient oxygen) reduces their capacity to do work. Exposure to carbon monoxide is similar to this in that it reduces the ability of the blood to carry oxygen to working muscles. Significant levels of carbon monoxide are found in tanks, troop carriers, fighting helicopters, and most commonly in heavy smokers especially in tense situations. It is not known to what extent carbon monoxide interferes with a soldier's capacity to work. Further, since these two forms of exposure can be combined in mountain operations, it is not known to what extent these two types of hypoxia will interact to decrement work capacity.

Progress:

In an initial study, physical work capacity was compared between hypoxias of equal severity produced by carbon monoxide, simulated high altitude and a combination of both. There was no difference in the resulting maximal work ability, i.e., the reduction in work capacity as compared to air controls was proportional to the reduction in arterial oxygen content in all cases.

In a second study, a complete analysis of oxygen delivery from the lungs to the tissue was made during rest and graded work up to maximal effort. While carbon monoxide did alter some qualitative aspects of oxygen delivery as compared to high altitude, it did not change the ultimate oxygen transport capacity which can be directly predicted from the level of arterial oxygen content.

Conclusions:

It has been concluded that the decrement in physical work capacity with hypoxia is a direct function of the decrease in arterial blood oxygen content, regardless of the type or source of the oxygen lack.

There is no evidence of an interaction between carbon monoxide and high altitude that would result in a reduced ability to do work other than that predicted by a simple additive function of the reductions in arterial oxygen content. Therefore, the physical performance of soldiers at high altitude in the presence of carbon monoxide could be predicted from the summation of the reduction in arterial oxygen content produced by each factor separately.

Title of Study: Performance in a stress situation and its relationship to catecholamine metabolism and affect state

Investigators: John G. Shershow, M.D., MAJ, MC; Allen Cymerman, Ph.D., and Sumner Robinson, Ph.D.

This study proposes to investigate the relationship of catacholamine metabolism to the performance of soldiers in a stress situation. It brings together several lines of research from both behavioral investigation and the biochemistry of behavior. Previous workers have shown that catacholamines, i.e., adrenalin, noradrenalin and their metabolites, are sensitive indicators of stress situations in both animal and human subjects. As an example of the significance of this, the antidepressant medications in psychiatry are thought to function by increasing the level of central noradrenalin in depressed patients. Little is known, however, of whether or not this mechanism applies to normal human subjects, specifically soldiers, under states of stress. Furthermore, recent investigations have clearly established in a variety of laboratory and field situations that high performance subjects can usually be characterized as high noradrenalin excretors, while low performers are low excretors of noradrenalin. Additionally, these high-performers tend to report much lower states of arousal and anxiety than the low excretors.

In this study, we will measure during a laboratory stress a central nervous system metabolite of noradrenalin, i.e. 3-methoxy-4-hydroxy phenylglycol (MHPG). In human urine we intend to: (a) Verify the high performer/high excretor, low performer/low excretor paradigm using an MHPG assay rather than the noradrenalin measurements which have been used by previous investigators, and (b) Test the hypothesis that MHPG measurement may be a useful way to differentiate high performance soldiers from low performance soldiers. This data may allow better assessment and conceivably pharmacologic prophylaxis of the man in the field undergoing stress.

To date we have been actively involved in setting up the assay procedure for the catacholamine compounds as well as devising and verifying the reliability and usability of a laboratory stressor. Pilot work with the stressor appears to indicate that it will be a useful, practical and sensitive instrument. As soon as we have run further reliability checks on our assay procedure, we will be in a position to begin to test the central hypotheses of the investigation.

(83104)

RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY

1. AGENCY ACCESSION	2. DATE OF SUMMARY	REPORT CONTROL SYMBOL
DA OA 6123	71 07 01	DD-DR&E(AR)636

3. DATE PREV SUM'RY	4. KIND OF SUMMARY	5. SUMMARY SCTY	6. WORK SECURITY	7. REGRADING	8. DISP'N INSTR'N	9a. SPECIFIC DATA - CONTRACTOR ACCESS	9. LEVEL OF SUM
70 12 31	D. Change	U	U	N/A	N/L	☒ YES ☐ NO	A. WORK UNIT

10. NO./CODES:	PROGRAM ELEMENT	PROJECT NUMBER	TASK AREA NUMBER	WORK UNIT NUMBER
a. PRIMARY	6.21.10.A	3A062110A827	00	048
b. CONTRIBUTING				
c. CONTRIBUTING	CDOG 141 (2a)			

11. TITLE (Precede with security classification code): (U) Biomedical Impact of Military Clothing and Equipment Design Including the Selection of Crew Compartment Environments (22)

12. SCIENTIFIC AND TECHNOLOGICAL AREAS:
013300 Protective Equipment; 022400 Bioengineering

13. START DATE	14. ESTIMATED COMPLETION DATE	15. FUNDING AGENCY	16. PERFORMANCE METHOD
64 01		DA	C. In-House

17. CONTRACT/GRANT
a. DATES/EFFECTIVE: N/A EXPIRATION:
b. NUMBER:
c. TYPE: d. AMOUNT:
e. KIND OF AWARD: f. CUM. AMT.

18. RESOURCES ESTIMATE	a. PROFESSIONAL MAN YRS	b. FUNDS (In thousands)
PRECEDING FISCAL YEAR 71	3.4	198
CURRENT FISCAL YEAR 72	2.0	174

19. RESPONSIBLE DOD ORGANIZATION
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ASSOCIATE INVESTIGATORS
NAME: Goldman, Ralph F. Dr.
NAME: DA

21. GENERAL USE
Foreign Intelligence Not Considered

22. KEYWORDS (Precede each with security classification code)
(U) Protection; (U) Biophysics; (U) Military Clothing; (U) Heat; (U) Cold; (U) Wind

23. (U) Investigate heat and moisture exchange in the Man-Clothing-Environment System, to provide a basis for improving thermal protection and recommending environments for crew compartments in military vehicles, and for increasing soldier effectiveness.

24. (U) Analysis of materials, uniforms and/or equipment items on heated "sweating" flat plates and copper manikins indicate the nature of changes in heat and moisture exchange produced by such items. Results provide guidance for military designers and identify stressful items or environments. These can be verified with soldiers under controlled chamber environments or in field studies.

25. (U) 70 07 - 71 06 Evaluations of experimental cold weather handwear, footwear and sleeping systems have been conducted for AMC developers. Insulating values have been measured on a 10% sample of molded insulated boots scheduled for field trials to provide a basis for assessing the effects of use on protection. Copper manikin studies show that a permanent press treatment does not increase the potential for heat stress in a fatigue uniform. Manikin measurements were also made on an Engineer Ordnance Demolition system, various types of cold weather face masks, and to assess liquid cooled and air ventilated distribution garments for tankers and other vehicle crewmen. Copper foot studies showed that a metal toe cap in a Navy work shoe did not reduce foot protection. Physical measurements showed that reflective layers in low-density clothing may increase protection by up to 50%, but that serious fabrication problems must be overcome to obtain this effect. Experiments with human subjects demonstrated the utility of electrically heated handwear for helicopter maintenance personnel at subzero temperatures and moderate wind speeds.

(Available to contractors upon originator's approval)

DD FORM 1 MAR 68 1498 PREVIOUS EDITIONS OF THIS FORM ARE OBSOLETE. DD FORMS 1498A, 1 NOV 68 AND 1498-1, 1 MAR 68 (FOR ARMY USE) ARE OBSOLETE

Title of Study: Design considerations of importance to the wearer of military clothing

Investigators: J. R. Breckenridge, G. Fonseca and H. Hanson

The conflicting requirements for clothing of minimum weight and cost and maximum insulation in the cold at rest, which simultaneously provides minimum impedance to heat loss from the working man, have frequently provided choices for the clothing developer which are insoluble. The unique techniques available at this Institute continue to provide highly detailed analyses of the effects of material choice and/or clothing design on the wearer, which help the AMC developer choose among his various options. Evaluations this past year have included new lightweight overboots (promising), over 30 new prototypes of sleeping bags (new materials appear promising, but launderability, flammability and compression recovery are problems), face masks in a variety of new designs (little real improvement here), new ventile materials which are water repellent, but not water vapor impermeable (a promising area), and proposed new CB protective materials (little improvement in terms of heat stress to the wearer).

A continuing ARIEM interest in improvement of cold weather protection, since available protective clothing for Arctic wear fails to provide adequate protection for the resting man, has produced significant information on the potential of reflective materials. An insulating "sandwich" made up of several layers of two ounce dacron batt between ripstop nylon inner surface and windproof outer surfaces, which has a normal insulated value of 2.3 clo units, can be increased to an insulation value greater than 3.5 clo by addition of three thin sheets (less than one mil each) of reflective insulation; comparable increases on the order of about 50% of insulation values can be shown across a wide range of insulating material by the addition of these reflective insulating layers. A major problem appears to exist in fabricating such "sandwiches" into practical clothing items since stitching the layers together dramatically reduces any benefits of the reflective layers. However, this area is being pursued in collaboration with the AMC Natick Labs, as it has one of the most promising potentials for improving cold weather clothing that we have seen to date.

Another major area of new research under this project deals with auxiliary heating. Previously, we have demonstrated the role of

heating the extremities with as little as three watts per hand and five watts per foot of auxiliary heat being sufficient to maintain an inactive man at -70°F in the face of ten mph winds, with relative comfort. Recent developments in liquid cooled and air ventilated distributing garments to be worn by tankers, aircrewmen, and other individuals not required generally to march in or otherwise carry the full weight of the conditioning equipment on their backs, are being studied. Such devices have definite applications within tanks, armored personnel carriers, under CB protective systems, etc., although their cost may render them unfeasible for general issue.

(83105)

RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY

1. AGENCY ACCESSION	2. DATE OF SUMMARY	REPORT CONTROL SYMBOL
DA OA 6146	71 07 01	DD-DR&E(AR)636

3. DATE PREV SUMRY	4. KIND OF SUMMARY	5. SUMMARY SCTY	6. WORK SECURITY	7. REGRADING	8a. GROUP MGT'N	8b. SPECIFIC DATA - CONTRACTOR ACCESS	9. LEVEL OF SUM
70 12 31	D. Change	U	U	N/A	N/L	☒ YES ☐ NO	A. WORK UNIT

10. NO./CODES:	PROGRAM ELEMENT	PROJECT NUMBER	TASK AREA NUMBER	WORK UNIT NUMBER
a. PRIMARY	6.21.10.A	3A062110A827	00	049
b. CONTRIBUTING				
c. CONTRIBUTING	CDOG 141 (2a)			

11. TITLE (Precede with Security Classification Code): (U) Prevention and Treatment of Disabilities Associated with Military Operations in the Cold (22)

12. SCIENTIFIC AND TECHNOLOGICAL AREAS: 012900 Physiology; 005900 Environmental Biology; 003500 Clinical Medicine

13. START DATE	14. ESTIMATED COMPLETION DATE	15. FUNDING AGENCY	16. PERFORMANCE METHOD
70 07		DA	C. In-House

17. CONTRACT/GRANT
a. DATES/EFFECTIVE: N/A EXPIRATION:
b. NUMBER:
c. TYPE: d. AMOUNT:
e. KIND OF AWARD: f. CUM. AMT.

18. RESOURCES ESTIMATE	a. PROFESSIONAL MAN YRS	b. FUNDS (In Thousands)
FISCAL YEAR 71 (PREVIOUS)	1.5	110
FISCAL YEAR 72 (CURRENT)	3.0	210

19. RESPONSIBLE DOD ORGANIZATION
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ASSOCIATE INVESTIGATORS
NAME: Goldman, Ralph F. Dr.
NAME: DA

21. GENERAL USE
Foreign Intelligence Considered

22. KEYWORDS (Precede EACH with Security Classification Code): (U) Cold Injury; (U) Frostbite; (U) Thermoregulation; (U) Microcirculation; (U) Acclimatization; (U) Performance Decrement; (U) Psychomotor Skills

23. TECHNICAL OBJECTIVE, 24. APPROACH, 25. PROGRESS (Furnish individual paragraphs identified by number. Precede text of each with Security Classification Code.)

23. (U) Measure and describe: the effects of localized and generalized cold exposure in inducing damage or reduced efficiency, the biological defenses which minimize, delay and repair the damage from the cellular level through the intact organism (soldier, animal, or model) and his military performance.

24. (U) A multi-faceted approach will emphasize: (1) actual or potential biochemical histological, and/or physiological changes associated with the site of cold injury; (2) techniques for initiating and strengthening natural defenses against the effects of cold (conditioning, acclimatization, indoctrination) and study of their practical limitations; and (3) types and extent of military performance adversely affected by cold (manual dexterity, target detection, vigilance, problem solving). Studies will use animal or human subjects, as appropriate.

25. (U) 70 07 - 71 06 Changes in frost nip susceptibility induced by changing body heat content and the effects of exercise were studied this year. Body heat storage was altered by pre-exposure to hot, cold, or comfortable conditions. It was anticipated that pre-exposure to heat would reduce susceptibility to frost nip and pre-exposure to cold would have the opposite effect by altering the blood circulation to the fingers. The results were contrary of what was expected; this is tentatively attributed to the skin wetness induced by the heat and skin dryness resulting from the cold. This work will be continued with dry versus wet finger exposures and the introduction of freezing moisture into the air stream. The effects of exercise on frost nip are equivocal, depending on when the exercise occurs, and further work is required.

*Available to contractors upon originator's approval

DD FORM 1 MAR 68 1498 PREVIOUS EDITIONS OF THIS FORM ARE OBSOLETE. DD FORMS 1498A, 1 NOV 65 AND 1498-1, 1 MAR 68 (FOR ARMY USE) ARE OBSOLETE

Title of Study: Factors in cold injury

Investigators: R. F. Goldman, Ph.D.; D. Fink, M.D., CPT, MC;
J. M. Witherspoon, M.D., CPT, MC and R. W. Newman, Ph.D.

Three tools have been refined to study responses of the human body to cold exposure: 1) Rapid whole body immersion in cold water, with analyses of the responses of skin and deep body temperature metabolic heat production, heart rate and blood pressure; 2) Direct calorimetry of heat loss from extremity, i.e., hand or foot, during water immersions; 3) Induction of a superficial frost nip in a finger exposed to high wind chill combinations of high wind and low temperature. Using these approaches singly or in combination, provides information both on factors altering surface heat loss and on factors altering heat input to the skin surface from within the body.

Studies this year have included changes in frost nip susceptibility induced by changing the body heat content, and the effects of exercise during frost nip exposure. Body heat storage was altered by having the subjects rest for one hour before the frost nip exposure in a hot room, a cold room, or in a comfortable environment as a control for the other two conditions. The anticipated response was that following the hot room exposure therewould be a reduced susceptibility to frost nip, associated with a greater circulatory heat input to the finger, and conversely, following the cold room exposure prior to frost nip, there would be an increased susceptibility to frost nip, as a result of a reduction in circulatory heat input to the finger; in fact, exactly the opposite occurred. The subjects had a greater susceptibility to frost nip following warm room temperature exposure than following cold room exposure. Analyses of factors which could have produced such an unexpected response leads to the conclusion that, while the average blood flow into the finger is of some significance, under the relatively acute and severe exposures for frost nip, vasoconstriction must occur fairly uniformly and early in the exposure. A major variable must now be recognized for which little evidence existed previously, i.e., the degree of skin wetness. The extent to which water is available in the skin appears to be a major factor in frost nip, i.e., conversion of tissue fluids to ice by crystallization in the skin. Pre-exposure to a cold room resulted in subjects with a relatively dry cuticle, whereas pre-exposure in the hot room resulted in men having a relatively saturated epidermis during the frost nip exposure challenge. These findings are being followed up with studies on initially wetted or initially

dried fingers, to confirm the relative contribution of skin wetness to frost nip susceptibility. In addition, the instrumentation for frost nip is being modified so that we can inject freezing moisture into the air stream to study this aspect of skin wettedness in freezing cold injury.

The effects of exercise on frost nip are equivocal. There are significant differences in the circulatory heat input to a finger if the exercise begins before, during or toward the end of the frost nip challenge. Further work is required on this subject.

(83106)

RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY

1. AGENCY ACCESSION	2. DATE OF SUMMARY	REPORT CONTROL SYMBOL
DA OA 6147	71 07 01	DD-DR&E(AR)636

3. DATE PREV SUMRY	4. KIND OF SUMMARY	5. SUMMARY SCTY	6. WORK SECURITY	7. REGRADING	8A. USER'N INSTR'N	8B. SPECIFIC DATA CONTRACTOR ACCESS	9. LEVEL OF SUM
70 12 31	D. Change	U	U	N/A	N/L	☒ YES ☐ NO	A. WORK UNIT

10. NO./CODES:	PROGRAM ELEMENT	PROJECT NUMBER	TASK AREA NUMBER	WORK UNIT NUMBER
a. PRIMARY	6.21.10.A	3A062110A827	00	050
b. CONTRIBUTING				
c. [illegible]	CDOG 141 (2a)			

11. TITLE (Procede with Security Classification Code): (U) Prevention and Treatment of Disabilities Associated with Military Operations in the Heat (22)

12. SCIENTIFIC AND TECHNOLOGICAL AREAS: 016200 Stress Physiology; 013400 Psychology; 003500 Clinical Medicine

13. START DATE	14. ESTIMATED COMPLETION DATE	15. FUNDING AGENCY	16. PERFORMANCE METHOD
70 07		DA	C. In-House

17. CONTRACT/GRANT
a. DATES/EFFECTIVE: N/A EXPIRATION:
b. NUMBER:
c. TYPE: d. AMOUNT:
e. KIND OF AWARD: f. CUM. AMT.

18. RESOURCES ESTIMATE	a. PROFESSIONAL MAN YRS	b. FUNDS (In thousands)
FISCAL YEAR PRECEDING 71	4.6	216
FISCAL YEAR CURRENT 72	6.5	273

19. RESPONSIBLE DOD ORGANIZATION
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20. PERFORMING ORGANIZATION
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PRINCIPAL INVESTIGATOR (Furnish SSAN if U.S. Academic Institution)
NAME: Fine, Bernard J. Dr.
TELEPHONE: 955-2853
SOCIAL SECURITY ACCOUNT NUMBER:

ASSOCIATE INVESTIGATORS
NAME: Mager, Milton Dr.
NAME: King, Allen B. MAJ DA

21. GENERAL USE
Foreign Intelligence Not Considered

22. KEYWORDS (Procede EACH with Security Classification Code): (U) Heat Stress; (U) Heat Tolerance; (U) Heat Disabilities; (U) Body Temperature; (U) Military Disabilities

23. TECHNICAL OBJECTIVE, 24. APPROACH, 25. PROGRESS (Furnish individual paragraphs identified by number. Procede text of each with Security Classification Code.)

23. (U) The objectives are the identification, prediction and prevention of heat-induced disabilities which critically impair the performance of military missions and the development of methods of treatment of casualties due to such conditions as dehydration, heat stroke and heat exhaustion collapse.

24. (U) The knowledge and techniques of relevant sciences and clinical medicine are applied to the solution of problems of military operations in hot environments. Approaches include: (a) assessing and predicting performance of tasks, e.g., vigilance, march rate, in heat; (b) determining effects of heat on biophysical, physiological, biochemical and psychological functioning; (c) defining effects of such factors as solar load, clothing and equipment interference and soldier's work requirements on his tolerance limits; and (d) studying methods of prevention and treatment of heat casualties, and improving their applicability in military situations.

25. (U) 70 07 - 71 06 (1) Limited epidemiological data indicated that not only was incidence of heat injury at a training base related to intensity of heat stress but also to preventive measures instituted by training cadre; (2) a pilot study (37 soldiers) to determine correlation of fibrinolytic activation with clinical states of injury indicated that intravascular clotting and plasminogen activation occurred with increasing frequency and intensity as severity of heat injury increased; (3) a strong effect has been shown for CO_2 in mediating sweat production. Reduction in blood flow to the skin mediated by hyperventilation-induced hypocapnia, appears to be responsible for an increase in core temperature noted in soldiers exposed to heat; (4) prediction of rectal and body temperature responses has been extended to include percent wettedness of the skin, which has been shown to be significantly related to hot weather comfort. It is now possible to predict those changes in clothing design, air motion and work rate which will significantly change the comfort of the soldier.

*Available to contractors [illegible]

DD FORM 1 MAR 68 1498 PREVIOUS EDITIONS OF THIS FORM ARE OBSOLETE. DD FORMS 1498A 1 NOV 68 AND 1498-1, 1 MAR 68 (FOR ARMY USE) ARE OBSOLETE

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Title of Study: Epidemiological study of heat stress illnesses

Investigator: George A. Beller, MAJ, MC

Background:

The reason for the present study was to acquire clinical experience in the management of heat casualties and to gather pertinent data concerning the epidemiology, clinical manifestations, and prevention of heat injuries.

Progress:

This study was performed during the month of July 1970, at Ft. Polk, Louisiana. All patients admitted to the heat ward were seen by the ARIEM research team to whom responsibility for primary medical care and in-patient management was delegated.

Conclusions:

During that month, 43 patients with heat stress illnesses were seen on the heat ward. Experience was acquired by the ARIEM physicians in the clinical evaluation and management of these patients. Limited epidemiologic data was collected and compared with similar data acquired the previous summer. It appears that the incidence of heat injuries is primarily related to the intensity of heat stress as represented by the WBGT index and to the preventive measures instituted by the training cadre. Heat stroke is a fortunately rare occurrence but in the Ft. Polk experience not necessarily associated with a great morbidity or any mortality.

Future Plans:

None.

Title of Study: The correlation of fibrinolytic activation with clinical status in heat injury

Investigator: Redmond P. Hogan, MAJ, MC

Background:

Diffuse bleeding is a frequent clinical complication of heat stroke. The hemorrhagic diathesis which occurs in this setting is known to result from activation of the fibrinolytic system, although it has not been shown whether primary fibrinolysis or generalized intravascular coagulation with secondary fibrinolysis is responsible for the clinical picture. Neither is it known to what extent vascular permeability changes may contribute to the symptom complex comprising heat stroke; but edema, petechiae, and hemorrhage are common pathological findings in many organs at autopsy.

The greater sensitivity of recently introduced assays for fibrinogen degradation products now allows detection of subclinical fibrinolytic activity. It is therefore a possibility that patients with less severe forms of illness caused by excessive body heat may also have elevated levels of fibrinogen degradation products. If this is true, the quantitation of these products may prove valuable clinically in establishing a diagnosis of heat injury, in formulating prognoses in proven cases, and in following the course of illness. The early warning afforded by these tests might allow the forestalling of severe complications through more timely initiation of therapy.

Progress:

The study was designed to examine blood from all patients admitted to the heat ward in Ft. Polk, Louisiana from June 17 to July 17, 1970. Their clinical status was assessed to allow categorizing the extent of the heat injury. The presence of active intravascular clotting was assessed by the ethanol gelation test and the state of plasminogen activation with resulting fibrinolysis was assessed by the staph clumping test. The observations indicated intravascular clotting and plasminogen activation occurred with increasing frequency and intensity as the severity of the heat injury increased.

Conclusion:

Although it was difficult to attach statistical significance to the results because of the low number of subjects (37), it does indicate further studies may be of value in determining the importance of intravascular clotting in the pathogenesis of heat injury.

Future Plans:

(1) To evaluate the effects of heat exposure in normal man without clinically detectable heat illness. (2) To evaluate in animal models the relationship of heat stroke and coagulation changes.

Title of Study: The role of hyperventilation in man's response to heat

Investigators: Sumner M. Robinson, Ph.D. and Allen B. King, MAJ, MC

Background:

Hyperventilation is a frequent accompaniment to situations of severe heat stress. It is not clear whether hyperventilation is primarily a result of heat stress or has an important causative role in the hyperthermia associated with exposures to extremes of heat. If such hyperventilation does have a role in causing a greater degree of hyperthermia, this could have important military consequences since the military situation, particularly in combat, is in itself an anxiety-producing situation which can cause hyperventilation apart from any heat exposure; and of course, there is a frequent need to perform moderate to heavy work in the heat, a situation which naturally increases the volume of air breathed. Thus, the military situation is replete with hyperventilatory stimuli when a soldier is in the heat such that there could be either a synergism or possibly a potentiation of the various causes of hyperventilation, to the detriment of the soldier's thermoregulatory mechanism.

Progress:

Chamber experiments were performed to test the hypothesis that hypocapnia (i.e. excess loss of carbon dioxide) rather than hyperventilation *per se* could cause hyperthermia. It was noted that hyperventilation indeed does cause an increase in core temperature in men exposed to 105°F and 10% relative humidity. The hyperthermia was not related to the extra energy cost of breathing, but rather to the hypocapnia accompanying the hyperventilation. This hypocapnia was associated with a fall in blood flow to the skin and a transient decrease in sweat rate. The changes in skin blood flow appear to be the prime cause for the observed temperature elevation. Future experiments will be designed to explore the various mechanisms that underlie the above descriptive findings.

Title of Study: Effects of heat on target location and detection: Heat balance analysis and target detection during thermal transients

Investigators: Bernard J. Fine, Ph.D., Joseph J. Fleishman, CPT, MSC, and John M. Witherspoon, MAJ, MSC

Background:

This study uses precise physiological measurements to study physiological-psychological relationships and interactions related to the perception of targets in the heat.

Despite its military importance, target detection performance in the heat does not appear to have been studied. However, studies of tracking in the heat indicate that decrements occur, particularly in peripheral vision. Similar effects have been noted at altitude and in studies involving non-thermal stress. Thus, peripheral decrements may be a response to stress, in general.

Noting (1) that perceptual decrements occur with heat and altitude stress and with non-thermal stress, (2) that hyperventilation occurs in all three stress situations, and (3) that the symptoms of "altitude sickness", "heat syndrome" and those associated with non-thermal stress appear to be remarkably similar, hypocapnia should be considered as a possible factor common to all of these situations. This is particularly true since minute changes in brain CO_2 levels have been shown to have marked effects on brain EEG patterns, which, in turn, may be related to level of perceptual functioning. Therefore, in this study, CO_2 levels were manipulated to determine the extent to which the physiological and psychological behaviors could be modified.

Progress:

Eighteen S_s, three per week, were exposed for approximately two hours daily to a fixed schedule of events including a target detection task and exercise (bicycle ergometer). Each S was tested on three "experimental" days after two days of intensive practice on the detection task. One experimental day was a control day (25°C, 50% R.H.) and two were heat days (50°C, 20% R.H.). On one of the heat days, S_s

breathed CO_2 at a critical point in the exposure. The sequence of the three days was changed each week according to a Latin Square procedure.

On a typical day, baseline physiological and detection measures were taken at rest in a neutral environment. S_s were then taken quickly into a hot chamber (neutral on control day). There, resting measurements were taken again. This was followed by an exercise period at about 40-50% VO_2 max. Immediately following exercise, S_s were again tested on the detection task. Depending on the day, CO_2 replacement occurred immediately following cessation of exercise, continuing during the subsequent detection task.

Physiological measures included: 11-point skin temperatures, rectal and tympanic membrane temperatures, heart rate, mixed expiratory O_2 and CO_2, end-tidal volume CO_2, respiratory rate and volume, and continuous body weights. Visual stimuli consisted of color slides, each containing a military target, e.g., tank, jeep, soldier, concealed to varying degrees in natural terrain backgrounds. Suitable equipment recorded elapsed time for target location for each slide.

Preliminary analyses indicate no overall effect of heat on target detection; half of the S_s improved in the heat and half showed decrements in detection performance. The direction of heat-induced change appears to be related to S_s' scores on a perceptual test tapping ability to discriminate figure from background (a standard test of field dependence).

Preliminary results on the effect of post-exercise hyperventilation on sweating indicate that hyperventilation was demonstrated in the post submaximal period by high ventilatory equivalents and falling alveolar PCO_2 levels, persisting at least for 30 minutes. Hyperventilation was severe enough to inhibit sweating, as measured by continuous evaporative weight loss measurements. CO_2 replacement improved sweating by increasing skin temperatures and increasing sweat production, but had little immediate effect on central body temperature.

Future Plans:

Analysis is continuing on the separate and interactive effects of heat stress on the physiological and psychological measures obtained.

Title of Study: Prediction of tolerance time for military operations in the heat

Investigators: Ralph F. Goldman, Ph.D., John M. Witherspoon, MAJ, MC, and Leander A. Stroschein

The work reported last year on the development of a prediction equation for rectal temperature response to any combination of uniform, temperature and humidity, and work rate has been extended to include the effects of varying work-rest cycles, of changing environmental conditions during the rest exposures and of gross differences in the relative fitness of the subjects.

Prediction of rectal temperature and body temperature responses has been extended to include estimation of the percent wettedness of the skin. This latter parameter has been shown to be significantly related to comfort in hot weather and affords for the first time, an opportunity to predict in advance those changes in clothing design, air motion, or work rate, which will significantly change the comfort status of the soldier; previously our capabilities were limited to prediction of tolerance or approaching tolerance limits. This new capability of predicting comfort should significantly contribute to the AMC development program.

Study of the interaction with body composition and physical fitness of the subjects was undertaken because field maneuvers in which USARIEM participated, had failed to show the anticipated differences in physiological responses to working in the heat expected between significantly overweight subjects or fit subjects. Studies conducted this past year have demonstrated that the failure to demonstrate differences in the field is a result of a type of self pacing. When subjects are forced, by working on a treadmill at a set speed, to work at a given rate than the predicted differences between fit and unfit subjects occur as both a function of weight difference and the relative differences in subcutaneous insulation. However, when the volunteers are free to adjust their work rate, as they were in the field maneuvers and in specially designed studies conducted this past year at the Institute, then very obviously the fatter subjects and those less physically fit do adjust their work rate, i.e. heat production, so that although their temperature responses measured during the

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operation do not significantly differ from those of fit subjects, their time to complete a march of a given distance is significantly different and/or they tend to select significantly easier portions of the trail to traverse, thus keeping their energy expenditure below that of their fitter companions.

Separate studies have been conducted on the effects of physical conditioning per se, and of state of acclimatization per se on the prediction of tolerance responses of troops. Data analysis of the results of these studies is continuing. However, it is quite evident that physical conditioning alone does significantly increase sweat production during subsequent heat exposures. In addition, a strong affect has been shown for carbon dioxide in mediating sweat protection, with hyperventilation and a reduction therefore in circulating blood levels of carbon dioxide, significantly reducing sweat protection.

(83107)

RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY

1. AGENCY ACCESSION	2. DATE OF SUMMARY	REPORT CONTROL SYMBOL
DA OA 6148	71 07 01	DD-DR&E(AR)636

3. CITY MARY SUMRY	4. KIND OF SUMMARY	5. SUMMARY SCTY	6. WORK SECURITY	7. RESEARCH	8. PRIM'N INSTN	8a. SPECIFIC DATA-CONTRACTOR ACCESS	9. LEVEL OF SUM
70 12 31	D. Change	U	U	N/A	N/L	[X] YES [ ] NO	A. WORK UNIT

10. NO./CODES	PROGRAM ELEMENT	PROJECT NUMBER	TASK AREA NUMBER	WORK UNIT NUMBER
a. PRIMARY	6.21.10.A	3A062110A827	00	051
b. CONTRIBUTING				
c. [illegible]	CDOG 141 (2a)			

11. TITLE (Procede with Security Classification Code): (U) Prevention and Treatment of Disabilities Associated with Military Operations at High Terrestrial Elevation (22)

12. SCIENTIFIC AND TECHNOLOGICAL AREAS: 012600 Pharmacology; 005900 Environmental Biology; 013400 Physiology

13. START DATE	14. ESTIMATED COMPLETION DATE	15. FUNDING AGENCY	16. PERFORMANCE METHOD
70 07		DA	C. In-House

17. CONTRACT/GRANT
a. DATES/EFFECTIVE: N/A EXPIRATION:
b. NUMBER:
c. TYPE: d. AMOUNT:
e. KIND OF AWARD: f. CUM. AMT.

18. RESOURCES ESTIMATE	a. PROFESSIONAL MAN YRS	b. FUNDS (In thousands)
PRECEDING FISCAL YEAR	71	3.8	265
CURRENT FISCAL YEAR	72	4.7	282

19. RESPONSIBLE DOD ORGANIZATION
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SOCIAL SECURITY ACCOUNT NUMBER:

ASSOCIATE INVESTIGATORS
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NAME: Kobrick, John L. Dr. DA

21. GENERAL USE
Foreign Intelligence Not Considered

22. KEYWORDS (Procede EACH with Security Classification Code): (U) Hypoxia; (U)Disabilities; (U)Performance; (U)Mountain Sickness; (U)Combat Effectiveness; (U)Pharmacology; (U)Vision; (U)Sensory Processes

23. TECHNICAL OBJECTIVE. 24. APPROACH. 25. PROGRESS (Furnish individual paragraphs identified by number. Procede text of each with Security Classification Code.)

23. (U) Exposure of soldiers to high terrestrial elevation results frequently in reduced efficiency as well as disabilities which are incompatible with the successful completion of military operations. The purpose of this unit is to investigate methods of prevention and treatment of these performance decrements and disabilities.

24. (U) Studies will be conducted in animals and man to (1) determine the mechanisms of the disorders which occur at altitude; (2) assess and predict the performance of perceptual and cognitive tasks, e.g., target detection, decision making, speed of reaction; (3) evaluate the efficacy of pharmacological agents in preventing or reducing performance decrements and illness; (4) enhance the rate of adaptation to this environment.

25. (U) 70 07 - 71 06 Animal - Although evidence of ultrastructural changes was present, no depression of myocardial contractile function could be demonstrated in the rat as a result of chronic exposure to hypobaric hypoxia. Human - A functional relationship established for cardiac output and oxygen consumption enables quantitation of the effects of reduced blood oxygenation at altitude, as well as differences in physical training and sex. Observations in the hypobaric facility have been confirmatory of a field study report (1968) in showing an inverse relationship between the severity of acute mountain sickness (AMS) and the alveolar CO_2 tension. Failure to increase ventilation at altitude is related to hypoxic sensitivity, while the headache of AMS appears to originate from the extracranial circulation. Impairments in peripheral vision, flicker fusion, dark adaptation and decision making induced by acute hypoxia show subsequent improvement; the time course bears no relationship to AMS. Both auditory and visual vigilance are decremented by hypoxia, suggesting disruption of a common central process.

* (Available to contractors upon originator's approval)

DD FORM 1 MAR 68 1498 PREVIOUS EDITIONS OF THIS FORM ARE OBSOLETE. DD FORMS 1498A, 1 NOV 68 AND 1498-1, 1 MAR 68 (FOR ARMY USE) ARE OBSOLETE

Title of Study: Myocardial function and ultrastructure in chronically hypoxic rats

Investigators: J. T. Maher; A. L. Goodman; W. D. Bowers; L. H. Hartley; LTC, MC; and E. T. Angelakos

Background and Rationale:

Cardiac output and stroke volume decrease in man consequent to prolonged exposure to high altitude. Previous studies have shown that the reduction of stroke volume is not a result of altered blood pH, pulmonary hypertension and right ventricular overload, depletion of myocardial norepinephrine stores, diminished sympathetic nervous activity, or reduction in blood volume and ventricular filling pressures. The findings suggest that myocardial function may be depressed by hypoxia secondary to lowered coronary arterial oxygen tension, reduced coronary blood flow, or both.

Moreover, morphological studies at the ultrastructural level on cardiac muscle from animals chronically exposed to high altitude have shown marked differences from sea-level controls. The alterations described include mitochondrial enlargement usually with a reduction in the number of cristae and in matrical density, dilation of the cisternae within the sarcoplasmic reticulum, and separation of the myofilaments. These disruptive changes in fine structure of the myocardium further suggest an accompanying functional decrement.

Progress:

Experiments were designed and performed to determine whether the decrease in stroke volume and ultrastructural damage observed following chronic hypoxic exposure are associated with alterations in intrinsic myocardial contractility. Myocardial function was studied in isolated cardiac muscle from 10 rats exposed to a simulated altitude of 5800 meters for 24 days (Hy) and compared with those of 9 weight-matched (WM) and 7 age-matched (AM) controls. Left ventricular columnae carneae were suspended in a chamber containing oxygenated Krebs solution at 30°C and were stimulated at a frequency of 30 per minute. The velocity of shortening at the lightest load (0.5 g/mm^2) did not differ significantly among groups (Hy = 2.09 ± .12, WM = 2.07 ± .10, AM = 2.02 ± .23 muscle lengths/sec). Peak isometric tension was likewise similar in muscles from the three groups (Hy = 2.64 ± .25, WM = 2.54 ± .23, AM = 2.58 ± .32 g/mm^2), as was passive compliance. However, both time from onset to

peak tension development and latency were significantly ($p < .05$) prolonged in Hy rats. Neither ventricular norepinephrine (NE) content nor inotropic responsiveness to exogenous NE showed significant group differences. Electron microscopic examination of the myocardium from Hy animals revealed structural alterations in the capillaries with marked swelling of the endothelia cells.

Summary and Conclusions:

Although evidence of ultrastructural changes was present, no depression of myocardial contractile function could be demonstrated in the rat as a result of chronic exposure to hypobaric hypoxia. The ventricular myocardium of Hy rats responded to the chronic increased work load by an increase in myocardial mass. Since cardiac hypertrophy is predominantly the result of an enlargement rather than a multiplication of myocardial cells, it has been suggested that this response may be detrimental since it must increase diffusion distances for metabolites. Although no depression of contractile function was herein demonstrated, this finding is not necessarily inconsistent with the above-mentioned thesis since the time to peak tension (TPT) was altered in the isometrically contracting muscles from Hy rats. This finding suggests that, although the maximum intensity of the active state remains unchanged, its duration is prolonged. It is conceivable, therefore, that the maximum force which the Hy muscle was capable of developing was preserved by employment of a compensatory mechanism, viz., an increase in TPT.

Future Plans:

None

Title of Study: The effect of isolated hemodynamic variables on cardiac output

Investigators: R. P. Hogan, MAJ, MC, and L. H. Hartley, LTC, MC

Background:

The ability of man to perform physical work is adversely affected by a decrease in cardiac output which occurs on prolonged exposure to high altitude. The purpose of this study is to define changes in a number of variables that may be contributing to this decrement in cardiac output. Specifically, the variables to be examined are: (1) blood viscosity, (2) filling pressure of the ventricle, (3) oxygen carrying capacity, (4) peripheral resistance, (5) heart rate, and (6) myocardial contractility.

The experimental animal will be the anesthetized dog. Eight dogs will be studied. They will be anesthetized and, under pressure monitoring, catheters will be placed in various heart chambers. Cardiac output will be done by dye dilution. The following measurements will be made: arterial pressure, arterial gases, cardiac output, left ventricular pressure, left ventricular dP/dt, hemoglobin, and blood viscosity in a capillary viscometer. Heart rate will be paced at 160/min. The filling pressure will be changed with infusion of whole blood and arterial pressure will be changed with the infusion of phenylephrine. These measurements will be repeated after each arterial and filling pressure change.

The animals will then be repaired surgically and taken to 14,000 feet altitude for seven days, and the studies will be repeated in the altitude chamber.

Progress:

Pilot studies have been done on anesthetized animals and all methods are functioning well.

Conclusions:

The study is feasible and should permit the questions being examined to be answered with the described techniques.

Further Plans:

The study will be performed in the summer of 1971.

Title of Study: The differential effects of high altitude hypoxia and hypocarbia on the renin-aldosterone system

Investigators: R. P. Hogan, MAJ, MC; L. H. Hartley, LTC, MC; T. A. Kotchen, MAJ, MC

Background:

Exposure of man to high altitudes results in decreases in plasma and interstitial fluid volumes and a probable increase in intracellular volume. Concomitantly there is an increase in plasma renin, but aldosterone secretion and excretion rates are paradoxically decreased, resulting in an elevation of total body potassium. A respiratory alkalosis ensues upon arrival at high altitude, and this gradually becomes renally compensated over the next several days, with normalization of arterial pH, but continued depression of P_{CO_2}.

Previous investigations have dealt with the possibility of a connection between respiratory alkalosis and the symptoms of acute mountain sickness, and conclusions have generally been that correction of pH ameliorates, but does not eliminate symptoms. Studies in which P_{CO_2} has been controlled have employed face masks, and have, therefore, been of short duration, and hypoxia has been intermittent.

Because there tends to be a correlation between the onset of symptoms of acute mountain sickness and the rates of change of extracellular fluid volume, total body potassium, and P_{CO_2}, there is reason to investigate the possible role which the latter factors may play in the etiology of acute mountain sickness. Further interrelating these variables is the fact that both alkalosis and elevated total body potassium are capable of causing fluid shifts into the intracellular space.

In this context, it should be of interest to investigate the interrelationships between the renin-angiotensin-aldosterone system, body fluid and electrolyte balance, and the hypoxia and hypocarbia which occur at altitude.

Progress:

The outline of the study is as follows: A total of six subjects will be used. They will be confined for 4 days at sea level, 3 days at simulated 4,000 meters altitude in the hypobaric chamber, and 2 days at

sea level again for recovery studies. This study will then be repeated, but CO_2 will be added to the chamber atmosphere during the simulated altitude to ensure an alveolar PO_2 equal to the first confinement, and a PCO_2 equal to sea level controls. Hence, they will be studied once in hypoxia and repeated with hypoxia and normocapnia, both altitudes of which can be compared not only with the other, but with sea level.

Measurements to be made include alveolar CO_2 and O_2, weight, HR, temperature, aldosterone excretion rate, and plasma renin levels at appropriate intervals. Blood and urine studies will be performed to allow determination of water and electrolyte balance.

Five subjects have been studied at altitude without added CO_2, and two of those five have been studied at altitude with added CO_2. All methods and procedures have been tested.

Conclusions:

(1) It is feasible to add CO_2 and adjust altitude to provide hypoxic and hypoxic normocapnia conditions. (2) The decreased aldosterone excretion observed at altitude is the same with and without added CO_2. (3) There are indications that symptoms are less in CO_2 than altitude alone. (4) The physiological effects of adding CO_2 are equivalent to lowering the altitude 4,000 feet, by virtue of greater pulmonary ventilation and higher blood O_2 content.

Future Plans:

In Fall, 1971, studies will be resumed to complete the full study as described in six subjects.

Title of Study: The effects of chronic hypoxia upon myocardial performance

Investigators: L. H. Hartley, LTC, MC; J. A. Vogel, Ph.D.; L. G. Jones, COL, MC; R. P. Hogan, MAJ, MC

Background, Rationale and Approach:

Physical performance of man is reduced after exposure to hypoxia. This can be quantitated by noting the decrease in the maximal oxygen uptake after acute and chronic hypoxia. Acutely, maximal oxygen uptake is decreased because of a decrease in arterial oxygen content. However, chronically, maximal oxygen uptake is reduced because of a decrease in stroke volume of the heart. It would appear, therefore, that some direct effect of the hypoxia upon the myocardium could be causing subnormal performance and as such could be a major contributor to the decrease in working capacity which occurs at high altitude. Studies on humans have indicated that the lower blood volume does not seem to explain the decreases observed because the decrease in stroke volume cannot be corrected by infusing dextran and returning filling pressure to normal. This suggests that there has occurred some alteration at the myocardial level which has an adverse effect upon the sea level man who is performing at high altitude. The present study was designed to elucidate these changes in order to determine if the stroke volume of the heart might be restored by pharmacological means. However, a precise understanding of the reasons for the decrease in the first place are necessary in order to determine what interventions might be beneficial. In this study the myocardial function of the heart in the intact animal was studied by construction of a "ventricular function curve". In this way direct assessment of the function of the myocardium is possible. As an additional study the papillary muscle of the right ventricle in the cat is also being studied to determine if changes in the contractile properties of the heart are altered even when the myocardium is removed from its usual environment.

Progress:

Seven mongrel dogs were studied at sea level and after 7 days of hypobaric hypoxia equal to 15,000 feet altitude. Two weeks prior to the study an arterial catheter, venous catheter, pulmonary arterial electromagnetic flow probe, atrial pacing electrode, and left ventricular transducer were chronically implanted. Prior to the induction of hypoxia and after 7 days of hypoxia, each animal underwent a series of studies. These included the measurement at ambient heart rate and at paced heart

rate (170) cardiac output (flow probe or dye dilution), arterial pressure, left ventricular pressure, and left ventricular dP/dt. These studies were repeated after infusing dextran to increase left ventricular end diastolic pressure at increments of 5 mm Hg until 500 ml were injected. At each increment the paced and unpaced hemodynamic studies were repeated. The principal point under study was the change in stroke work for any filling pressure before and after chronic hypoxia.

Conclusions:

A definite reduction in left ventricular work occurred after hypoxia. At a 15 mm Hg left ventricular end diastolic pressure, the mean product of stroke volume and aortic mean pressure was 5820 at sea level and 4750 at altitude ($p < .05$). However, the cachectic state of the animals and complications of their chronic implants has cast doubt upon hypoxia being the sole factor operative in the study.

Future Plans:

The dog study will be repeated with acute catheterization of animals before and during chronic hypoxia, and after recovery from hypoxia.

Title of Study: Acute mountain sickness and the role of carbon dioxide

Investigator: Milton Landowne, M.D.

Subjects studied in the hypobaric facility have demonstrated an inverse relation between the severity of acute mountain sickness and alveolar CO_2 tension, in confirmation of the field study report of 1968. In these subjects a procedure for assessing ventilatory response to CO_2 at sea level yielded a deducible, but inconclusive relationship between responses and the severity of the symptoms induced by exposure to simulated altitude. Variability was large. To reduce this and to improve specificity, we have undertaken to add control of alveolar CO_2 and O_2 tension to the test procedure and establish its reproducibility.

Title of Study: The relationship of cardiac output and oxygen uptake during exercise, maximal oxygen uptake and the influence of hypoxia and physical training

Investigator: Milton Landowne, M.D.

Optimal physical performance is of prime importance to the infantry man, particularly under environmental conditions of altitude and/or additional work loads. This research seeks to understand and identify the factors which determine, limit or improve performance. Further clarification of the relationships between muscular work, oxygen consumption and circulatory function has been attained by interpretative analysis of our cardio-respiratory experiments, and the data of other workers. The approach provides a means of evaluating the performance of individuals as well as groups under differing conditions. It may be used to make comparisons even when the relative or absolute work loads, or other reference measure to be compared, are not the same. It has the further potential advantage that it may not be necessary to test subjects at strenuous or maximal levels of exercise. The most satisfactory relationship we have derived thus far, while not completely appropriate from a theoretical viewpoint, is based upon the fact that increased oxygen uptake is achieved by increases (1) in the rate of blood flow through muscle and (2) in the fraction of oxygen extracted from the blood, up to the respective virtual limits of maximal muscular vascular dilatation, and of complete extraction of oxygen from arterial blood.

I. We have established that the relation between cardiac output ($\dot{Q}$) and oxygen uptake ($\dot{V}O_2$) is curvilinear and may be aptly described for many individuals as $VO_2 = AQ + (e^{-C\dot{Q}}-1)\ B/C$, where A relates to arterial O_2 content and C to the rate of increase in extraction fraction with increasing flow. This has enabled us to describe (see Summary Table) and understand "normal" performance, the effects of acute hypoxia (altitude), of physical training, and sex differences.

On acute exposure to simulated altitude, A was reduced significantly in each of two studies. This effect in performance is due to the reduced blood oxygenation.

Physical training resulted in a significant increase in C. This reflects a favorable change in effective muscle vascularity and/or the uniformity of perfusion-extraction.

Sex differences are demonstrable. Women showed significantly lower A (reflecting a lower hemoglobin) and greater C (reflecting a generally lesser relative muscle mass and usage).

II. From the data of 2.a. (see Table I), and the arterial and femoral venous blood oxygen, estimates were made of blood flow to exercising muscle, the vascular conductances and relative equivalent radius of the vascular segments involved in exercise. These indicate that muscle blood flow in exercise at sea level is limited by a maximum equivalent radius (mean ± S.E. relative to resting sea level) of 2.53 ± .13 times, which is not changed (2.58 ± .18) for exercise at acute simulated altitude. This limit appears to be primarily responsible for the maximal oxygen uptake, with both an anatomical and functional basis.

TABLE I

Values of parameters A, B and C in the relation:

$$\dot{V}_{O_2} = A\dot{Q} + (e^{-C\dot{Q}} - 1)\, B/C,$$

where $\dot{V}_{O_2}$ = oxygen uptake, and $\dot{Q}$ = cardiac output, in liters/minute, normalized to 70 kg body weight.

C min/l.	A	B
1. Means and standard deviations for 63 healthy males:		
.076 ± .026	.28 ± .04	.26 ± .05
2. Mean and standard errors of the differences between sea level and acute simulated altitude (4 Km):		
a. For six ARIEM subjects:		
.056 ± .033	-.065 ± .005 ($p < .0001$)	.032 ± .07
b. For five Swedish subjects (data of Stenberg, et al):		
.004	-.053 ± .01 ($p < .01$)	-.05
3. Mean and standard error of the differences between before and after physical training for five subjects (data of Saltin, et al):		
-.029 ± .005 ($p = .004$)	.019 ± .02	-.031 ± .03
4. Mean differences and pooled S.E. between eleven women and twelve men (data of Ästrand):		
.027 ± .008 ($p = .004$)	-.059 ± .011 ($p < .001$)	.007 ± .02

Title of Study: Effect of acute hypoxia or hypobarism on CSF pressure and cerebral hydration in animals

Investigators: James A. Vogel, Ph.D.; Malcolm A. Gleser, CPT, MC; and James G. Lifton

Acute mountain sickness remains the major debilitating factor in the performance of troops rapidly moved to high altitude land areas. Its cause is still unknown. One possibility is that it is related to brain malfunction which, in turn, is caused by increased movement of water into brain tissue, resulting in increased intracranial pressure.

In order to test this hypothesis, anesthetized dogs have been acutely exposed to simulated high altitude environments. A substantial rise in cerebrospinal fluid pressure, an indicator of intracranial pressure, is consistently seen with this treatment.

In a second study, two conscious dogs with chronically implanted intracranial pressure transducers were subjected to atmospheres of 10% and 12% oxygen for 24 periods. No increase in cerebrospinal fluid pressure was observed in either dog.

We must, therefore, conclude that the acute anesthetized preparation is not predictive of the chronic conscious state in the dog. Thus, we do not have evidence of significant rise in cerebrospinal fluid pressure in the dog during the period when symptoms of acute mountain sickness develop in man.

Title of Study: The pathogenesis of acute mountain sickness

Investigators: Allen B. King, CPT, MC, and Sumner M. Robinson, Ph.D.

Acute mountain sickness (AMS) is a self limited illness induced by exposure to the low oxygen pressures of high terrestrial elevations. Since it is noted in a significant percentage of individuals during their initial exposure to hypoxia, AMS represents a potential threat to combat effectiveness in military operations at high altitude. Preventive measures have been, at best, only partially effective, mainly as a result of the lack of clarification of the step by step synthesis of AMS. The purpose of this study area is to elucidate the factors which lead to AMS, and thus provide a better rationale for the prevention and treatment of this illness.

Substudy 1: The relationship beteeen the ventilatory responses to altitude and acute mountain sickness

Previous studies have documented that individuals vary with respect to their ventilatory responses to altitude, and that ventilation appears to be related to the severity of AMS. In our recent hypobaric chamber studies we have reaffirmed the relationship between ventilation and the degree of illness at altitude. Further, the failure to increase ventilation at altitude was established as being related either to a low hypoxic sensitivity or an inability of the respiratory centers to adapt to the changing levels of carbon dioxide in the body.

Substudy 2: The headache of acute mountain sickness

Headache is the most frequent and severest symptom of AMS, and is distinguished by a gradually increasing intensity during the first 24 to 48 hours at altitude. This symptom was studied in 30 subjects at simulated altitudes of 14,000 or 15,000 feet and was characterized as being associated with a vasodilatation of the extracranial circulation, more specifically the temporal artery. In the majority of subjects with moderate to severe headache, its intensity was fully relieved by temporal artery compression. It appears that the headache of AMS is primarily the result of the stretching of extracranial arterial walls and stimulation of pain fibers located in these areas. In this respect, the headache of AMS is analagous to the headache of migraine.

Our future investigations will include studies on the relationship between the fall in body levels of carbon dioxide and the degree of vasodilatation in the extracranial circulation.

Title of Study: Effects of extended hypoxia on visual performance and retinal vascular state

Investigators: John L. Kobrick, Ph.D. and COL Budd Appleton, M.D.

Background and Progress:

Eight human subjects were exposed to 15,000 feet equivalent hypobaric elevation for 48 hours in an altitude chamber during which they were measured five times at periodic intervals for near and far visual acuity, stereopsis, binocular depth perception, critical flicker fusion, dark adaptation, and response time to peripheral visual signals. The central retinal fundi were also examined clinically and photographed. Performance on all visual tasks showed similar decrements which occurred rapidly and reached their maximum extent within approximately one hour of exposure and thereafter gradually recovered over the remaining interval. The peripheral visual response time data duplicated and thus verified the results obtained in previous experiments in which this task was used for short hypoxic exposures of the same severity, indicating this task to be a reliable and sensitive indicator of stress effects on visual performance. The similarity and consistency of the trends of impairment across a variety of visual indices in this study strongly indicate that the effects noted are apparently due to hypoxia acting directly on the visual system rather than to the influence of subjective feeling states, since they preceded by several hours the onset of subsequent illness symptoms. The retinal vascular changes observed corroborate former findings in the literature of engorgement and increased blood vessel diameter and tortuosity, but did not immediately abate upon return to normoxia. Signs of retinal hemorrhage or edema previously reported by others during exposure to higher elevations than those used in this study were not observed. The data have significance for military applications since they show that many varieties of visual performance apparently recover quite rapidly after the initial decrement phase, and that the soldier may be expected to show effective performance in visual tasks quite soon after abrupt transport to altitude. Furthermore, the data indicate that the soldier may be able to perform effectively despite his feelings of illness and discomfort, which apparently do not effectively predict his potential capability, provided that he is motivated to continue to perform.

Conclusions:

The effects of hypoxia exposure intervals of up to 48 hours upon several varieties of visual performance are characterized by impairment

of function which is rapid and reaches its maximum in most cases within the first few hours. However, significant recovery can be expected after this initial decrement, which approaches near normoxic levels within 48 hours. Illness symptoms do not predict effective performance capability. Retinal hemorrhage or edema should probably not be expected to occur at 15,000 feet elevation within 48 hours of exposure.

Future Plans:

Study of effects of extended hypoxia on other forms of visual perception is planned for FY 72.

Title of Study: Effects of hypoxia and acetazolamide on visually evoked cortical potentials for colored stimuli

Investigator: John L. Kobrick, Ph.D.

Background and Progress:

Twenty human subjects were trained to observe white, red, yellow, and blue circular visual targets of 2° angular subtense which appeared foveally, and also displaced 20° and 40° medially on the horizontal axis. Evoked cortical potentials were obtained from electrodes placed on the occipital midline, and were recorded for later analysis on an FM instrumentation tape recorder. Each subject received three four-hour sessions in the order: normoxia, 15,000 feet hypoxia simulated by breathed oxygen-nitrogen gas mixture, normoxia. In each session, each subject was recorded once each hour while viewing each stimulus condition employed. Ten subjects received six 250-milligram acetazolamide tablets at 8-hour intervals for 48 hours prior to each testing session; the other 10 subjects received placebo tablets of equivalent appearance. The data should provide some indication of the basic influence of acetazolamide on neural counterparts of visual color response, since this drug was shown in previous research to mitigate hypoxia-produced decrements in size and shape of the visual field for color detection as measured by clinical perimetry. These data should have value for predicting military performance under hypoxia, especially since acetazolamide presently shows considerable promise as an effective medication for mountain sickness. Data collection has been completed, and a system for computerized data analysis is now being fabricated.

Future Plans:

Data analyses are proceeding. Future studies on the effects of acetazolamide on visual processes at high elevations are planned for FY 72.

Title of Study: Simple decision-making at high altitude

Investigator: Richard L. Cahoon, Ph.D.

Background:

The ability to make correct decisions quickly is an advantage at sea level, but at high elevations it can be critical for survival. This is particularly true of the combat soldier who must deal not only with a potentially hazardous environment but also the added stress of combat. In spite of its importance, however, little is known of this cognitive process in a hypoxic environment.

Previous research in this area has traditionally dealt with choice reaction time, and has shown only peripheral applicability to the decision-making process. The present study was designed to test the effects of a high altitude atmosphere on decision-making at two levels of task complexity. Hypotheses for this study were that speed and accuracy of decision-making would deteriorate at high altitude, and that the decrement would increase with task complexity.

Progress:

A study was conducted in which eight military volunteer test subjects were exposed to 15,000 feet altitude in the high elevation simulation facility for a period of 48 hours. After 3 hours, 20 hours, 24 hours, and 45 hours of exposure, each subject performed the following four card-sorting tasks.

a. Simple Psychomotor - Ss sorted a pack of 96 blank cards sequentially into two bins as fast and accurately as possible.

b. Simple Cognition - Ss sorted a pack of 96 cards into two labeled bins according to color (red or green).

c. Complex Psychomotor - Ss sorted a pack of 96 blank cards into 16 bins as quickly and accurately as possible.

d. Complex Cognition - Ss sorted a pack of 96 cards into 16 labeled bins according to size, shape, and color of the geometric figure printed on each as well as the presence or absence of a black dot.

Analyses of variance of these tasks indicated that all tasks took significantly longer to complete at altitude than at sea level, and that the cognition tasks also showed significantly more errors at altitude than at sea level. The greatest decrement occurred within the first five hours of exposure and a slow recovery to near sea level performance followed.

Conclusion:

The hypotheses were supported. There was a strong effect of altitude on the decision-making tasks and the complex tasks suffered more than the simple tasks. In addition, it was found that subjects sacrificed speed to maintain accuracy when under the stress of hypoxia. This was successful for the psychomotor tasks but only partially successful for the cognition tasks. Finally, the pattern of performance over the 48-hour exposure period was similar for all tasks, with the greatest effect of altitude occurring early in the exposure period.

Future Plans:

This task has been shown to be a measure of the simple decision-making process which is sensitive to hypoxic stress. It is now planned to use this task to test the effects of heat on this process, and the feasibility of using such a task in studies of sleep deprivation is also being explored.

Title of Study: Auditory vigilance under hypoxia

Investigators: Richard L. Cahoon, Ph.D., and E. Ralph Dusek, Ph.D.

Background:

Previous vigilance research from this laboratory found that visual vigilance performance deteriorated significantly under the stress of hypoxia. Analysis of the data from these studies indicated that the process being affected by the oxygen deficit was attentional in nature rather than sensory. Subjects detected fewer signals under hypoxia than at sea level because of an inability to constantly observe the display for the required two-hour period, rather than an inability to discriminate signals from non-signals. It was felt that one possible way to reduce this decrement was to present the signals to the subjects in a way that did not require them to constantly observe a display. An auditory presentation was a logical way to accomplish this.

Progress:

A study was conducted in which four oxygen conditions (21% O_2, 12.8% O_2, 11.8% O_2, and 10.9% O_2) were administered to 20 subjects according to a Latin-square design. Subjects breathed the oxygen mixtures from a pre-mixed gas tank through a face mask which was modified to measure the subject's PO_2. The task for each subject was to listen to 1000 H_Z tones 1/2 second long which were presented every five seconds for a two-hour period. All but 36 of these tones were of equal intensity. The 36 "special" tones were slightly louder than the others and were the "critical" signals for the subjects to detect. He did so by pressing a hand-held push button.

Analyses of variance of the data indicated a severe decrement in vigilance performance at oxygen levels of 11.8% O_2 (15,000 feet) and 10.9% O_2 (17,000 feet) when measured by the percentage of correct detections. There was also a decrease in the d' measure of Signal Detection Theory indicating a drop in the detectability of the critical signals. These findings paralleled those of the visual vigilance studies.

Conclusions:

The decrement found in both auditory and visual vigilance performance under hypoxia indicates that the process being affected is common

to both sensory modes and is probably central in nature. The data suggest that it is an attention process and not simply observing responses which is at the basis of the vigilance process.

Future Plans:

It is planned to study the process of attention as it is affected by hypoxia in an attempt to discover its physiological nature and its sensitivity to environmental stress. In addition, the study of performance in Army radio communications systems at altitude by auditory vigilance methods is being explored.

Project No: 3A061102B71R

Title: Research in Biomedical Sciences

Task: 05 Environmental Biochemistry

(82101)

RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY

1. AGENCY ACCESSION	2. DATE OF SUMMARY	REPORT CONTROL SYMBOL
DA OA 6140	71 07 01	DD-DR&E(AR)636

3. DATE PREV SUMRY	4. KIND OF SUMMARY	5. SUMMARY SCTY	6. WORK SECURITY	7. INTERDISC	8a. GRP'D INVST'N	8b. SPECIFIC DATA-CONTRACTOR ACCESS	9. LEVEL OF SUM
70 12 31	D. Change	U	U	N/A	N/L	☒ YES ☐ NO	A. WORK UNIT

10. NO./CODES:	PROGRAM ELEMENT	PROJECT NUMBER	TASK AREA NUMBER	WORK UNIT NUMBER
a. PRIMARY	6.11.02.A	3A061102B71R	05	055
b. CONTRIBUTING				
c. [illegible]	CDOG 141 (a)			

11. TITLE: (U) Disease Susceptibility of Soldiers in Harsh Environments (22)

12. SCIENTIFIC AND TECHNOLOGICAL AREAS: 002300 Biochemistry; 003500 Clinical Medicine; 012900 Physiology

13. START DATE	14. ESTIMATED COMPLETION DATE	15. FUNDING AGENCY	16. PERFORMANCE METHOD
70 07		DA	C. In-House

17. CONTRACT/GRANT
a. DATES/EFFECTIVE: N/A EXPIRATION:
b. NUMBER:
c. TYPE: d. AMOUNT:
e. KIND OF AWARD: f. CUM. AMT.

18. RESOURCES ESTIMATE	a. PROFESSIONAL MAN YRS	b. FUNDS (In Thousands)
FISCAL YEAR PRECEDING 71	1.8	101
FISCAL YEAR CURRENT 72	1.5	108

19. RESPONSIBLE DOD ORGANIZATION
NAME: USA Rsch Inst Env Med
ADDRESS: Natick, Massachusetts 01760

RESPONSIBLE INDIVIDUAL
NAME: Jones, LeeRoy G. COL
TELEPHONE: 955-2811

20. PERFORMING ORGANIZATION
NAME: USA Rsch Inst Env Med
ADDRESS: Natick, Massachusetts 01760

PRINCIPAL INVESTIGATOR (Provide SSAN if U.S. Academic institution)
NAME: Casey, Francis B. CPT
TELEPHONE: 955-2861
SOCIAL SECURITY ACCOUNT NUMBER:

ASSOCIATE INVESTIGATORS
NAME: Bowers, Wilbert D. Dr.
NAME: Hysell, David K. MAJ DA

21. GENERAL USE
Foreign Intelligence Considered

22. KEYWORDS (Provide KEY DoD Subject Coverage Code)
(U) Stress; (U) Disease; (U) Environmental Extremes; (U) Temperature; (U) Fatigue; (U) Immune Response; (U) Defense Mechanisms

23. TECHNICAL OBJECTIVE, 24. APPROACH, 25. PROGRESS (Provide individual paragraphs identified by number. Precede text of each with security classification code.)

23. (U) Disease causes more combat noneffectiveness than do battle injuries. There is an Army requirement to study factors which influence disease susceptibility and to provide prophylactic and/or therapeutic measures (Institute of Land Combat/Advanced Materials Concept Agency material data sheet S/MD-14, dtd May 1969). Fatigue, exposure to temperature extremes or altitude increase susceptibility to disease and diminish the efficacy of therapeutic regimens. The objective of this research is to predict the extent to which environmental extremes and fatigue influence disease susceptibility and combat effectiveness.

24. (U) Existing models will be used to establish the conditions and extent to which any one or combination of environmental extremes and fatigue alter resistance to bacterial and viral diseases relevant to military operations. Changes in the body's defense mechanisms (e.g., mucous membrane sensitivity, antibody production) resulting from acute, cyclic, or chronic exposure to environmental stress will be studied by immunological and biochemical techniques. Studies will be conducted in laboratory animals and in human volunteers under simulated field conditions.

25. (U) 70 07 - 71 06 Studies have been undertaken using mice acutely heat stressed at 37°C with 80-90% relative humidity and injected with sheep red blood cells as an antigen representative of a disease causing agent. Using intravenously injected carbon particles, stressed animals demonstrated a slightly increased, but statistically questionable increased rate of non-specific particle clearance from the body. Immunity to antigen by stressed animals was markedly depressed seven to ten days after injection as evidenced by Jerne hemolysis-in-gel assay of antibody producing spleen cells.

26. Availability to contractors upon originator's approval

DD FORM 1 MAR 66 1498 PREVIOUS EDITIONS OF THIS FORM ARE OBSOLETE. DD FORMS 1498A, 1 NOV 65 AND 1498-1, 1 MAR 66 (FOR ARMY USE) ARE OBSOLETE

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Title of Study: The effect of acute exposure to harsh environments and fatigue on immunity to disease

Investigator: Francis B. Casey, CPT, MSC

Background, Rationale, and Approach:

Disease causes more combat noneffectiveness than do battle injuries. There exists, therefore, an Army requirement to study factors which: (a) influence disease susceptibility and (b) to provide prophylactic and/or therapeutic measures (Institute of Land Combat/Advanced Materials Concept Agency material data sheet S/MD-14, dtd May 1969). It was towards satisfying the former requirement that this study was initiated.

Investigations conducted by many workers, notably, Selge, to elucidate the physiology of stress have emphasized the role of adrenal cortical hormones, thyroxine, and catecholamines. Studies have been undertaken to determine what effect these substances have on one of the important lines of defense against disease; namely, the development and maintenance of immunity against disease agents. The results of these studies have varied greatly and it has been impossible to extract a sufficient amount of data to predict how an individual's immune capability to disease would be affected by expected combat and non-combat physically stressful environments and conditions.

This study a priori exposes the whole animal to the stress condition in question rather than attempt to simulate the physiology of the stress by introducing parentally administered drugs and hormones. As the first phase of this study, random bred mice were exposed to 37°C and 60-80% relative humidity. Mice housed at 22°C with 15-25% relative humidity for the duration of each experiment served as the control population.

The immune response of all animals to a specific antigenic challenge was quantitated as the number of spleen lymphocytes producing humoral antibody determined by the hemolysisiin gel technique of Jerne.

The ability of animals to phagocytize carbon particles was utilized to assess the role of the macrophage in an earlier phase in the initiation of immunity as well as a nonspecific line of defense against disease agents.

Progress:

With respect to the effects of the heat-high humidity environmental stress on phagocytosis, comparative carbon clearance rates of intravenously injected carbon particles were performed on stressed mice. Heat stressed animals had a moderately increased rate of phagocytic clearance; however, the statistical difference was not determined due to the low population numbers utilized.

Studies relative to the effects of the heat-high humidity environmental stress on the kinetics of the primary immune response have thus far focused on the early appearing gamma M class of antibody. An initial exposure of mice simultaneously to 39°C and antigenic challenge resulted in total mortality of the animals within 12 hours post-exposure and immunization. Sham injected and non-injected animals also exposed to 39°C lived four and six times longer, respectively. It appears that the commitment on the part of the animal to antibody production in itself constitutes a severe physiologic stress which is mortally compounded by the environmental stress. Subsequent experiments have been conducted at 37°C rather than 39°C.

Groups of mice were injected with a specific antigen (sheep red blood cells), acutely exposed to the hot-wet environment, and maintained in that environment throughout the experiments. Spleen lymphocytes were assayed for antibody (gamma M) production on days 3, 4, 5, 7, and 10 post-immunization. Mice similarly injected and maintained at 22°C were the control animals. Peak antibody responses were found in both groups of mice on day 4 post-immunization without significant differences in peak titer. Significant differences were found to consistently exist on days 7 and 10, the heat stressed animals having a lower titer of specific antibody. It has not as yet been determined if this lower titer represents an increased catabolism of antibody proteins or an earlier shift to the late, more protective class of gamma G antibody.

On the other hand, preliminary results indicate that if the animals are heat stressed for 4 days prior to immunization, peak titers of gamma M antibody still occur on day 4 post-immunization, but the titers are slightly higher for the heat stressed animals. Again, however, the antibody titers on days 7 and 10 of the heat stressed animals were lower than the control animals.

Plasma corticosterone levels of stressed and control animals were determined with no significant differences observed between the two populations.

Future Studies:

The present investigation with respect to acute exposure to heat-high humidity will be extended to determine if there are any effects on the late gamma G antibody response which is of more significant importance in relation to diseases other than enteric infections. In addition, the effects of fatigue-sleep deprivation on the immune response will be studied utilizing existing model systems for such investigations.

Attempt will be made to determine if the increased non-specific phagocytases observed is due to increased blood flow facilitating contact of the foreign particles with phagocytic macrophages or if additional cellular components are recruited for this purpose under the heat-high humidity stress conditions.

(82102)

RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY

1. AGENCY ACCESSION	2. DATE OF SUMMARY	REPORT CONTROL SYMBOL
DA OA 6141	71 07 01	DD-DR&E(AR)636

3. DATE PREV SUM'RY	4. KIND OF SUMMARY	5. SUMMARY SCTY	6. WORK SECURITY	7. REGRADING	8a. GROUP MARK'N	8b. SPECIFIC DATA - CONTRACTOR ACCESS	9. LEVEL OF SUM
70 12 31	H-Terminated	U	U	N/A	N/L	☒ YES ☐ NO	A. WORK UNIT

10. NO./CODES	PROGRAM ELEMENT	PROJECT NUMBER	TASK AREA NUMBER	WORK UNIT NUMBER
a. PRIMARY	6.11.02.A	3A061102B71R	05	056
b. CONTRIBUTING				
c. CONTRIBUTING	CDOG 141 (22)			

11. TITLE (Precede with Security Classification Code)

(U)Biological Processes that Limit Military Performance Under Environmental Stress (22)

12. SCIENTIFIC AND TECHNOLOGICAL AREAS

005900 Environmental Biology; 012600 Pharmacology; 002300 Biochemistry

13. START DATE	14. ESTIMATED COMPLETION DATE	15. FUNDING AGENCY	16. PERFORMANCE METHOD
70 07		DA	C. In-House

17. CONTRACT/GRANT

a. DATES/EFFECTIVE: N/A EXPIRATION:

b. NUMBER:

c. TYPE: d. AMOUNT:

e. KIND OF AWARD: f. CUM. AMT.

18. RESOURCES ESTIMATE	a. PROFESSIONAL MAN YRS	b. FUNDS (In thousands)
PRECEDING FISCAL YEAR 71	1.6	127
CURRENT FISCAL YEAR 72	0	0

19. RESPONSIBLE DOD ORGANIZATION

NAME: USA Rsch Inst Env Med

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TELEPHONE: 955-2811

20. GENERAL USE

Foreign Intelligence not Considered

20. PERFORMING ORGANIZATION

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PRINCIPAL INVESTIGATOR (Furnish SSAN if U.S. Academic Institution)

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TELEPHONE: 955-2870

SOCIAL SECURITY ACCOUNT NUMBER:

ASSOCIATE INVESTIGATORS

NAME: Robinson, Sumner M. Dr.

NAME: DA

22. KEYWORDS (Precede EACH with Security Classification Code) (U) Heat; (U) Altitude; (U) Biochemistry; (U) Cold; (U) Pharmacology; (U) Drugs; (U) Protein Metabolism; (U) Military Operations

23. TECHNICAL OBJECTIVE, 24. APPROACH, 25. PROGRESS (Furnish individual paragraphs identified by number. Precede text of each with Security Classification Code.)

23. (U) Exposure of military personnel to extremes of environment imposes limitations on the ability to perform mental and physical tasks. Determination of the biological processes which are involved in these limitations will provide a better rationale for the maintenance and/or improvement of the soldier's performance.

24. (U)Selective organ systems, such as brain and muscle, will be examined during the deterioration of mental and physical performance when experimental animals are subjected to environmental extremes. Chemical and structural changes which are critical to this process will be defined, and physiological and pharmacological methods will be implemented to arrest or reverse the deterioration.

25. (U) 70 07 - 71 06 Qualitative and quantitative techniques were developed for the determination of labeled catecholamines in rat brain. Tritiated and endogenous norepinephrine and dopamine were determined after intracisternal injection of metabolic precursors utilizing ion exchange chromatography, liquid scintillation counting and fluorimetry. Brain catecholamine levels were reduced by acute exposure of rats to hypobaric hypoxia. A new steady state was established after 24 hours exposure. Brain norepinephrine turnover rates at this time were normal despite increased conversion of metabolic precursors into norepinephrine. Changes in uptake of these precursors from cerebrospinal fluid may be responsible for the observed alterations. This work unit is being abolished due to the dispersion of investigators into other areas and work units.

*Available to contractors upon originator's approval

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Title of Study: The Influence of Environmental Extremes on Central Biogenic Amine Metabolism

Investigators: Allen Cymerman, Ph.D. and Sumner M. Robinson, Ph.D.

The modification of brain amine metabolism has been described in animals exposed to various stresses such as heat, cold, and electroshock. We have previously indicated that hypobaric hypoxia also causes a change, although temporary, in central amine metabolism. The exposure of rats to conditions of environmental hypoxia equivalent to 18,000 feet for periods up to 30 hours results in a decrease of brain norepinephrine (NE) and dopamine (DM). The greatest decrease occurs after 12 hours exposure. By 24 hours, normal levels of both amines are re-established.

To ascertain whether an overall change in the metabolism of these amines occurred, turnover rates were determined. These rates were estimated by two different methods: (1) measuring the rate of disappearance of endogenous norepinephrine after synthesis inhibition by α-methyltyrosine and (2) the rate of disappearance of ^{3}H-norepinephrine after intracisternal injection of ^{3}H-DOPA. Brain norepinephrine turnover rates 24-30 hour altitude-exposed rats, determined by either method, were not significantly different from sea level controls.

Further experiments were conducted in an attempt to identify the cause(s) of the observed reduction in brain catecholamines. Accordingly we introduced, via intracisternal injection, highly labeled L-dihydroxyphenylalanine (L-DOPA) and L-tyrosine, both metabolic precursors of norepinephrine and dopamine. These two compounds are thought to be central neurotransmitters and quite possibly associated with the increase in toxicity of centrally-acting drugs in altitude-exposed animals.

Two hours after the injection of ^{3}H-DOPA, a 3-4 fold increase in the specific activities of DM and NE in animals exposed to altitude for 6 hours or longer was obtained. Similar experiments using ^{3}H-tyrosine produced similar qualitative results. That is, animals exposed to altitude longer than 4-6 hours have higher specific activities of NE when compared to sea level controls whether L-tyrosine or L-DOPA was used as a precursor. These two precursors in the synthesis of NE can be used to determine any possible effects on tyrosine hydroxylase, the rate-limiting enzyme in NE synthesis. Our results indicate that brain tyrosine hydroxylase is not greatly affected by exposure to altitude. Although not conclusively demonstrated by our experiments, it appears

quite plausible that increased utilization of NE and DM could occur with exposure to altitude, especially if analogies are made with the changes in brain amine metabolism resulting from other stresses.

The increased uptake and conversion of the tagged precursors from the cerebrospinal fluid may reflect changes in CSF pressure or acid-base balance that have been demonstrated with exposure to altitude and associated with the symptoms of acute mountain sickness in man.

(82103)

RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY

1. AGENCY ACCESSION	2. DATE OF SUMMARY	REPORT CONTROL SYMBOL
DA OA 6142	71 07 01	DD-DR&E(AR)636

3. DATE PREV SUM'RY	4. KIND OF SUMMARY	5. SUMMARY SCTY	6. WORK SECURITY	7. REGRADING	8a. DISP'N INSTR'N	8b. SPECIFIC DATA - CONTRACTOR ACCESS	9. LEVEL OF SUM
70 12 31	D. Change	U	U	N/A	N/L	☒ YES ☐ NO	A. WORK UNIT

10. NO./CODES:	PROGRAM ELEMENT	PROJECT NUMBER	TASK AREA NUMBER	WORK UNIT NUMBER
a. PRIMARY	6.11.02.A	3A061102B71R	05	057
b. CONTRIBUTING				
c. CONTRIBUTING	CDOG 141 (22)			

11. TITLE (Precede with Security Classification Code): (U) Development of Cold Injury Models and Characterization of Frostbite, Non-Freezing Cold Injuries and Whole Body Heat Loss Common to the Soldier(22)

12. SCIENTIFIC AND TECHNOLOGICAL AREAS: 002300 Biochemistry; 005900 Environmental Biology; 012900 Physiology

13. START DATE	14. ESTIMATED COMPLETION DATE	15. FUNDING AGENCY	16. PERFORMANCE METHOD
70 07		DA	C. In-House

17. CONTRACT/GRANT
a. DATES/EFFECTIVE: N/A EXPIRATION:
b. NUMBER:
c. TYPE: d. AMOUNT:
e. KIND OF AWARD: f. CUM. AMT.

18. RESOURCES ESTIMATE	PRECEDING/SUMMARY	a. PROFESSIONAL MAN YRS	b. FUNDS (In thousands)
FISCAL YEAR	71	3.2	161
	72	4.5	294

19. RESPONSIBLE DOD ORGANIZATION
NAME: USA Rsch Inst Env Med
ADDRESS: Natick, Massachusetts 01760

RESPONSIBLE INDIVIDUAL
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TELEPHONE: 955-2811

20. PERFORMING ORGANIZATION
NAME: USA Rsch Inst Env Med
ADDRESS: Natick, Massachusetts 01760

PRINCIPAL INVESTIGATOR (Furnish SSAN if U.S. Academic Institution)
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TELEPHONE: 955-2863
SOCIAL SECURITY ACCOUNT NUMBER:

ASSOCIATE INVESTIGATORS
NAME: Hysell, David K. MAJ
NAME: Casey, Francis B. CPT DA

21. GENERAL USE
Foreign Intelligence Considered

22. KEYWORDS (Precede each with Security Classification Code): (U) Arctic Military Operations; (U) Cold Injury; (U) Frostbite; (U) Thermoregulation; (U) Cryobiology

23. TECHNICAL OBJECTIVE, 24. APPROACH, 25. PROGRESS (Furnish individual paragraphs identified by number. Precede text of each with Security Classification Code.)

23. (U) Study factors involved in frostbite and other non-freezing injuries, as well as whole body heat loss in both animals and man, to provide a rational basis for treatment and prevention of those cold injuries sustained by the military.

24. (U) The following areas are being investigated in humans and animals: (1) the suitability of animal model systems to mimic those clinical cold injuries seen during military operations in cold climates; (2) cell destruction following frostbite; (3) physiological, ethnic and other factors; (4) physiological changes in man subjected to whole body cooling.

25. (U) 70 07 - 71 06 Experimental preparations of the microvascular beds of rabbit and rat mesentery have been studied to obtain information about platelet aggregate emboli that occlude small blood vessels following a freeze-thaw injury. Ways to promote their dissolution are being sought. Levels of serum complement have been found to be elevated during the two weeks after a freeze injury, which might implicate the involvement of complement. Tissue measurements after frostbite show wide variability in amounts of tissue lost. Data suggests that deep anesthesia is protective against experimental frostbite. Experiments with the ability of mitochondria to utilize oxygen indicate that graded levels of cold injury can result in predictable and graded levels of mitochondrial dysfunction. This model might separate that portion of the frostbite lesion due to the freeze per se and that due to the subsequent vascular collapse. Analysis of blister fluids resultant from severe cold injuries show that neutral lipid and phospholipid profile of blister fluid is identical to that of plasma, indicating that blister fluid lipid is plasma and not tissue. Ultrastructural observations of frozen-thawed skeletal muscle indicate severe damage inflicted upon endothelial cells. In soldier volunteers acute mild (12% O_2) hypoxia decreases shivering and reduces both skin temperatures and the fall of rectal temperatures during spontaneous rewarming when CO_2 is replaced to pre-exposure alveolar pCO_2 levels.

Available to contractors upon determination of need-to-know.

DD FORM 1 MAR 68 1498 PREVIOUS EDITIONS OF THIS FORM ARE OBSOLETE. DD FORMS 1498A, 1 NOV 68 AND 1498-1, 1 MAR 68 (FOR ARMY USE) ARE OBSOLETE

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Title of Study: Microcirculatory thrombosis secondary to cold injury

Investigator: A. W. Klein, CPT, MSC

Background:

Historically, military operations conducted in moderately cold to very cold weather have produced significant numbers of casualties. The damage that results from a severe cold injury is thought to be the result of multiple factors. It has been demonstrated that the freezing of tissue results in the physical disruption of cells, their substructural components, and other components of tissues. One of the factors which contributes to the cold injury lesion is the collapse of the microcirculation. Just how this occurs is not fully understood, but there probably exists a strong relationship between microemboli and microvascular stasis.

Preparations of living microvascular networks enable one to study the flow through fine vessels and capillaries and to manipulate the surroundings in such a manner as to stop the circulation for further study. After such microcirculatory beds are frozen and thawed, light, colorless aggregates of material slide through the microcirculation. These sometimes appear to become lodged at anastomoses and the flow stops. Under similar conditions, these embolic structures can be obtained and studied via the electron microscope. It has been shown that many emboli have platelets as their primary component and it would be expected that cold injury might also have platelets forming the emboli. Whether or not these colorless emboli are platelets in the cold injured tissue remains to be seen. Platelets also tend to aggregate following non-specific injury and this quality can be artificially inhibited or enhanced pharmacologically. It is proposed to study platelets following cold injury and their properties pertaining to aggregation.

Progress:

Animal preparations of microvascular beds have been viewed and photographed to obtain information about the clear emboli that appear following a freeze-thaw episode. Currently isolated platelets are being studied for their aggregative properties following freeze-thaw, and parallels are being sought between the behavior of platelets *in vitro* and *in vivo*.

Title of Study: Studies of the immunologic contributions to the genesis of frostbite lesions: the possible role of serum complement

Investigator: Francis B. Casey, CPT, MSC

Background, Rationale, and Approach:

Data obtained from this Institute and elsewhere suggests that the lesion referred to as frostbite is the result of prolonged, cold induced microvascular shutdown due in part to the formation of microthrombi. Drawing from similarity of xenograft rejection and frostbite lesion genesis, it is possible that serum complement, activated by non-immunologic factors, could contribute to the formation of microthrombi.

Fresh plasma from rabbits subjected to experimental frostbite of the ear were assayed from complement by standard complement titration techniques.

Progress:

Anesthetized rabbits were subjected to experimental frostbite by immersion of the ear to a depth of 8 cm into -25°C bath of dry ice, ethylene glycol, ethanol, and water for a period of two minutes. Plasma samples were obtained by cardiac puncture. Prefreeze and 60 minute post-thaw samples were obtained on the day of immersion and on days 2, 4, 7, 10, 14, 17, 22 and 31 thereafter. Complement titers baselined for the first two days and began to increase on day 4, peaking on day 14 and slowly returned towards baseline levels. Control animals were not subjected to induced frostbite but were either administered anesthesia or simply bled on the days of sampling. Complement titers on a limited number of control animals remained near baseline or showed a slight depression. Normal variation of plasma complement levels was ±15% whereas the titers in animals subjected to frostbite were elevated as much as 60% over baseline levels.

Attempts to deplete rabbit complement using either Zymosan or Carrageenan have not been satisfactory.

Future Studies:

Recently, a purified preparation of the third component of rabbit complement (C_3) has been prepared and an antibody to that component will be obtained by immunizing a sheep. The sheep anti-rabbit C_3 will be used for fluorescent antibody studies of histologic sections of tissue from the frostbite lesion.

An attempt will be made to deplete rabbit complement using the non-toxic fraction of cobra venom and determining what altered effect, if any, this has on the genesis of the experimental frostbite lesion.

Title of Study: Tissue loss evaluation secondary to cold injury at various times and temperatures

Investigators: Albert W. Klein, CPT, MSC and David K. Hysell, MAJ, VC

Background:

Progress toward treating cold injuries, principally frostbite, has been hampered to a large degree by the lack of a predictable model. In the past, unsuccessful attempts have been made to inflict a freeze-thaw injury upon an experimental animal in such a way that a specific and predictable amount of tissue was to be lost from the resultant gangrenous lesion. A standardized injury such as this is needed prior to the possible evaluation of potentially therapeutic techniques.

Progress:

In order to determine the factors which were of major importance in the final determination of the amount of tissue lost after a frostbite insult, a wide range of parameters were recorded during the experimental freeze injuries. The freeze injuries have been of two different types: a rapid cooling freeze and a slow cooling freeze. The rapid freeze was pursued first. The freeze was inflicted upon the measured distal portions of the ears of rabbits and the temperatures were plotted and were examined in portions to separate the cooling rates, heat of fusion, time durations of various cold intervals, and thawing rate, for each animal. Correlations were run in order to determine which factors might be related to tissue loss. The important factors were concluded to be: a) The rate of tissue cooling, b) The temperature of the freezing media, c) The duration of the freeze insult and d) The rate of rewarming.

The slow freeze type of injury was initiated because rate of freeze appears to be of prime importance, because clinical freeze injuries are of the slow freezing rate, and in order to stretch out the plotted curve for insult to tissue loss. Initial data on this freezing method indicated that depth of anesthesia is a major factor in the amount of tissue subsequently lost after a freeze-thaw insult. The only other pertinent report of this in the scientific literature indicates that "deep anesthesia results in severe tissue loss." Our initial data indicates the converse, that deep anesthesia is protective.

It is postulated that this effect may be due to the extreme inhibition of the peripheral sympathetic arteriolar constrictors and the resultant vasodilatation.

Title of Study: Mitochondrial Dysfunction as an assay for freeze-thaw injury

Investigators: A. W. Klein, CPT, MSC and D. Therriault, Ph.D.

Background:

The damage that is inflicted upon living mammalian tissues by cold injuries such as frostbite is accepted as the effects of two mechanisms: (1) Cell death resultant from the freezing per se, and (2) the further complication of ischemic tissue necrosis or gangrene as a result of the vascular injury and shut-down.

From previous experiments, it was found that the extent to which seemingly similar freeze insults caused the extremity tissue of experimental animals to become gangrenous and to slough-off, was highly variable. It is not known how much damage is due to the freeze injury directly and how much might be due to the vascular involvement. Part of the aim of this work is to formulate a model which will quantify the freeze damage that occurs following a freeze-thaw insult of standardized severity. In addition, it should be possible to break down the total lesion into the component due to the freeze and that due to the vascular collapse.

The basis for the above approach lies in the response of mitochondria to freezing. Severe freezing uncouples the electron transport systems of mitochondria so that they no longer use oxygen, but this effect can be approached gradually.

Progress:

The initial data from this work indicates that graded levels of cold insult, as judged by decreasing temperatures or increasing durations of exposure, cause graded levels of mitochondrial dysfunction. Tissues in vitro subjected to short exposures (10 min.) at temperatures of -2° to -5°C exhibit almost no decrease in the ability of mitochondria to use oxygen while long exposures to these temperatures result in moderate levels of mitochondrial dysfunction. Short exposures (10 min.) at temperatures of -8° to -10°C result in moderate decreases in mitochondrial function while longer exposures (1/2 hour) are highly deleterious. Intermediate temperatures of 5.5° to 7.5°C and intermediate durations of exposure (1/2 hour) result in decreases of mitochondrial function which lay along the scale between the two extremes.

Tissues are currently being processed for E.M. fine structural reflections of these decreased levels of mitochondrial function.

Title of Study: Tissue damage resulting from freezing and non-freezing insult: changes in membrane and intercellular lipids at site of local cold injury

Investigator: Donald G. Therriault, Ph.D.

Background:

Tissue damage from cold is by no means rare in temperate and arctic latitudes. As a result of the need for troops in all branches of the service to operate in the arctic and in sub-zero weather, both the prevention and the treatment of frostbite demand much in the way of experimental investigation.

The battle has raged for quite some time as to whether it is direct damage of the cold to the cell which produces tissue injury or the subsequent thrombosis and circulatory stasis producing necrosis secondary to anoxia. As has been demonstrated on many occasions following a freezing injury, the vasculature is re-established with good blood flow and it is only subsequent to this that thrombosis occurs. This indicates that some change has occurred at the local level; either the release from tissue of a substance capable of producing coagulation; and/or an alteration in membrane structure that could induce coagulation, change permeability and thus effect the vitality of the tissue.

Tissue, subject to freezing, is acted upon by numerous physical stresses and chemical reactions due to the removal of free water from the system in the form of ice crystals which increases the tonicity of the remaining intracellular fluid. It is feasible that the removal of phospholipid due to an increase in the tonicity of intracellular fluid is capable of causing alterations in membranes which may adversely affect the system as well as provide an agent in a localized area that might precipitate changes in the coagulation scheme. It is well established, for instance, that the removal of lipids from membranes leads to a loss of enzyme activity at the membrane. It is also known that certain phospholipids exhibit procoagulant activity. The purpose of this study is to investigate whether the freezing of tissue *in vivo* causes the release of lipids from cell membranes.

Progress:

Quantitative analysis of the individual lipid classes from plasma and blister fluid obtained from adult albino New Zealand rabbits was carried out. Blister fluid was obtained by freezing injury to the ears of the rabbit. The results show that the neutral lipid and phospholipid profile of blister fluid is identical to that of plasma, indicating that the origin of blister fluid lipid is plasma and not tissue.

Future Plans:

Tissue lipid determinations will be done pre-freeze and at various times post-freeze. Cell particulates (i.e., plasma membrane) will be isolated by differential ultracentrifugation prior to and at post-freeze intervals, and lipid analysis carried out to determine to what extent freezing affects cell membranes.

Title of Study: Ultrastructural studies of muscle cells and vascular endothelium immediately following freeze-thaw insult

Investigators: Wilbert D. Bowers, Ph.D., Roger Hubbard, Ph.D. and David K. Hysell, MAJ, VC

Background:

A variety of model systems for studying frostbite or cold injury have been employed in various laboratories and many of the basic parameters involved in freeze-thaw injury have been established. Direct injury to tissue results from the freeze-thaw process which may or may not be reversible. Indirect injury results from alterations of the vasculature and subsequent occlusion. However, current methods for evaluating the severity of the injury are inadequate and the molecular mechanisms remain a matter of conjecture. A comprehensive ultrastructural study to establish a suitable model of frostbite injury and examine alterations in skeletal muscle cells and vascular endothelial cells resulting from the freeze-thaw process was initiated. The contributions of changes in vascular permeability, the role of phospholipids and fatty acids, chilling in conjunction with hypoxia, and ice crystal formation are parameters under investigation.

Progress:

A freezing technique has been devised which permits controlled freezing of hind limbs of mice. This system is currently being utilized to inflict cold injury and measure the contribution of separate parameters to the ultimate tissue damage.

Preliminary studies on a small number of animals which were either frozen and thawed or super cooled support the work of others who indicate that inner mitochondrial membranes are quite sensitive to the freeze-thaw cycle. Severe capillary damage was also evident. Super cooling, without freezing, produced no detectable change in muscle structure. The results obtained with freezing and thawing and super cooling in this model system, although confirmatory in nature, are basic to all other experiments. Experiments to determine the extent of alterations in vascular permeability, the contribution of chilling in conjunction with hypoxia, the role of fatty acids, and ice crystal organization in the ultimate injury are in progress.

(82107)

RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY

1. AGENCY ACCESSION	2. DATE OF SUMMARY	REPORT CONTROL SYMBOL
DA OA 6149	71 07 01	DD-DR&E(AR)636

3. DATE PREV SUM'RY	4. KIND OF SUMMARY	5. SUMMARY SCTY	6. WORK SECURITY	7. REGRADING	8a. DISP'N INSTR'N	8b. SPECIFIC DATA CONTRACTOR ACCESS	9. LEVEL OF SUM
70 12 31	D. Change	U	U	N/A	N/L	[X] YES [ ] NO	A. WORK UNIT

10. NO./CODES:	PROGRAM ELEMENT	PROJECT NUMBER	TASK AREA NUMBER	WORK UNIT NUMBER
a. PRIMARY	6.11.02.A	3A061102B71R	05	058
b. CONTRIBUTING				
c. CONTRIBUTING	CDOG 141 (2a)			

11. TITLE (Precede with Security Classification Code): (U)Development of Measures to Assess the Impact of Environmental Stresses on Critical Military Performance (22)

12. SCIENTIFIC AND TECHNOLOGICAL AREAS: 005900 Environmental Biology; 013400 Psychology; 012900 Physiology

13. START DATE	14. ESTIMATED COMPLETION DATE	15. FUNDING AGENCY	16. PERFORMANCE METHOD
70 07		DA	C. In-House

17. CONTRACT/GRANT
a. DATES/EFFECTIVE: N/A EXPIRATION:
b. NUMBER:
c. TYPE: d. AMOUNT:
e. KIND OF AWARD: f. CUM. AMT.

18. RESOURCES ESTIMATE		a. PROFESSIONAL MAN YRS	b. FUNDS (In thousands)
FISCAL YEAR	PRECEDING 71	2.4	112
	CURRENT 72	1.8	115

19. RESPONSIBLE DOD ORGANIZATION
NAME: USA Rsch Inst Env Med
ADDRESS: Natick, Massachusetts 01760
RESPONSIBLE INDIVIDUAL
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TELEPHONE: 955-2811

20. PERFORMING ORGANIZATION
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TELEPHONE: 955-2823
SOCIAL SECURITY ACCOUNT NUMBER:
ASSOCIATE INVESTIGATORS
NAME: Dusek, E. Ralph Dr.
NAME: DA

21. GENERAL USE
Foreign Intelligence not Considered

22. KEYWORDS (Precede EACH with Security Classification Code): (U) Environmental Stress; (U) Military Performance; (U) Perception; (U) Cognition; (U) Motor Skills.

23. TECHNICAL OBJECTIVE, 24. APPROACH, 25. PROGRESS (Furnish individual paragraphs identified by number. Precede text of each with Security Classification Code.)

23. (U) Severely debilitating effects of heat, cold, and high terrestrial elevation are identifiable by end points of exhaustion, cold injury, or collapse. However, such exposures can have less dramatic but highly significant effects on the soldier's efficiency and on unit mission performance. It is the objective of this research to develop sensitive and appropriate measures of these effects.

24. (U) Biochemical, physiological, and psychological methods will be developed to assess military performance; tasks sensitive to the effects of heat, cold, wind, moisture, work, and hypoxia on the soldier's perceptual, intellectual, and motor abilities will be studied.

25. (U) 70 01 - 71 06 Electrocortical measures were taken on subjects exposed to 14,000 ft. altitude for a 30-hour period. Complex data reduction methods are being used to determine if changes in frequency distributions of the EEG's correlate with the severity of symptoms of acute mountain sickness as indicated by subjective and physiological measures. Preliminary analysis indicates large inter-subject differences but intra-subject consistency in frequency distribution. Reliability tests of congnitive tasks revealed sixteen with high reliability and eight relatively free of learning effects, making them preferable for use in stress studies. Computer operated laboratory tasks which simulate information transmission in military operations are being developed. A target detection task was developed as a measure of perceptual behavior under stress, and is currently in use in a heat stress study. The use of Self-paced treadmill tasks for measuring voluntary march rate under different load carriage systems has been explored, and found not to correlate with test subject preferences for pack type.

*Available to contractors upon originator's approval

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Title of Study: Development of an electro-cortical measure of mountain sickness

Investigator: Richard L. Cahoon, Ph.D.

Background:

Although a number of symptoms of acute mountain sickness are cerebral in nature, a review of the EEG literature has shown a lack of any attempt to correlate EEG variables with these symptoms. Studies relating EEG changes with hypoxia have concentrated on conditions created by short term severe anoxia produced experimentally or by disease. There is, at present, no electrophysiological measure of cerebral changes that occur in conjunction with symptoms of acute mountain sickness produced by less severe but more protracted exposure to environmental hypoxia - the very conditions which the soldier is most likely to encounter at high terrestrial elevation. The present study was designed to develop such an index by taking EEG measures on human test subjects exposed to high altitude for a period long enough for symptoms of acute mountain sickness to appear.

Progress:

In conjunction with CPT King and Dr. Robinson, a study was conducted in which six groups of four subjects each were exposed to a simulated altitude of 14,000 feet for a period of 30 hours. During this period, two-minute EEG samples were taken from three positions on the head every four hours during the waking hours. A sea-level control sample was obtained before each altitude exposure period.

All samples were recorded on a Grass Model 6 electroencephalograph and an Ampex 1300 analog tape recorder for off line analysis at a later time. Records are being analyzed for shifts in percentage of energy found in classical frequency bands (4-8 H_z, 8-13 H_z, >13 H_z) and for changes in amplitude and dominant alpha frequency.

Conclusions:

Preliminary data indicate a large individual variance but a consistency of response within individuals. Gross shifts in EEG variables over time are not apparent, but more concrete conclusions await further statistical analysis.

Future Plans:

Statistical analyses of the EEG variables recorded will be carried out to determine significant shifts over the period of exposure. It is also of interest to determine the degree of predictive value these EEG measures have for severity of cerebral symptoms. Data collected by King and Robinson on the severity of symptoms exhibited by each subject will be compared with the EEG measures for that subject to determine whether such measures can be used to differentiate between moderate and severe cases.

Title of Study: Learning curves for tasks to be used repeatedly in investigating the effects of environmental stress on psychological functioning

Investigators: Joseph J. Fleishman, CPT, MSC and E. Ralph Dusek, Ph.D.

Background:

In order to measure the effects of extreme environments on military effectiveness of soldiers, it is frequently necessary and/or desirable to measure psychological and physiological responses repeatedly and concurrently. The present research was designed to assess the stability and sensitivity of 63 psychological tasks which appear relevant for use in the above type studies. In the use of such tasks, it is particularly important that practice, boredom, and/or fatigue effects associated with the tasks be minimal to avoid confounding with the effects attributable to the environmental variables.

Progress:

Ninety enlisted men were administered 63 psychological tasks repeatedly. The effects of practice were assessed under normal ambient room conditions.

Conclusions:

Practice effects and effects attributable to different groups of subjects were significant with the Repetitive Psychometric Tests (RPM), a battery of six tests in 21 forms each. The results for these tests indicate that the forms are not strictly equivalent, but that they may be used in making repeated measures in longitudinal studies with minimal confounding of results if difficulty level of forms is considered.

A second battery of cognitive tests were administered repeatedly to some 90 soldiers. Reliability of the tests was good. Twenty-one of the tests appear suitable for use in long term stress studies.

Future Plans:

As a result of this work, three papers have recently been submitted to journals for publication, one of which is already accepted. The tests will be used in specific studies of the effects of environmental stresses during FY 72.

Title of Study: The development of a multiple cue probability learning task for the evaluation of complex information processing

Investigators: Stanley M. Halpin, Ph.D. and Arlene Sampson

This study is aimed at the development of a task which can serve as a laboratory analog to information transmission and processing found in modern military operations. Successful completion of this project should yield a set of tasks sensitive to various environmental stressors and which are valid indicators of complex mental processes.

The task presently being studied requires subjects to make predictions about the relationships of a set of numbers, based on prior experience with similar relationships. Previous research has shown that the ability to perform such a task correlates with the ability to perform other cognitive tasks.

Twenty subjects have been run in a pilot study. Although the initial computer program used to produce the stimuli proved inadequate, sufficient information was obtained to determine that this task is challenging to the subjects, and that it is sensitive to individual differences. It is planned to revise the computer program producing the stimulus sets and to then obtain baseline performance data. Future studies will use this task to test the degree of cognitive performance impairment induced by various environmental stressors.

Title of Study: Development of measures of march rate

Investigator: R. F. Goldman, Ph.D.

The ability to accurately predict the physiological cost of marching at fixed rates over various terrains with varying loads allows study of what the soldier will do under these various conditions, as opposed to what it will cost him to work at a specified rate. The self-pacing treadmill, i.e., one which automatically adjusts itself to the soldier's progression without any awareness on his part that his speed of march has altered, is a promising tool for analyzing the subtle effects of various load carriage systems, ambient environmental conditions, or physiological state, e.g., dehydration, elevated body heat stores, etc., on this aspect of military performance.

One of the most significant areas where improvement is hoped for is in the load carriage systems used by the soldier. A proposed new load carriage system, a "hip pack", where the weight can be balanced at will between the hips or the shoulders, was previously shown to have an identical energy cost per pound of load as equivalent weight in conventional load systems. The self-pacing treadmill was used to assess whether the "increased comfort" claimed for this new pack would result in the men feeling sufficiently less stress to unconsciously increase their voluntary march rate, on this unique treadmill. The study was completed this year and, rather surprisingly, failed to show any difference between the march rates adopted with this new hip pack as opposed to the standard hip pack, when equivalent weights were carried with both systems, although the soldiers expressed a distinct preference for the hip pack. Thus, although such preferences have been shown to be variable from subject group to subject group and easily controlled, at the moment we apparently have no better method for assessing the effects of load carriage systems.

Future plans include assessment of these different types of load carriage systems, using a heart-rate controlled treadmill; i.e., a treadmill whose rate is servo-controlled to maintain a pre-selected heart rate, established by the investigator. Such a measuring system should be very sensitive. If we cannot distinguish between load carriage systems in terms of the march rate established with these different load carriage systems at a specified heart rate, then we must conclude that, in fact, there is no difference whatever in physiological cost of these systems, no difference in the rate at which the men will

march while carrying them, and finally, no difference in the energy cost demanded by such load carriage systems. In such an event, it is highly improbable that such measuring techniques as the test course at GETA, Fort Lee, VA (or Fort Benning, GA) would show any differences between less widely differing load carriage systems. We would be forced to the conclusion that, although a very difficult and variable measure, subjective acceptance by the soldier is in fact the only available means for selection of load carriage systems.

(82106)

RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY

1. AGENCY ACCESSION	2. DATE OF SUMMARY	REPORT CONTROL SYMBOL
DA OB 6120	71 07 01	DD-DR&E(AR)636

3. DATE PREV SUMRY	4. KIND OF SUMMARY	5. SUMMARY SECTY	6. WORK SECURITY	7. REGRADING	8A. ORG'N INSTR'N	8b. SPECIFIC DATA-CONTRACTOR ACCESS	9. LEVEL OF SUM
70 12 31	D. Change	U	U	N/A	N/L	[X] YES [ ] NO	A. WORK UNIT

10. NO./CODES:	PROGRAM ELEMENT	PROJECT NUMBER	TASK AREA NUMBER	WORK UNIT NUMBER
a. PRIMARY	6.11.02.A	3A061102B71R	05	059
b. CONTRIBUTING				
c. CONTRIBUTING	CDOG 141 (2a)			

11. TITLE (Precede with Security Classification Code)

(U) Biological Processes that Limit Heavy Physical Work Ability of the Soldier (22)

12. SCIENTIFIC AND TECHNOLOGICAL AREAS

002300 Biochemistry; 012900 Physiology; 005900 Environmental Biology

13. START DATE	14. ESTIMATED COMPLETION DATE	15. FUNDING AGENCY	16. PERFORMANCE METHOD
70 07		DA	C. In-House

17. CONTRACT/GRANT

a. DATES/EFFECTIVE: N/A EXPIRATION:

b. NUMBER:

c. TYPE: d. AMOUNT

e. KIND OF AWARD: f. CUM. AMT.

18. RESOURCES ESTIMATE	a. PROFESSIONAL MAN YRS	b. FUNDS (In thousands)
FISCAL YEAR PRECEDING 71	4.7	257
FISCAL YEAR CURRENT 72	6.5	391

19. RESPONSIBLE DOD ORGANIZATION

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TELEPHONE: 955-2873

SOCIAL SECURITY ACCOUNT NUMBER

ASSOCIATE INVESTIGATORS

NAME: Giamber, Samuel R. MAJ

NAME: Maher, John T. Mr. DA

21. GENERAL USE

Foreign Intelligence Not Considered

22. KEYWORDS (Precede EACH with Security Classification Code) (U) Work; (U) Endurance; (U) Fatigue; (U) Energy Metabolism; (U) Cardiovascular; (U) Military Performance; (U) Blood Flow; (U) Muscle Metabolism

23. TECHNICAL OBJECTIVE. 24. APPROACH. 25. PROGRESS (Furnish individual paragraphs identified by number. Precede text of each with Security Classification Code.)

23. (U) The soldier's ability to carry out his mission is often limited by his capacity to do sustained heavy physical work. The objective of this research is to identify and characterize those biological processes that affect his ability to perform heavy work, thus providing a rational basis for improving the soldier's performance.

24. (U) In humans and animals subjected to either exhaustive exercise or graded levels of work, the following will be investigated: (1) the nature of O_2 transport; (2) myocardial structure and function; (3) utilization of substrate by skeletal muscle; (4) release of substrate by adipose and other tissues; (5) suitability of animals as model systems; (6) function of the neuroendocrine system.

25. (U) 70 07 - 71 06 Animal studies have revealed (1) skeletal muscle is able to use its endogenous muscle lipid stores as a source of energy; (2) inhibition of free fatty acid release concomitant with rising lactate levels in blood, during heavy physical work, is not due to the inhibition of lipolysis by lactate; (3) impaired myocardial performance due to exhaustive work is not due to mitochondrial damage and disruption of oxidative phosphorylation. - A mathematical model was developed, which facilitates the interpretation of cardiac performance and may yield an index of contractility to assess heart function in man.

In human studies it was found that blood norepinephrine levels were lower and insulin higher during heavy work, after training. This may indicate that the neuroendocrine system is an important determinant in mediating the beneficial effects of training.

*Available to contractors upon originator's approval.

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Title of Study: Development of a laboratory physical endurance test

Investigators: Malcolm A. Gleser, CPT, MC and James A. Vogel, M.D.

Background:

Physical fatigue is a common and severe problem of soldiers on the move. Even in the modern Army, the physical endurance of soldiers is one of the limiting factors in Army plans and maneuvers. Many factors which affect endurance, such as sleep, nutrition, proper clothing and the will to succeed, have been carefully supplied to the soldier. However, despite many years of research, the underlying physiological causes of fatigue are still unknown. A set of good, reproducible laboratory tests to measure endurance is essential for detailed studies into the various causes of fatigue.

Progress:

We have chosen bicycle riding to exhaustion as a good test of endurance and we are studying many of the factors which effect the results of this test. In the first study, we demonstrated that endurance time is not significantly affected by interposed rest periods ranging from 0 to 20% of the riding time. Further, we demonstrated a significant training effect over the first 3-4 test sessions independent of any changes in maximal oxygen consumption.

In progress, currently, is a study to determine the effects of varying work intensity on the endurance capacity of subjects (both physically trained and untrained).

Future Plans:

We plan to study the effects of hypoxia, hyperoxyxia, sleep loss and many pharmaceutical agents on endurance capacity. With these tests we hope to establish which variables are important to control in using this endurance test to study the causes of fatigue.

Title of Study: Factors influencing lipid utilization during exercise

Investigator: Roger W. Hubbard, Ph.D.

Human performance has been defined as ability plus the disposition to withstand stress. Within this definition are included both the psychological or motivational aspects of performance as well as the physiologic or metabolic factors. One measure of human performance is the capacity for physical work, and certainly this must be considered a relevant factor in military operations. Recent research has identified certain key factors controlling the ability to perform heavy work, i.e. the metabolic fuel supply, the redistribution of blood flow and the accumulation of blood lactic acid. Our investigations have been directed towards the interrelationships between these factors and the biological processes that limit heavy physical work.

During severe exercise there is an apparent shift in the metabolism of working muscle from the combustion of primarily lipid in the form of fatty acids to the utilization of carbohydrate as glucose. Since the supply of energy available in the body as glucose is small compared to the stores of fat, this metabolic shift in body fuel utilization could restrict the degree or duration of heavy work. Precisely what causes this change in metabolic mixture is unknown. It is possible, however, that the rate of fatty acid metabolism has outstripped its availability. The major sources for fatty acids in the body are the adipose tissue deposits, some of which are found between muscle groups. In a previous study we have determined how such factors as the age, body weight and food intake of the animal alters its ability to release fatty acid on the hormonal demand of norepinephrine. By relating cell function with the structural changes in adipose tissue, it was shown that the lipolytic response to catecholamines was affected by both the number and size of the adipocytes. These findings were consistent with observations by others on the hormonal response of adipose tissue to insulin.

It was necessary, therefore, to extend these findings and to determine whether experimentally induced changes in muscle cell size and number would affect the metabolic response of that tissue also. In order to define the changes that occur in skeletal muscle with training as either hypertrophy or hyperplasia, it was necessary to measure tissue DNA. Since the existing methodology for the extraction of DNA proved inadequate for muscle, the major factors affecting recovery were investigated. The results indicated that the ability of hot acid extraction (Schneider

process) to release the chromogen (indole reaction) from DNA is opposed by two major factors: (1) the capacity of the hot hydrolysis to entrap solubilized but incompletely hydrolyzed DNA in a protein precipitate and (2) the ability of the hydrolysis to destroy the chromogen for the reaction. From these experiments, it has been possible to define the optimum conditions for recovering DNA under a wide variety of circumstances and to supply limits beyond which further increases in time, temperature and acidity of extraction are impractical. Further research in this area is now in progress.

The interrelationship between blood flow and cell metabolism has been studied *in vitro* by measuring the effect of blood borne intermediates such as lactic acid on isolated fat cells. The results indicated that the accumulation of lactate does not appear to have any primary inhibitory effect on lipolysis; therefore, the inhibition of free fatty acid release seen concomitantly with rising lactate levels *in vivo* is mediated by some other factor. Future research on the role of blood flow through adipose tissue during exercise is planned.

Title of Study: Energy metabolism and body fuel utilization during sustained physical work

Investigators: Donald G. Therriault, Ph.D., L. Howard Hartley, LTC, MC, George A. Beller, MAJ, MC, James A. Smoake, CPT, MC

Background and Rationale:

During rest, the skeletal muscle uses only about 30% of the oxygen consumed by man. However, during moderate to heavy work, it will account for 70-90% of the oxygen consumption. Clearly, during heavy work and even during moderate work, skeletal muscle catabolizes most of the fuel that is consumed by the individual.

The nature of the fuel utilized by the contracting musculature during work has been a subject of debate for many years. Ten years or so ago, many believed carbohydrate to be the sole fuel for muscular activity. It subsequently has been shown conclusively that both carbohydrate and lipid serve as fuel for contracting muscles. However, there is still considerable uncertainty regarding the quantitative role of each substrate at any given work load.

Considerable evidence exists from human and dog studies to indicate that fat in the form of free fatty acids, serves as a major source of energy for muscular work. Though there may be no question as to the importance of free fatty acids during moderate work, little is known about the relative role of lipid metabolism during heavy work.

Recent studies in Sweden indicate that during heavy work, the glycogen store of the working muscle progressively decreases. It was shown that the capacity for prolonged heavy leg exercise in man is directly correlated to the glycogen store in the working muscle(s). These experiments seem to support the conclusion that the intensity of work affects the relative contributions of fat and carbohydrate to the working muscle. During moderate exercise fat is the main energy supply. The closer the subject works to his maximum capacity the more important is carbohydrate. However, no assessment of the participation of lipids during these periods of heavy work has been carried out. Some of the questions that still remain unanswered are: Does the muscle utilize its endogenous stores of lipid? Is the muscle capable of extracting and utilizing circulating free fatty acids? Since the muscle cells contain enzymes which readily oxidize long-chain fatty acids to carbon dioxide

and water, it is difficult to understand why fatty acids cannot support heavy work in muscles, even when depleted of glycogen stores.

The eventual sources of energy for the resynthesis of ATP must be either fat and glycogen stores in the muscle cell, or fatty acids and glucose which can be taken up from the blood. The mechanisms which control the relative participation of each of these energy sources during heavy work remain a mystery which must be solved if we wish to eventually increase the capacity of the soldier to perform sustained heavy work.

Progress:

We have thus far been successful in establishing an animal model in which, if properly trained, the dog will run on a treadmill until exhausted. The criteria of exhaustion are muscle glycogen depletion, elevated blood lactate, and the inability to continue running on the treadmill. At a heavy work load the dog will run for less than one hour, at which time his muscle glycogen levels have been depleted by 80% and blood lactate levels have reached four times resting levels. At moderate work loads the dog will run for much longer periods of time. Under these conditions, muscle glycogen depletion is considerably less than at heavy work loads and blood lactate levels are not as high.

Arterio-venous difference in free fatty acids, triglycerides and glucose were measured in a limited number of dogs, at various time intervals during moderate and heavy work. Muscle neutral lipid and glycogen levels were also measured before and after these work periods. The results indicate that in addition to muscle glycogen, the dog is able to use his endogenous muscle lipid stores as a source of energy. The results also strongly suggest that at moderate work loads the circulating free fatty acids are taken up and utilized by the muscle, whereas at heavy work loads the extraction of free fatty acids by the muscle may be blocked. Circulating triglycerides do not seem taken up by muscle at any work load.

Future Studies:

More data must be accumulated to definitely establish the fate of circulating free fatty acids, and the role of muscle lipid at moderate and heavy work loads. It still remains to be shown whether the utilization of muscle lipid occurs normally during physical exercise or is a consequence of the decreased uptake of free fatty acids.

Title of Study: The effects of muscular exercise and physical training on neuroendocrine metabolic profile

Investigators: L. H. Hartley, LTC, MC, L. G. Jones, COL, MC, and J. W. Mason, M.D. (Walter Reed Army Institute of Research)

Background:

The duration that a heavy submaximal work load can be sustained relates closely to the time required for muscle glycogen to disappear. During these heavy loads lactate concentration increases in the blood. If an individual undergoes vigorous physical training with resulting increase in maximal O_2 uptake, his endurance time increases and the lactate levels in the blood are less. These observations suggest that O_2 availability may be determining the endurance time and lactate levels. However, recent studies by Kajser indicate that O_2 may not be the sole determinant of these factors. Since it is known that substrate utilization is greatly affected by neurohormonal agents, the present study was done to determine the response of the neuroendocrine system to muscular exercise.

Progress:

Seven normal male subjects were studied during bicycle exercise before and after a vigorous physical conditioning program. Brachial venous blood was obtained during short mild, moderate, and maximal exercise, and on another day, during heavy work (70-80% of maximal O_2 uptake) blood was sampled after 40 minutes of exercise and at exhaustion. Physical conditioning resulted in 15% increase in maximal O_2 uptake, and a marked increase in endurance time. After the physical conditioning program, the study was repeated. Several publications have resulted.

Conclusions:

A predictable change in plasma neurohormones occurs with exercise, and although qualitatively unchanged after training, important changes quantitatively occurred. Norepinephrine was lower and insulin was higher after training during heavy work.

These changes may be of great importance since they could affect endurance time. The lower norepinephrine levels after training could lead to a lesser rate of glycogen utilization, lower lactate levels, and greater endurance time; it may even be of importance in the reduction of

heart rate after training. The higher insulin levels would allow greater access of the circulating glucose to the muscle cell which also would spare glycogen. This study indicates that some of the beneficial effects of training may be mediated through the neuroendocrine system, and may be important determinants of working ability on heavy work loads.

Future Plans:

Animal studies are underway to relate the sympathetic nervous system and substrate utilization.

Title of Study: The response of plasma renin levels to graded exercise

Investigators. L. H. Hartley, LTC, MC, T. A. Kotchen, MAJ, MC (Walter Reed Army Institute of Research), L. G. Jones, COL, MC, J. W. Mason, M.D. (Walter Reed Army Institute of Research)

Background:

During mild exercise, renal blood flow does not change, but with increasing intensity of work renal blood flow decreases. The present study was performed to see if plasma renin levels are related in a regular fashion to increasing work loads, and if they follow a time course possibly related to renal blood flow changes.

Progress:

Seven young male subjects and two investigators were studied at rest and during submaximal and maximal O_2 uptake. Plasma levels of renin were determined on blood obtained during 8 minutes of submaximal exercise and 5 minutes of maximal exercise. Renin levels did not change with mild (45% of maximal O_2 uptake), but increased at moderate (70%), and maximal work. The pattern of response of renin and norepinephrine were similar, suggesting that catecholamines may be of importance in renin release. The pattern of response also could suggest that renin may increase in the plasma in response to renal blood flow decrease.

The principal importance of this study lies in the aid in delineating the regulatory factors in renin secretion.

Future Plans:

None.

Title of Study: Effect of training at low work loads

Investigators: S. R. Giamber, MAJ, MC, and L. H. Hartley, LTC, MC

Background:

Training programs have utilized various regimes whereby maximum aerobic capacity has been increased. Halleman and Venroth demonstrated that half an hour's training four times a week at a heart rate of 115-125 beats/min leads to a lower heart rate at rest and during submaximal exercise. Only with further more intensive training that elicited heart rates of 170-180 were they able to show increase in both maximal oxygen uptake and stroke volume. Karvonen concluded from his studies that to improve exercise tolerance one must increase heart rate at least 60% of the difference between the resting and maximal rate. Other studies by Karvonen et al reported that heart rates of 150 beats/min were necessary for significant training. Roskamm felt that training must take place at 70% of the difference between resting and maximal heart rate. On the other hand, Durnin observed that walking that elicited heart rates of 120-130 resulted in a significant decrease in heart rate to a set work task. Faria trained young men for a brief period of time - five days a week for four weeks - by exercising them up to a specified heart rate which terminated that period of exercise. He also concluded that heart rates of 140-150 must be elicited in order to increase working capacity after the training episode.

A recent study in Alaska showed a 5-8% increase in maximum $\dot{V}O_2$ in a group of men who did light work for ten days during cold exposure. The work load during their daily activities (example, walking with a pack) was estimated to be about 50% of maximum $\dot{V}O_2$. Their heart rates were in the range of 100-120 during this activity.

Consequently, a controlled experiment with men working at only 50% of their maximum ability was performed. In addition, these young men exercised for only nine one-hour periods over a period of three weeks.

Progress:

The study was completed in March 1971.

Conclusions:

The average maximal O_2 uptake before the study was 3.31 liters/min and 46.55 ml/kg. After training this had increased to 3.51 liters/min and 49.81 ml/kg. This represented an increase of 6% for the group (nine men). This represented a significant rise with the P value of $< .01$. Of the nine subjects, one showed no increase; three had an increase of .10 liters/min and five had greater than .1 liters/min increase in their maximum VO_2.

The heart rate response to a fixed submaximal load did not diminish in spite of their increase in aerobic power. The average oxygen consumption during their training period was 1.71. Before training, they had an average heart rate of 126 and after training this same work load was done with an average heart rate of 127. This slight difference in heart rate was, of course, not significant.

This latter finding of increase in maximum VO_2 without a decrease in heart rate for any submaximal load is at variance with previous studies. It appears that low level exercise at very low work loads may dissociate this phenomenon.

Future Plans:

None.

Title of Study: Responses of rat myocardium to exhaustive exercise

Investigators: J. T. Maher, A. L. Goodman, R. P. Francesconi, W. D. Bowers, and L. H. Hartley, LTC, MC

Background and Rationale:

Ekelund and colleagues studied the effects of prolonged, non-steady state exercise in young men and observed an increase in end-diastolic volume and in duration of mechanical systole at exhaustion. Finding no other causes, they reasoned that a change in the properties of the myocardium accompanied by less effective ventricular emptying was responsible.

Inferences of functional changes in the myocardium at exhaustion have been drawn from animal studies, as well. Following exhaustive exercise, King and Gollnick observed changes in the fine structure of rat myocardium including extensive mitochondrial damage and myofibrillar disruption. While it has not been established that these morphologic alterations are associated with functional changes, their findings do suggest impairment of oxidative phosphorylation, and hence reduced work capacity of the muscle.

Accordingly, the present study was initiated to evaluate functional properties of cardiac muscle consequent to exhaustion, and where possible, to relate changes to alterations in cellular structure, content, and response to inotropic interventions.

Progress:

Contractile, metabolic, and ultrastructural properties of isolated cardiac muscle were studied in sedentary control rats and compared with rats exhausted by treadmill exercise. Left ventricular trabecular muscles were suspended in Krebs solution at 30°C and stimulated at a frequency of 30/min. The length-active tension curves were depressed with peak developed tension of 1.1 ± 0.2 compared with 2.5 ± 0.3 g/mm^2, exhausted and controls, respectively. Force-velocity relations were also altered, exhibiting significantly less velocity of shortening at the same afterload in muscles from exhausted rats. Time from onset to peak tension development, latency, and passive compliance were not significantly different. The augmentation of isometric tension in response to exogenous norepinephrine (NE) was markedly depressed in muscles from exhausted rats. Myocardial concentrations of adenosine triphosphate (ATP), creatine phosphate (CP), and NE

were maintained at exhaustion. Moreover, there were no demonstrable changes in the fine structure of the myocardium after exhaustive exercise.

Summary and Conclusions:

Results from this study support the view that exhaustion in the rat is associated with a depression in the intrinsic contractile state, characterized by a reduction in both peak isometric tension and velocity of shortening. The mechanism responsible for the impaired myocardial performance remains obscure. Under the conditions of these experiments, it is clear that the functional depression was not accompanied by a fall in either NE levels or in total ATP, the immediate energy source for muscular contraction. The absence of discernible changes in fine structure of the mitochondria, while not confirming the observations of King and Gollnick, is nevertheless, compatible with our finding of maintained energy stores. The decreased inotropic responsiveness to exogenous NE may help to explain the *in vivo* alterations in heart volume and duration of mechanical systole at exhaustion. However, this decreased sensitivity does not by itself account for the defect in contractility which we observed *in vitro*.

Future Plans:

Studies have been designed to pursue the mechanism(s) responsible for changes in myocardial function consequent to exhaustion.

Title of Study: A mathematical method for analyzing myocardial performance *in vitro*

Investigators: Arnold L. Goodman, J. T. Maher, and L. H. Hartley, LTC, MC

Background:

The isolated mammalian papillary muscle has been extensively studied as a useful model of heart muscle performance. The parallel fiber structure of this preparation allows its mechanical performance to be studied by techniques well established for skeletal muscle investigation; namely, the determination and interpretation of force-velocity and length-tension relationships. However, two key differences between heart and skeletal muscle complicate the analysis of the classical skeletal muscle approach. In contrast to skeletal muscle, heart muscle, under normal circumstances, cannot be tetantized; and secondly, heart muscle develops maximum isometric tension only when it is subjected to a substantial resting tension.

Sonnenblick was among the first to apply the techniques of striated muscle investigation to cat papillary muscle performance (*in vitro*).[1] As his work and that of others continued on this preparation it became apparent that a more involved relationship is necessary to characterize the contractile state of the myocardium, requiring simultaneous consideration of force-velocity-length-time relations (FVLT). FVLT relations are obtained by phase-plane analysis and quick release, which require complicated experimental procedures and precise analysis of data.

Since other studies in progress in this laboratory were designed to indicate changes in myocardial function in response to exhaustive exercise and hypobaric hypoxia, it was appreciated that a simpler method of determining the parameters needed to characterize myocardial contractility would prove valuable not only for the studies on hand but also for the design and execution of future investigations. Accordingly, an effort was made using the combined techniques of statistical analysis and the calculus, whereby FVLT relations could be obtained from the more simply measured force-velocity parameters.

Progress:

A mathematical model of the mechanical performance of the rat tabecula carnea muscle *in vitro* has been developed which quite accurately describes the instantaneous relationships between amount of, and velocity of

shortening and load. Further, this model permits expression of the rate and extent of force development, mechanical latency and effects of inotropic intervention on the intensity and duration of the active state.

At a given initial muscle length (preload), velocity of shortening (V) can be described as a sine wave function of time and load;

$$V = V_{max} [\sin(\omega t + \phi) - \sin \phi]$$

Where omega (ω) is an angular velocity whose magnitude is invariant with increasing afterloads, V_{max} is the theoretical velocity of shortening against no load, derived by least squares regression analysis of the virtually linear force-velocity relation. Sin ϕ is the ratio of a particular load; Pi, to the isometric load; Po, at the particular preload, i.e. sin ϕ = Pi/Po.

By integrating $V(t, \phi)$ with respect to time the amount of shortening (S) can be expressed as:

$$S = S_{max} [\cos \phi - \cos(\omega t + \phi) - \omega t \sin \phi]$$

when S_{max} is the amount of shortening against no load.

S is expressed in mm, V in mm/sec, t is time in seconds, and $\omega = V_{max}/S_{max}$ as radius/sec; ϕ, as a ratio, is dimensionless.

Knowing the initial length (Li) at a preload instantaneous muscle length (L) is simply

$$L = Li - S(t,\phi)$$

When Pi = Po, $\phi = \sin^{-1}$, Pi/Po = $\pi/2$, and S = V = 0.

When Pi = 0, ϕ = 0 and S = S_{max} and V = V_{max}.

By differentiating $V(t,\phi)$ with respect to time, the resultant acceleration (ω) of the load, Pi, can be determined

$$a = \omega V_{max} \cos(\omega t + \phi).$$

From this, using Newton's first law, F = ma, the resultant force F (i.e., the difference between the upward pull of the muscle and the downward pull of gravity) can be determined.

$$F_r(t,\phi) = Pi\ a(t,\phi)$$

The actual muscle force, F_m, can be expressed by

$$F_m = Pi\ g + F_r(t,\phi)$$

where g = acceleration due to gravity.

The duration of the twitch is $2\pi/\omega$, the time to peak velocity = $\pi/2\omega$. The effect of the addition of norepinephrine is to shorten the duration of the active state, and can be thought of as increasing ω.

The equations for $S(t,\phi)$ and $V(t,\phi)$ are identical with equations describing the performance characteristic of a sinusoidally forced simple harmonic oscillator, which is in agreement with currently proposed models of muscle function. Omega (ω) is the rate of force development at a particular preload or initial length, by the relation

$$F_m = F_o\ Sin(\omega t)$$

where $F_o = P_o\ g$.

Conclusions:

This model can serve to facilitate the interpretation of the performance of isolated myocardium *in vitro*. Together with continued *in vitro* investigation it may yield an index of contractility that can be employed to assess cardiac function in intact subjects.

Future Plans:

To test experimentally the hypothesis.

Title of Study: Ventricular function in man during prolonged, exhaustive exercise

Investigators: J. T. Maher, G. A. Beller, MAJ, MC, and L. H. Hartley, LTC, MC

Background and Rationale:

The central circulatory response to prolonged exercise is characterized by a (1) progressive fall in stroke volume, (2) fall in mean arterial pressure, (3) fall in central venous pressure, and (4) a progressive rise in heart rate keeping cardiac output essentially constant. While the basis of these findings remains to be clarified, it has been suggested that there may be a change in myocardial performance secondary to impaired contractility at the end of an exhausting exercise period of prolonged duration. If impaired filling were a major determinant, one would expect a decrease in heart volume of a magnitude related to the decrease in stroke volume. However, as their subjects approached exhaustion, Ekelund and co-workers observed a roentgenologically-determined increase in end-diastolic heart volume in spite of a further increase in heart rate which theoretically should decrease heart volume because of decreased filling time. The left ventricular ejection fraction (stroke volume/end-diastolic volume) must have decreased in these subjects if stroke volume decreased while the end-diastolic volume increased. A diminished ejection fraction reflects a depression in ventricular contractile performance.

Progress.

Ten young enlisted men without evidence of cardiac abnormalities were studied at rest and during supine exercise to exhaustion. Pilot studies were conducted to select a work load which the subjects could sustain for about one hour and which increased their heart rates to 130 beats per minute after 10 minutes work. The duration of the systolic time intervals, corrected for heart rate, were determined from simultaneous fast speed recordings of the electrocardiogram, phonocardiogram, and carotid arterial pulsation employing a high-speed, multichannel photographic system. The intervals measured included: total electromechanical systole ($Q - S_2$), left ventricular ejection time (LVET), and the pre-ejection period (PEP). In states of decreased myocardial performance, there is an abbreviation of the LVET and a prolongation of the PEP at a time when the $Q - S_2$ remains within normal limits.

The ratio of PEP/LVET offers an index of myocardial performance which is superior to the assessment of either LVET or PEP alone. This ratio remains relatively constant among normal individuals. With diminished ventricular performance, this ratio increases since PEP lengthens while the LVET shortens. In individuals with cardiac disease, the PEP/LVET ratio correlates closely with the cardiac output, stroke volume, and left ventricular ejection fraction.

Conclusions:

While the studies have been completed, no conclusions can yet be drawn since the data are being subjected to statistical analyses.

Future Plans:

To complete analysis of data.

(82104)

RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY

1. AGENCY ACCESSION	2. DATE OF SUMMARY	REPORT CONTROL SYMBOL
DA OA 6143	71 07 01	DD-DR&E(AR)636

3. DATE PREV SUMRY	4. KIND OF SUMMARY	5. SUMMARY SCTY	6. WORK SECURITY	7. REGRADING	8a. DISP'N INSTR'N	8b. SPECIFIC DATA - CONTRACTOR ACCESS	9. LEVEL OF SUM
70 12 31	D. Change	U	U	N/A	N/L	☑ YES ☐ NO	A. WORK UNIT

10. NO. CODES	PROGRAM ELEMENT	PROJECT NUMBER	TASK AREA NUMBER	WORK UNIT NUMBER
a. PRIMARY	6.11.02.A	3A061102B71R	05	060
b. CONTRIBUTING				
c. [illegible]	CDOG 141 (2a)			

11. TITLE (Precede with Security Classification Code): (U)Development and Characterization of Models of Heat Injuries and Disabilities and Other Heat Responses of the Soldier. (22)

12. SCIENTIFIC AND TECHNOLOGICAL AREAS: 005900 Environmental Biology; 003500 Clinical Medicine

13. START DATE	14. ESTIMATED COMPLETION DATE	15. FUNDING AGENCY	16. PERFORMANCE METHOD
70 07		DA	C. In-House

17. CONTRACT/GRANT
a. DATES/EFFECTIVE: N/A — EXPIRATION:
b. NUMBER:
c. TYPE — d. AMOUNT:
e. KIND OF AWARD — f. CUM. AMT.

18. RESOURCES ESTIMATE		a. PROFESSIONAL MAN YRS	b. FUNDS (In thousands)
FISCAL YEAR	PRECEDING 71	2.0	90
	CURRENT 72	0.2	17

19. RESPONSIBLE DOD ORGANIZATION
NAME: USA Rsch Inst Env Med
ADDRESS: Natick, Massachusetts 01760
RESPONSIBLE INDIVIDUAL
NAME: Jones, LeeRoy C. COL
TELEPHONE: 955-2811

20. PERFORMING ORGANIZATION
NAME: USA Rsch Inst Env Med
ADDRESS: Natick, Massachusetts 01760
PRINCIPAL INVESTIGATOR (Furnish SSAN if U.S. Academic Institution)
NAME: Alpert, Arnold Dr.
TELEPHONE: 955-2877
SOCIAL SECURITY ACCOUNT NUMBER
ASSOCIATE INVESTIGATORS
NAME: Breckenridge, John R. Mr.
NAME: Newman, Russell W. Dr. DA

21. GENERAL USE: Foreign Intelligence not Considered

22. KEYWORDS (Precede EACH with Security Classification Code): (U)Disabilities; (U) Military Heat Stress; (U)Pathology Model; (U)Physiology; (U) Biochemistry; (U)Behavior; (U) Tolerance; (U)Heat.

23. TECHNICAL OBJECTIVE, 24. APPROACH, 25. PROGRESS (Furnish individual paragraphs identified by number. Precede text of each with Security Classification Code.)

23. (U) Develop and characterize models, i.e., experimental equivalents or analogues, of heat stress and heat-induced injuries and disabilities in the soldier.

24. (U) Models will be produced using experimental animals, mathematical and physical stimulation, or human subjects. The injury, disability or response will be induced directly by heat or indirectly by chemicals or other agents. Physiological, pathological, biochemical, behavioral or other studies will then determine the nature and usefulness of the model in examining methods of prevention, amelioration, and treatment. Physical and mathematical analogues of heat responses will be produced and studied for predictive value in determining the soldier's tolerance to heat stress.

25. (U) 70 07 - 71 06 Experimental validation of a physical model for predicting solar heat load on a clothed man was continued, using a manikin dressed in tropical fatigues or in cold-wet uniform. Agreement of predicted and experimental values within 4 k cal/hr was obtained by revision of the model parameters and alterations in experimental techniques. As a possible model for the hyperpyrexia of heatstroke Landrace pigs were chosen in which to chemically induce a self-sustaining elevated body temperature. Induction with halothane was attempted on the basis of a reported rare malignant hyperpyrexic reaction observed in humans during anesthesia and a 25% hyperpyrexia susceptibility in Landrace pigs. The response could not be produced in 21 pigs obtained from two sources indicating that the response is not random but is probably genetically determined. Later reports confirmed this.

*Available to contractors upon originator's approval

DD FORM 1498 (1 MAR 68) — PREVIOUS EDITIONS OF THIS FORM ARE OBSOLETE. DD FORMS 1498A (1 NOV 65) AND 1498-1 (1 MAR 68) FOR ARMY USE ARE OBSOLETE

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Title of Study: Development of a heat stroke model

Investigators: Arnold Alpert, Ph.D.; Aubrey E. Boyd, MAJ, M.D.; Milton Mager, Ph.D.

Heatstroke is a potential threat to the soldier in a variety of military operations, particularly if the water supply is limited, if work requirements cannot be strictly controlled, or if an emergency permits no prior acclimatization. However, rational therapy is hindered by a lack of knowledge, particularly biochemical, of heatstroke. An animal model is required to permit experimentation aimed at gaining further knowledge of this injury.

Heatstroke is characterized by a classical triad: (1) central nervous system effects, (2) cessation of sweating, and (3) hyperpyrexia (increased temperature). Of these, only a self-sustaining hyperpyrexia in animals can unequivocally be compared to the hyperpyrexia of heatstroke in man. This has not been achieved in currently proposed models. Recent reports suggested the possibility of inducing a self-sustaining runaway temperature increase using chemical agents. Hence, chemical induction of hyperpyrexia was chosen as a possible route towards development of a heatstroke model or, at least, of the hyperpyrexia of heatstroke.

Induction with halothane was attempted on the basis of a reported rare malignant hyperpyrexic reaction observed in humans during anesthesia. The hyperpyrexia could not be produced in rats. On the basis of a reported susceptibility, Landrace pigs were used in further attempts at producing a hyperpyrexia (21 pigs from two sources). None could be obtained, indicating that the halothane sensitivity is not randomly distributed among these animals. This sensitivity to halothane and possibly to heat stress is probably a genetic defect. Later reports confirmed this. Susceptible animals are being sought.

Title of Study: Evaluation of solar heat load on man

Investigators: J. R. Breckenridge and R. F. Goldman, Ph.D.

Available information on the effects of solar heat load on man in the past has always expressed solar heat load in gross terms; either the sun was shining so there was a solar heat load, or the subject was in the shade, and there was no solar heat load. Several years ago this Institute initiated a program to refine these gross estimates of solar heat load and develop a method for quantitatively expressing the net solar heat to a soldier. His temperature regulating mechanisms would have to be able to handle this additional heat for continuing military performance under a solar heat load.

The original approaches were at the physical and theoretical biophysical level, with a review of the physical factors comprising such a solar heat load concluding that direct incident, diffuse, and terrain albedo reflection were the three parameters to be considered. The biophysical assessment indicated that time of day (i.e., associated solar angle), factors of position, the man's surface area and any changes in surface area produced by clothing, and the absorptance and transmissivity of the clothing, plus the relationship of its total insulation to the still air superficial insulating layer had to be considered.

Subsequent work led to the evaluation of these predictions, using a heated copper manikin erected on a specially constructed platform on the roof of the USARIEM building. The initial data obtained primarily demonstrated the inadequate solar measurement instrumentation available for this task and new instrumentation was ordered. This past year has seen this instrumentation used to collect two series of direct measurements of the new solar heat load to the wearer with several different uniform ensembles. After revision of a number of minor errors in the theoretical physics approach initially used, revision of some of the uniform parameters that had been furnished by the clothing developer, but proved to be incorrect, and a major adjustment in the treatment of diffuse radiation, the revised model will now predict with an accuracy of 5 to 10 watts.

This model will be of great use in the proposed development of a new desert uniform by the Army Materiel Command. Future plans also include a field study in which the predicted solar load will be additive to a metabolic heat load so that we may evaluate whether metabolic heat, produced internally in the body, and solar heat load, injected into the body from the surround, are simply additive in the burdens placed upon the

temperature regulation of the soldier. Additional work is also required in handling the net solar heat load when the man is sweating heavily, since there is still a significant discrepancy between the predicted net solar heat load to the man and that measured on the sweating, heated copper manikin.

(82105)

RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY

1. AGENCY ACCESSION	2. DATE OF SUMMARY	REPORT CONTROL SYMBOL
DA OA 6144	71 07 01	DD-DR&E(AR)636

3. DATE PREV SUMRY	4. KIND OF SUMMARY	5. SUMMARY SCTY	6. WORK SECURITY	7. REGRADING	8A. DISP'N INSTR'N	8B. SPECIFIC DATA-CONTRACTOR ACCESS	9. LEVEL OF SUM
70 12 31	D. Change	U	U	N/A	N/L	☒ YES ☐ NO	A. WORK UNIT

10. NO./CODES	PROGRAM ELEMENT	PROJECT NUMBER	TASK AREA NUMBER	WORK UNIT NUMBER
a. PRIMARY	6.11.02.A	3A061102B71R	05	061
b. CONTRIBUTING				
c. ~~CONTRIBUTING~~	CDOG I41 (2a)			

11. TITLE (Precede with Security Classification Code): (U) Development and Characterization of Models to Study Acute Mountain Sickness and High Altitude Pulmonary Edema in Military Operations (22)

12. SCIENTIFIC AND TECHNOLOGICAL AREAS: 013400 Psychology; 012900 Physiology; 005900 Environmental Biology

13. START DATE	14. ESTIMATED COMPLETION DATE	15. FUNDING AGENCY	16. PERFORMANCE METHOD
70 07		DA	C. In-House

17. CONTRACT/GRANT
a. DATES/EFFECTIVE: N/A EXPIRATION:
b. NUMBER:
c. TYPE: d. AMOUNT:
e. KIND OF AWARD: f. CUM. AMT.:

18. RESOURCES ESTIMATE	PRECEDING/CURRENT FISCAL YEAR	a. PROFESSIONAL MAN YRS	b. FUNDS (In thousands)
	71	2.9	103
	72	1.6	120

19. RESPONSIBLE DOD ORGANIZATION
NAME: USA Rsch Inst Env Med
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RESPONSIBLE INDIVIDUAL
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TELEPHONE: 955-2811

20. PERFORMING ORGANIZATION
NAME: USA Rsch Inst Env Med
ADDRESS: Natick, Massachusetts 01760

PRINCIPAL INVESTIGATOR (Furnish SSAN if U.S. Academic Institution)
NAME: Hogan, Redmond P. MAJ
TELEPHONE: 955-2894
SOCIAL SECURITY ACCOUNT NUMBER:

ASSOCIATE INVESTIGATORS
NAME: Smoake, James A. CPT
NAME: Bandaret, Louis E. Dr. DA

21. GENERAL USE: Foreign Intelligence not Considered

22. KEYWORDS (Precede EACH with Security Classification Code): (U) Altitude; (U) Pulmonary Edema; (U) Mountain Sickness; (U) Acclimatization; (U) Hypoxia; (U) Performance; (U) Military Operations

23. TECHNICAL OBJECTIVE. 24. APPROACH. 25. PROGRESS (Furnish individual paragraphs identified by number. Precede text of each with Security Classification Code.)

23. (U) Development of models, i.e., predictive procedures, for identifying and characterizing those aspects of acute mountain sickness (AMS) and high altitude pulmonary edema (HAPE) relevant to the success of military operations at high terrestrial elevations.

24. (U) Models will be developed for studying (1) etiology of AMS and HAPE; (2) their symptomatology; (3) related functional deficits and disabilities; and (4) factors affecting recovery, in order to develop procedures for improving military effectiveness under high mountain conditions.

25. (U) 70 07 - 71 06 Methods are being developed for identifying and quantitating AMS in squirrel monkeys. These models will be used in the assessment of therapeutic regimens and acclimatization procedures. Exposure of rats to P_B = 190 mmHg at 24-hour intervals resulted in a four-fold increase in tolerance after four exposures. No further tolerance was achieved through additional exposure. Attempts to produce high altitude pulmonary edema in squirrel monkeys by duplication of conditions known to be associated with increased incidence of HAPE in man were unsuccessful. This suggests a disease mechanism which is species specific or idiosyncratic to individuals within a species. The theory is being investigated that at altitude susceptible individuals have defective fibrinolysis, resulting in a series of reactions which eventuate in HAPE. Changes in dog, rat, and rabbit myocardial ultrastructure have been detected by electron microscopy. Biochemical correlates are being investigated in an attempt to identify the responsible mechanisms.

*Available to contractors upon originator's approval

DD FORM 1498 PREVIOUS EDITIONS OF THIS FORM ARE OBSOLETE. DD FORMS 1498A 1 NOV 65 AND 1498-1 1 MAR 68 FOR ARMY USE ARE OBSOLETE

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Title of Study: Development of behavioral indices of acute mountain sickness in the squirrel monkey

Investigator: L. E. Banderet, Ph.D.

Background and Approach:

This work was begun by the late Dr. Martin Gerben

The response patterns of squirrel monkeys exposed to high altitude in clear plexiglass chambers are observed. High altitude can be simulated by means of hypobarism or hypoxic gas mixtures. The animals have access to food and water, and no special training or restraint is required.

The monkeys in these experiments react in a characteristic fashion upon acute exposure to hypoxia and exhibit a different mode of behavior after more prolonged exposure, e.g., 6-10 hours. After these characteristic modes of behavior have been identified, they can be used in an assessment battery which allows rough quantitation of a test animal's response to altitude. This assessment battery can be used in evaluation of the effects of drugs and of various acclimatization procedures on the symptoms of acute mountain sickness.

Such an animal model also provides a means of testing conditions which would be deemed unsafe for human volunteers. In addition, an animal model provides an expedient way of testing a large number of subjects over a long period of time and does not present the logistic complications which make human studies so difficult.

Progress:

Significant behavior modes identified thus far include 1) time spent by monkey with eyelids closed, 2) time required for anorexia from onset of hypoxia, 3) time required for recovery from anorexia after hypoxia is terminated, 4) postural changes and 5) changes in motor behavior and activity level.

Title of Study: Development of a model for high altitude pulmonary edema

Investigator: J. A. Smoake, CPT, MSC

Background:

The incidence of high altitude pulmonary edema in the Indian troops stationed in the Himalayan Mountains since 1962 has been reported to vary from 23 to 155 cases per 1,000 troops. The major obstacles in studying high altitude pulmonary edema are that it is unpredictable, that it is an emergency in humans and does not lend itself to routine clinical study, and the incidence is generally unpredictable at altitudes in which military operations would be conducted. Two factors have been commonly associated with the development of high altitude pulmonary edema: 1) re-exposure of altitude acclimated individuals to high altitude after short periods at sea level; and 2) physical exertion after rapid ascent of unacclimated persons to high terrestrial altitudes. A combination of these factors should maximize the possibility of producing high altitude pulmonary edema.

Progress:

Eight squirrel monkeys were trained to exercise by swimming. Prior to exposure to high altitude, data was obtained on body weights, rectal temperature, chest X-rays, blood pressure, heart rates, arterial P_{O_2}, P_{CO_2}, and pH. The monkeys were then exposed to 16,000 feet simulated altitude (gas mixture) and exercised for up to two hours. Following exercise, the monkeys were exposed to hypobaric pressure simulating 16,000 feet. Data on body weights, rectal temperature, heart rates and chest X-rays were determined daily for the first week of exposure to simulated high altitude and once a week thereafter. After seven weeks of exposure to simulated high altitude, the monkeys were returned to sea level pressure for two weeks, and then re-exposed to 16,000 feet for one week. Chest X-rays were taken daily during the re-exposure.

Conclusion:

No evidence of pulmonary edema appeared in the eight monkeys. Several monkeys died during the course of the first seven weeks of the study. Neither post-mortem examination nor histological section of the lung gave indication of pulmonary edema.

Future Plans: None

Title of Study: A proposed mechanism for the pathogenesis of high altitude pulmonary edema

Investigator: R. P. Hogan, MAJ, MC

Background:

The hypothesis is offered that exposure to high altitude and exercise produce either generalized or localized pulmonary blood hypercoagulability. In normal individuals, this tendency is counteracted by activation of the fibrinolytic system, but in individuals susceptible to high altitude pulmonary edema, fibrinolysis is inhibited so that microclots are allowed to form in pulmonary pre-capillary aterioles. Vessels which remain unoccluded are overperfused, and the increased intra-to-extravascular pressure gradient results in edema formation.

Whayne and Severinghaus (Physiologist 10:342, 1967) produced pulmonary edema in rats by embolization of latex microspheres, and Singh et al. (Ind. J. Med. Res. 57:210, 1969) found significant prolongation of the clot lysis time in patients with acute high altitude pulmonary edema, but shorter than normal lysis times during convalescence. In contrast, controls had shorter than normal lysis times upon exposure to altitude.

Since this study is largely exploratory, several animal species will be studied to find the one giving optimal response. Monkeys, dogs and pigs have been used. They were anesthetized, placed in hypoxic environment, and exercised by electrical stimulation. During this time, epsilon-amino caproic acid was infused to inhibit plasminogen activator, thus inhibiting body defenses against the hypercoagulable states which develop as a result of hypoxia. The presence of intravascular clotting was assessed by means of the protamine gelation and staph clumping tests. Pulmonary edema was sought by clinical examination, X-ray and pathological examination of the lungs. The anticipated pulmonary hypertension resulting from pulmonary intravascular coagulation was monitored by means of a catheter in the pulmonary artery.

Progress:

Pilot studies, utilizing four hours of exposure to hypoxia, show definite intravascular coagulation, but pulmonary edema has not yet been produced.

Conclusions:

1) Intravascular coagulation occurs during four hours of exposure to hypoxia. 2) Normoxic controls do not develop significant intravascular coagulation during epsilon-amino caproic acid infusion. 3) No evidence of pulmonary edema has been observed, but the animals studied thus far are known to have a low pulmonary vascular response to hypoxia, and there is reason to believe that a critical relationship exists between clot size and pulmonary vessel diameter. Exposure times have been much shorter than those usually associated with HAPE in humans.

Future Plans:

To repeat the study using cats, which are known to develop pulmonary hypertension upon exposure to hypoxia. An awake, semi-chronic preparation will be employed so that these animals can be exposed to hypoxia for several days.

Title of Study: Ultrastructure of myocardium in sea level and altitude exposed animals

Investigators: Wilbert D. Bowers, Ph.D., Roy F. Burlington, Ph.D. and Bertwell K. Whitten, Ph.D.

Background:

Bischoff et al. (Fed. Proc. 28:1268, 1969) conducted a survey, at the ultrastructural level, of myocardium from dogs, rabbits and rats in relation to studies of cardiac hypertrophy in these animals. The ultrastructure of heart muscle from dogs and rabbits maintained at 14,000 feet showed swollen mitochondria, expanded cisternae within the sacroplasmic reticulum, increased numbers of lipid droplets, and slight separation of myofilaments in localized areas. Mitochondrial degeneration and elongation were also observed along with enlargement of transverse tubules. Localized areas of edematous capillary endothelial cells were detected.

The alterations found in rat myocardium were limited to moderate mitochondrial swelling in localized regions. It was concluded from this work that rats appear to be less susceptible to lower oxygen levels and are able to withstand prolonged periods under hypoxic conditions without cellular alterations.

Work of Drs. Burlington and Whitten with rats and ground squirrels has established biochemical parameters such as phosphate potentials and levels of intermediary metabolites for hypoxic and normoxic heart muscles. Ultrastructural studies of these tissues aid in defining mechanisms through which altitude exposure induces changes in these animals.

Progress:

Heart muscle mitochondria in tissue from rats exposed to 14,500 feet for 6-12 weeks differ from those of sea level animals. Incubation in a medium containing succinate, rotenone, and rutamycin (Harris et al. Science 165:700, 1969) prior to fixation produced "condensed" or "energized" configurations in mitochondria of altitude-exposed hearts. Similar conditions produced "zig-zag" and "branched" configurations in mitochondria of sea level tissue. This difference in response to the same incubation conditions may relate to changes in mitochondrial membranes which result from prolonged altitude exposure. After similar altitude exposure, isolated perfused rat hearts showed a higher phosphate potential

and greater lactate production than sea level hearts when both were subjected to hypoxia. Changes in mitochondria could complement the increased glycolytic capacity and aid in protecting altitude-acclimated rats from the effects of hypoxia.

Title of Study: The effects of repeated exposure to hypoxia on time to unconsciousness

Investigator: J. A. Smoake, CPT, MSC

Background:

In previous studies done in this laboratory, rats were exposed to 190 mm Hg until the animals lost consciousness. The time that the animals remained conscious after reaching 190 mm Hg is referred to as "tolerance time". Daily exposures of rats to 190 mm Hg until they lost consciousness resulted in an increased tolerance over three exposures. Tolerance times increased from 8 minutes on the first exposure to 16 minutes on the second exposure to 32 minutes on the third exposure. The purpose of the present project is to define the factors and the time course responsible for the enhanced tolerance with successive exposures to the extreme altitude.

Three experiments were planned to answer the proposed questions. In the first experiment, rats were to be exposed three times to 190 mm Hg for determination of tolerance time at two hour intervals. In the second experiment, rats were exposed every other hour to 190 mm Hg for determination of tolerance time until a maximum value of tolerance time was obtained. The third experiment was designed to determine tolerance time of rats to 190 mm Hg at a thermoneutral temperature.

Progress:

The original observation that rats enhance their tolerance time to 190 mm Hg with repeated daily exposures to 190 mm Hg was reaffirmed. Maximal tolerance was obtained upon the fourth daily exposure to 190 mm Hg. However, when the animals were given repeated exposures to 190 mm Hg at two hour intervals, only 2 of 9 animals demonstrated a noticeable increase in tolerance time from one exposure to the next. When the animals were exposed to 190 mm Hg in a thermoneutral environment of 81°F, the tolerance times were greatly reduced (about 2.5 minutes) when compared to controls (about 8 minutes) at room temperature. Concentration of hemoglobin was determined before the first exposure and after the last exposure to 190 mm Hg. Each group of animals showed an increase in hemoglobin concentration, but there were no differences in hemoglobin changes between the groups.

Deep body temperature was found to decrease exponentially with time at 190 mm Hg.

Conclusion:

Rats exposed every 24 hours to 190 mm Hg demonstrated an enhanced tolerance to 190 mm Hg with each successive exposure to the severe altitude; a maximum tolerance time was obtained upon the fourth exposure to 190 mm Hg. Increases in hemoglobin which occur after exposure to severe hypoxia do not appear to play a major role in the development of tolerance to 190 mm Hg. The ability of animals to enhance their tolerance time to 190 mm Hg may be a function of the ability of the animal to reduce his body temperature.

Future Plans:

To further define the fact sponsible for development of tolerance to severe hypoxia.

Project No: 3A061101A91C

Title: In-House Laboratory Independent Research

(81101)

RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY

1. AGENCY ACCESSION	2. DATE OF SUMMARY	REPORT CONTROL SYMBOL
DA OB 6121	71 07 01	DD-DR&E(AR)636

3. DATE PREV SUMRY	4. KIND OF SUMMARY	5. SUMMARY SCTY	6. WORK SECURITY	7. REGRADING	8. DISS'N INSTR'N	9. SPECIFIC DATA-CONTRACTOR ACCESS	9. LEVEL OF SUM
70 12 31	D. Change	U	U	N/A	N/L	☒ YES ☐ NO	A. WORK UNIT

10. NO./CODES:	PROGRAM ELEMENT	PROJECT NUMBER	TASK AREA NUMBER	WORK UNIT NUMBER
a. PRIMARY	6.11.01.A	3A061101A91C	00	020
b. CONTRIBUTING				
c. CONTRIBUTING				

11. TITLE (Precede with Security Classification Code): (U) Factors Limiting Military Performance at Sea Level and High Altitude and their Modification by Acclimatization and Adaptation (22)

12. SCIENTIFIC AND TECHNOLOGICAL AREAS: 005900 Environmental Biology; 012900 Physiology; 016200 Stress Physiology

13. START DATE	14. ESTIMATED COMPLETION DATE	15. FUNDING AGENCY	16. PERFORMANCE METHOD
70 07		DA	C. In-House

17. CONTRACT/GRANT
a. DATES/EFFECTIVE: N/A EXPIRATION:
b. NUMBER:
c. TYPE: d. AMOUNT:
e. KIND OF AWARD: f. CUM. AMT.

18. RESOURCES ESTIMATE	a. PROFESSIONAL MAN YRS	b. FUNDS (In thousands)
FISCAL YEAR PRECEDING 71	2.0	82
FISCAL YEAR CURRENT/Y 72	0.2	5

19. RESPONSIBLE DOD ORGANIZATION
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RESPONSIBLE INDIVIDUAL
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20. PERFORMING ORGANIZATION
NAME: USA Rsch Inst Env Med
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PRINCIPAL INVESTIGATOR (Furnish SSAN if U.S. Academic Institution)
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TELEPHONE: 955-2800
SOCIAL SECURITY ACCOUNT NUMBER:

21. GENERAL USE
Foreign Intelligence not Considered

ASSOCIATE INVESTIGATORS
NAME: Vogel, James A., Ph.D
NAME: Hogan, Redmond P. MAJ DA

22. KEYWORDS (Precede EACH with Security Classification Code): (U) High Altitude; (U) Exercise; (U) Military Performance; (U) High Altitude Natives; (U) Atropine

23. TECHNICAL OBJECTIVE. 24. APPROACH. 25. PROGRESS (Furnish individual paragraphs identified by number. Precede text of each with Security Classification Code.)

23. (U) High altitude environments which are potential theaters of war are known to lead to decreased physical performance and disease. These effects vary in duration from days to years, however, potential opponents might be fully acclimatized. Several altitude populations have the ability to perform at high elevations almost at sea level efficiency, and one such population is Andean in Peru. It is proposed to study the mechanism of disability which results from high altitude exposure, and the means by which natural acclimatization occurs in an effort to determine ways of speeding acclimatization and normalizing performance at altitude.

24. (U) The proposed experiment includes the study of human subjects during exercise to determine the extent and cause of disability at great terrestrial altitudes and comparison with normal function at sea level. Also, high altitude natives will be studied during exercise to determine the degree of superiority of their performance at high elevations and the mechanism of this superiority at altitude. Finally it will be determined if the physical performance of sea level subjects can be improved by pharmacological agents at great terrestrial altitudes, i.e., 16,000 ft., where the disability of the subjects and physiological changes are greatly developed.

25. (U) 70 07 - 71 06 Four S.L. subjects were found to have a reduced cardiac output and maximal O_2 uptake at 2 days and at 10 days of exposure to 14,000 ft. elevation. Four S.L. subjects had decreased endurance time during heavy submaximal work at 2 days and slight improvement by 10 days. These changes were not due to muscle glycogen decrements. At 16,000 ft. elevation even more decrement in working capacity occurred. The decrement in maximal heart rate at altitude was partially reversed by atropine. Eight high altitude natives had superior work capacities compared to sojourners at altitude, and this superior performance was due to better pulmonary gas exchange and transport of O_2 to working muscles. The studies indicate the time course of acclimatization to high altitude and give clues to methods of optimizing this performance. Eight manuscripts are in preparation.

*Available to contractors upon originator's approval

DD FORM 1498 PREVIOUS EDITIONS OF THIS FORM ARE OBSOLETE. DD FORMS 1498A, 1 NOV 68 AND 1498-1 1 MAR 68 (FOR ARMY USE) ARE OBSOLETE

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Title of Study: Peru Study I. The effects of 2 days and 10 days of high altitude exposure on physical working capacity

Investigators: L. H. Hartley, LTC, MC; J. A. Vogel, Ph.D.; R. P. Hogan, MAJ, MC; J. Cruz, M.D. (Peru); and B. Saltin (Sweden)

Background:

After exposure to high altitude, man's physical working capacity is decreased. This can be demonstrated by decreases in maximal O_2 uptake and on the working time to exhaustion (endurance time) at submaximal loads. The purpose of this study was to define the changes which occur in physical working capacity at 2 days and at 10 days of high altitude exposure, and examine possible mechanisms involved.

Progress:

Studies were done in August and September 1970, at sea level in Lima, Peru, and at 14,000 feet altitude in Cerro de Pasco, Peru. Subjects were eight normal Peruvian medical students. Four were studied with cardiac output, and four with endurance and muscle biopsies.

Methods used included upright bicycle exercise, dye dilution cardiac output, needle biopsy of the quadriceps femoris muscle for glycogen, and O_2 uptake by the Douglas bag technique, and all analyses were by standard techniques on equipment taken to Peru from USARIEM.

Measurements included: O_2 uptake, cardiac output, alveolar-arterial PO_2 differences, hemoglobin dissociation curves, pulmonary arterio-venous shunts of blood flow, endurance time, and muscle glycogen levels.

Conclusions:

A decrease occurred in working capacity at 2 days as judged both by maximal O_2 uptake and endurance time. At 10 days the reduction in maximal O_2 uptake persisted, although endurance time improved slightly. This reduction was accompanied by decreased cardiac output, due in turn to a decreased stroke volume. The pulmonary gas exchange was improved as judged by a slightly narrower alveolar-arterial PO_2 difference which was even narrower at 10 days than 2 days. Pulmonary blood flow had a slightly lesser arterial to venous shunt indicating less efficient distribution of

blood to ventilated lung at altitude. Hemoglobin dissociation curves shifted to the right at 10 days; this has the effect of improving O_2 delivery to the tissues. The glycogen levels of resting muscle were not different at altitude than at sea level and hence play no part in the reduction in endurance time observed. The reason for the improvement in endurance time with sojourn at altitude cannot be explained.

In summary, marked changes in the O_2 transport system of normal man occur at 2 days and are little changed after 10 days of sojourn at altitude. The principal reason for the decrement in working capacity appears to be related to the decreased cardiac output.

Future Plans:

Animal studies are underway to define the mechanisms of the cardiovascular effects of prolonged hypoxia. Manuscripts in preparation.

Title of Study: Peru Study II. Changes in submaximal and maximal heart rate response to altitude and its alteration with atropine and O_2 administration

Investigators: L. H. Hartley, LTC, MC; J. A. Vogel, Ph.D.; and J. Cruz, M.D. (Peru)

Background:

On ascent to high altitude a decrease in cardiac output occurs. This is partly due to a decreased stroke volume, but also is contributed to by a lesser heart rate response. This is especially marked during maximal exercise. The reduction occurs with increasing frequency as the altitudes become more extreme, and is a constant finding above 14,000 feet elevation. The mechanism of this decrement has never been defined. One possible mechanism is autonomic imbalance with an increase in parasympathetic influence. This study was performed at 16,000 feet elevation to ensure the maximal heart rate reduction, and the effects of acute O_2 administration, intravenous atropine, and one day and five days of return to sea level on the heart rate reduction were studied.

Progress:

This study was carried out during August of 1970 during a Peruvian field study. Five Peruvian medical students were studied at sea level, after five days at Ticlio, Peru, (16,000 feet elevation) and at one and five days after return to sea level. Exercise was performed on the bicycle ergometer and maximal work loads were defined as those which yielded an O_2 uptake which could not be increased by increasing the work load, by endurance times of less than five minutes, or by blood lactate values in the maximal range. Mean maximal O_2 uptake ($\dot{V}_{O_2}$ max) decreased from 3.07 to 2.12 liters/min. Maximal heart rates (HR max) were decreased from 189 to 168 beats/min. Acute O_2 administration to restore sea level PO_2 did not change the maximal heart rate. Administration of 1.0 mgm atropine sulfate intravenously increased the HR max in all but one subject with a group mean of 10 (range 2-18). Despite the increase in heart rate, the $\dot{V}_{O_2}$ max did not increase. On return to sea level at one day, mean HR max was 179 and at five days was 181. The $\dot{V}_{O_2}$ max at one day was 2.48 and increased further to 3.23 liter/min at five days.

Conclusions:

(1) A definite reduction in maximal heart rate occurred at 16,000 feet altitude; this was partially restored with atropine administration, but not affected by acute O_2 inhalation. (2) The failure of $\dot{V}O_2$ max to rise with the atropine administration suggests that either cardiac output did not rise due to a reciprocal fall in stroke volume or the increase in cardiac output was distributed to non-muscular tissue, possibly to the skin, secondary to vasodilation induced by the atropine. (3) The reduction in HR max may be mediated by autonomic imbalance in the direction of parasympathetic preponderance. (4) Physical working capacity required a few days to be restored to normal after return to sea level. (5) The increase in the final $\dot{V}O_2$ max over the original $\dot{V}O_2$ max and the lesser final HR max probably reflected a training effect during the experiment.

Future Plans:

Manuscripts in preparation.

Title of Study: Peru Study III. The physiological response to exercise in natives of the Peruvian Andean Mountains.

Investigators: L. H. Hartley, LTC, MC; J. A. Vogel, Ph.D.; R. P. Hogan, MAJ, MC; J. Cruz, M.D. (Peru); and B. Saltin (Sweden)

Background:

High altitude natives perform better physically at altitude than do sea level sojourners. This is seen in the daily mining activities of high altitude natives (Dill, 1968). Soccer players of altitude natives are able to run almost constantly during 90 minute games at 14-15,000 feet altitude while sea level subjects are quickly exhausted. It is a classic fact that sea level teams are very likely to lose to high altitude teams when playing at high elevations (J. Cruz, Personal Observation). This tendency was also reflected in the Mexico City Olympics (7,500 feet) during which winners in long distance events were predominantly from countries of high elevation. It is also noteworthy that even prolonged sojourn of sea level residents at altitude does not seem to result in the same level of performance as high altitude natives.

Physiological studies seem to support the thesis that Andean mountain native people are superior performers during exercise at altitude. It is not precisely interpretable, however, because physical conditioning and diet may also be important factors in the results. Maximal $\dot{V}O_2$ of natives at altitude is quite high in comparison to max. $\dot{V}O_2$ of sojourners, and the maximal $\dot{V}O_2$ can increase even further after descending to sea level. Cardiac output during exercise is clearly decreased in sojourners, and remains decreased even if residence at altitude continues for many years. However, in Andean altitude natives the cardiac output response to exercise is normal, suggesting some type of cardiovascular adaptation occurs after many generations. Furthermore, heart rate at maximal work has not been found to be reduced in high altitude natives of either the Andes or the Himalayas as is seen during sojourn of one or more weeks at high altitude.

Pulmonary diffusing capacity may also be an important limiting factor, although this point is controversial. The principal point in support of this has been the decreased alveolar-arterial PO_2 differences observed in a few studies done on Peruvian natives.

The purpose of studying the Peruvian natives was to document their superiority and to determine the mechanisms by which this occurred.

Progress:

In August and September of 1970, eight young males of Andean mountain ancestry were studied at Cerro de Pasco, Peru (elevation 14,000 feet), and again after 10 days at Lima (sea level). They were studied during rest and upright bicycle exercise, both at submaximal and maximal intensity. Measurements made included O_2 uptake, cardiac output (dye dilution), alveolar-arterial PO_2 differences, hemoglobin dissociation curves, pulmonary arterial-venous shunts of blood flow, endurance time, and muscle glycogen levels. The subjects were then moved to sea level where the studies were repeated after 10 days.

Their results were compared to a group of eight sea level residents studied after 10 days of sojourn at the same altitude. The altitude and sea level residents were of similar habitual physical activity and age, and the altitude natives were slightly smaller. The altitude residents were superior to the sea level residents at high altitude in the following respects: The work load leading to exhaustion in about one hour was 36% higher, maximal O_2 uptake was higher (49 vs 32 ml/kg x min), alveolar-arterial PO_2 differences were narrower both at rest (11.5 vs 14.6) and during exercise (15.0 vs 20.3 mm Hg), hematocrits were higher (50 vs 45%), arterial O_2 content was higher (20.9 vs 19.2 vol%), and submaximal and maximal cardiac outputs were higher due to greater stroke volume (92 vs 82 ml). The natives had no greater muscle glycogen levels to explain the improved endurance. Although a shift to the right in the hemoglobin dissociation curves was observed, it was no greater in the altitude than in the sea level residents at 14,000 feet.

Conclusions:

The better working capacity of the high altitude natives than sojourners at altitude was explainable by superior O_2 transporting abilities. These in turn were due to better pulmonary gas exchange and greater cardiac output. No metabolic or local factors that would favor the native over the sojourner at high altitude were identified.

Future Plans:

Manuscripts in preparation.

(81102)

RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY

1. AGENCY ACCESSION	2. DATE OF SUMMARY	REPORT CONTROL SYMBOL
DA OA 6138	71 07 01	DD-DR&E(AR)636

3. DATE PREV SUM'RY	4. KIND OF SUMMARY	5. SUMMARY SCTY	6. WORK SECURITY	7. PROGRAMING	8. OMB'C INSTR'N	9A. SPECIFIC DATA-CONTRACTOR ACCESS	9. LEVEL OF SUM
70 12 31	D. Change	U	U	N/A	N/L	☑ YES ☐ NO	A. WORK UNIT

10. NO./CODES:	PROGRAM ELEMENT	PROJECT NUMBER	TASK AREA NUMBER	WORK UNIT NUMBER
a. PRIMARY	6.11.01.A	3A061101A91C	00	021
b. CONTRIBUTING				
c. CONTRIBUTING				

11. TITLE (Precede with Security Classification Code): (U) Historical Analysis, Development and Distribution of Military Environmental Medical Information (22)

12. SCIENTIFIC AND TECHNOLOGICAL AREAS: 005900 Environmental Biology; 000600 Escape, Rescue and Survival

13. START DATE	14. ESTIMATED COMPLETION DATE	15. FUNDING AGENCY	16. PERFORMANCE METHOD
70 07		DA	C. In-House

17. CONTRACT/GRANT
a. DATES/EFFECTIVE: N/A EXPIRATION:
b. NUMBER:
c. TYPE: d. AMOUNT:
e. KIND OF AWARD: f. CUM. AMT.

18. RESOURCES ESTIMATE		a. PROFESSIONAL MAN YRS	b. FUNDS (In Thousands)
FISCAL YEAR	PRECEDING 71	0.2	8
	CURRENT 72	2.0	35

19. RESPONSIBLE DOD ORGANIZATION
NAME: USA Rsch Inst Env Med
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RESPONSIBLE INDIVIDUAL
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TELEPHONE: 955-2811

20. PERFORMING ORGANIZATION
NAME: USA Rsch Inst Env Med
ADDRESS: Natick, Massachusetts 01760

PRINCIPAL INVESTIGATOR (Furnish SSAN if U.S. Academic Institution)
NAME: Goldman, Ralph F. Dr.
TELEPHONE: 955-2831
SOCIAL SECURITY ACCOUNT NUMBER

ASSOCIATE INVESTIGATORS
NAME: Vogel, James A. Dr.
NAME: Halpin, Stanley Dr. DA

21. GENERAL USE
Foreign Intelligence Considered

22. KEYWORDS (Precede each with Security Classification Code)
(U) Training; (U) Military Information; (U) Military Tactics

23. TECHNICAL OBJECTIVE, 24. APPROACH, 25. PROGRESS (Furnish individual paragraphs identified by number. Precede text of each with Security Classification Code.)

23. (U) Address collection and retention of available knowledge on the effects of heat, cold, work and high terrestrial elevations on military performance, evaluate techniques for its dissemination and conduct research on improving the communication between the military man with an environmental problem and the scientists with relevant information.

24. (U) Analyze information on the impact of extreme terrestrial environments on past and present military operations; evaluate historical solutions to these problems. Develop effective liaison with U.S. AMC, CDC, Navy and Air Force elements developing protective items of planning tactical operations where such problems can be anticipated, as well as with similar groups abroad. Expand dissemination by lectures at military academies and training courses, and preparation of material for military manuals. Ascertain present state of military environmental medicine knowledge and doctrine by Army Medical Department Personnel.

25. (U) 70 07 - 71 06 Collection and analysis of relevant historical events begun. Liaison with NATO, Quadripartite and Commonwealth groups has been actively pursued. Operationally relevant meetings in Finland, England and India have been attended. Contact made with Spec Forces, Ft. Devens, CDC (Inst of Land Combat; Dir of Doctrine), USA (Tank Automotive Comm.; Personnel Command; Behavioral Sciences Lab) and USN (Training Devices Center; Marine Development (Center). Attempts to present at West Point were negated, but presentations at Army "Occupational Medicine" course were added. Two year scientist exchange arranged with Army Personnel Research Establishment, British MOD, to obtain their extensive military environmental information and unique field experience. Scientific support in environmental problems is being furnished to a widening group, including USN, CDC, ARPA, but expanded travel is an obvious requirement.

*Available to contractors upon originator's approval

DD FORM 1 MAR 66 1498 PREVIOUS EDITIONS OF THIS FORM ARE OBSOLETE DD FORMS 1498-1 1 NOV 65 AND 1498-1 1 MAR 66

Title of Study: Improving Dissemination of Available Environmental Medical Information

Investigator: R. F. Goldman, Ph.D.

This work unit was specifically established to improve distribution of available military environmental medical information from the research scientist, to an audience which has both a need for the information and perhaps does not know how to appropriately phrase the question so that it can be answered by available information. The orientation has been to search for new points of contact with the Army, e.g. West Point, Command and General Staff School, Limited Warfare Laboratory, Institute of Land Combat, etc., and try to arrange presentations to appropriate groups at these Institutes on the type of available military environmental medical information and how this can be used to answer militarily practical problems.

This is a service to be provided by USARIEM at no cost to the recipient, i.e., the essential funding (salary and travel funds) will come from within the USARIEM's budget. Unfortunately, a common answer has been that available curricula are too crowded.

Some distinct improvements have been made this year. Formerly, the Basic Sciences (Research Fellowship) course, was given by a few USARIEM members at Walter Reed Research Institute in Washington, DC, for a relatively small class. This year the five students came to USARIEM for the one week of lectures. This allowed far greater contact of the students with the research material, the equipment involved, the types of problems and also a better first hand exposure to the problems of running a research laboratory which comprises civilian scientists, military scientists, technicians, etc. A second positive accomplishment under this work unit was the delivery of lectures on the assessment of the environment to the Environmental Health Agency Course at Edgewood Arsenal by USARIEM staffers for the first time this year. Thirdly, a two year exchange of scientists with the Army Personnel Research Establishment of the United Kingdom was finalized.

Hopes for increased information exchange with the Army C & GS did not materialize. Future plans must include expanded travel and a continuing attempt to communicate to the general military community the type of operationally useful information that is available at USARIEM. The formation of the new TRICAP Division at Fort Hood is a case in point.

It is recommended that USARIEM staff make a special effort to arrange for a presentation on the available knowledge of the physiology of desert operations. In addition, an effort to ascertain the current state of knowledge of US Army physicians on military environmental medicine is proposed.

(81103)

RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY

1. AGENCY ACCESSION	2. DATE OF SUMMARY	REPORT CONTROL SYMBOL
DA 0A 6139	71 07 01	DD-DR&E(AR)636

3. DATE PREV SUM'RY	4. KIND OF SUMMARY	5. SUMMARY SCTY	6. WORK SECURITY	7. REGRADING	8a. CLASS'N METH'N	8b. SPECIFIC DATA - CONTRACTOR ACCESS	9. LEVEL OF SUM / A. WORK UNIT
70 12 31	D. Change	U	U	N/A	N/L	☒ YES ☐ NO	

10. NO./CODES:	PROGRAM ELEMENT	PROJECT NUMBER	TASK AREA NUMBER	WORK UNIT NUMBER
a. PRIMARY	6.11.01.A	3A061101A91C	00	023
b. CONTRIBUTING				
c. CONTRIBUTING				

11. TITLE (Precede with Security Classification Code)

(U) Effects of Multiple Environmental Stresses on Military Personnel (22)

12. SCIENTIFIC AND TECHNOLOGICAL AREAS

012900 Physiology; 005900 Environmental Biology

13. START DATE	14. ESTIMATED COMPLETION DATE	15. FUNDING AGENCY	16. PERFORMANCE METHOD
70 07		DA	C. In-House

17. CONTRACT/GRANT

a. DATES/EFFECTIVE: N/A EXPIRATION:

b. NUMBER:

c. TYPE: d. AMOUNT:

e. KIND OF AWARD: f. CUM. AMT.

18. RESOURCES ESTIMATE		a. PROFESSIONAL MAN YRS	b. FUNDS (In thousands)
FISCAL YEAR	PRECEDING 71	1.4	43
	CURRENT 72	3.0	90

19. RESPONSIBLE DOD ORGANIZATION

NAME: USA Rsch Inst Env Med

ADDRESS: Natick, Massachusetts 01760

RESPONSIBLE INDIVIDUAL

NAME: Jones, LeeRoy G. COL

TELEPHONE: 955-2811

20. PERFORMING ORGANIZATION

NAME: USA Rsch Inst Env Med

ADDRESS: Natick, Massachusetts 01760

PRINCIPAL INVESTIGATOR (Furnish SSAN if U.S. Academic Institution)

NAME: Shershow, John C. MAJ

TELEPHONE: 955-2849

SOCIAL SECURITY ACCOUNT NUMBER:

ASSOCIATE INVESTIGATORS

NAME: Kobrick, John C. Dr.

NAME: Cymerman, Allen Dr. DA

21. GENERAL USE

Foreign Intelligence

22. KEYWORDS (Precede EACH with Security Classification Code)

(U) Carbon Monoxide;(U)Sleep Loss;(U) Multiple Stresses; (U)Military Performance;(U)Psychological Stress;(U)High Altitude;(U)Vision

23. TECHNICAL OBJECTIVE, 24. APPROACH, 25. PROGRESS (Furnish individual paragraphs identified by number. Precede text of each with Security Classification Code.)

23. (U) Natural occurring stresses are often experienced in combinations, e.g., cold plus altitude, heat plus confinement, physical plus psychological, etc., but are almost exclusively investigated as separate entities. Information does not presently exist as to whether many of these stresses combine in an additive or synergistic (greater than additive) fashion. The objectives of the work unit are (1) to examine multiple stresses important in military operations for their relative effect on mental and physical performance as compared to that by each stress alone; (2) to identify the occurrence of additive and potentiative responses; (3) to explore mechanisms of any synergistic effects and, thereby, suggest ameliorative measures.

24. (U) The combined stresses of carbon monoxide and high altitude hypoxia were the first combined stress investigated in man.

25. (U) 70 07 - 71 06 Physical work capacity was reduced during carbon monoxide exposure in proportion to the reduction in arterial blood oxygen content and similar to the reduction with equivalent high altitude hypoxia. When the two forms of hypoxia were combined, the resulting decrement was no more than would be predicted from the sum of their individual effects, i.e., there was no interaction to produce a more than additive effect. The manner of delivery of oxygen to working muscles with carbon monoxide was not different from that of high altitude, indicating that the only consequential effect of carbon monoxide on work ability is that of reducing oxygen content of the blood. Mental performance, dark adaptation and peripheral vision also failed to show a compounding effect to a combination of hypoxias. Hypobarism produces a .5% increase per 1000 feet of increasing altitude in clothing insulation value.

*Available to contractors upon originator's approval

DD FORM 1 MAR 66 1498 PREVIOUS EDITIONS OF THIS FORM ARE OBSOLETE. DD FORMS 1498A 1 NOV 65 AND 1498-1 1 MAR 66 (FOR ARMY USE) ARE OBSOLETE

Title of Study: Effects of extended hypoxia and cigarette smoking on dark adaptation, peripheral vision, aqueous outflow, and intra-ocular pressure

Investigators: John L. Kobrick, Ph.D. and Ralph Rosenthal, MAJ, M.D.

Background and Progress:

Eight human subjects were exposed to 15,000 feet equivalent hypobaric elevation for 48 hours in an altitude chamber during which they were measured five times at periodic intervals for dark adaptation threshold, extent and contour of peripheral visual field - measures which are basically related to many visual tasks performed by the soldier, aqueous outflow rate in the anterior chamber of the eye, and the intra-ocular pressure. Four subjects smoked cigarettes prior to measurement, the other four subjects did not smoke. Data collection has been completed, and analysis is underway.

Conclusions:

Preliminary inspection indicates that contrary to previous findings reported in the literature, smoking had little if any effect upon any of the measures obtained. Also, the hypoxic stress employed had only slight effect upon dark adaptation and peripheral vision as measured, but did affect aqueous outflow and intra-ocular pressures. Further analyses are continuing.

Future Plans:

The nature of future studies in this area is contingent on the results of this study.

Title of Study: Altitude and convective heat transfer

Investigator: G. Fonseca

In addition to the well known problems of hypoxia which occur with altitude, there has always been a question as to the extent to which convective heat transfer is altered by change in barometric pressure with increasing altitude. Burton some years ago suggested that the available insulation of a clothing system increased linearly, as the square root of the barometric pressure decreased. However, this was derived from purely theoretical considerations and had never been directly measured. The present study was designed to evaluate this suggested relationship.

A standard military clothing system, Cold-Wet uniform, representative of the type of protective clothing that would be worn at high terrestrial elevations, was studied on a heated, sweating copper manikin to evaluate the change in insulation value with increasing altitude, if any. Altitudes from sea level to 20,000 feet were studied at 5,000 foot increments. The insulation value of this standard uniform ensemble at sea level was 3.18 clo units. The insulation value increased to 3.29 clo at 5,000 feet, 3.3 clo at 10,000 feet, 3.51 clo at 15,000 feet and 3.58 clo at 20,000 feet. Thus, a change of 20,000 feet in altitude, corresponding to a change in barometric pressure from 754 millimeters of mercury to 350 millimeters of mercury, produced a change of approximately 10% in insulation value, with the insulation being increased at increasing altitude.

The magnitude of the change is relatively small and not apt to have military significance. However, the fact that insulation increased with increasing altitude indicates that this is a positive factor in coping with the problems of performance of military tasks at high terrestrial elevations, where cold is the accompaniment of the high terrestrial elevation. No further work is planned on this specific project, although the information obtained will be used in studies on temperature regulation at high terrestrial elevations to be conducted under other work units.

(81106)

RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY

1. AGENCY ACCESSION	2. DATE OF SUMMARY	REPORT CONTROL SYMBOL
DA OA 6136	71 07 01	DD-DR&E(AR)636

3. DATE PREV SUM'RY	4. KIND OF SUMMARY	5. SUMMARY SCTY	6. WORK SECURITY	7. REGRADING	8a. GROUP INSTR'N	8b. SPECIFIC DATA - CONTRACTOR ACCESS	9. LEVEL OF SUM
70 12 31	D. Change	U	U	N/A	N/L	☑ YES ☐ NO	A. WORK UNIT

10. NO./CODES:	PROGRAM ELEMENT	PROJECT NUMBER	TASK AREA NUMBER	WORK UNIT NUMBER
a. PRIMARY	6.11.01.A	3A061101A91C	00	025
b. CONTRIBUTING				
c. CONTRIBUTING				

11. TITLE (Precede with Security Classification Code)

(U) Development of a Non-Sedating Analgesic for Military Use (22)

12. SCIENTIFIC AND TECHNOLOGICAL AREAS

012600 Pharmacology; 003500 Clinical Medicine

13. START DATE	14. ESTIMATED COMPLETION DATE	15. FUNDING AGENCY	16. PERFORMANCE METHOD
69 07		DA	C. In-House

17. CONTRACT/GRANT

a. DATES/EFFECTIVE: N/A EXPIRATION:
b. NUMBER:
c. TYPE: d. AMOUNT:
e. KIND OF AWARD: f. CUM. AMT.

18. RESOURCES ESTIMATE		a. PROFESSIONAL MAN YRS	b. FUNDS (In thousands)
FISCAL YEAR	PRECEDING 71	1.4	17
	CURRENT 72	0.2	11

19. RESPONSIBLE DOD ORGANIZATION

NAME: USA Rsch Inst Env Med

ADDRESS: Natick, Massachusetts 01760

RESPONSIBLE INDIVIDUAL
NAME: Jones, LeeRoy G. COL
TELEPHONE: 955-2811

20. PERFORMING ORGANIZATION

NAME: USA Rsch Inst Env Med

ADDRESS: Natick, Massachusetts 01760

PRINCIPAL INVESTIGATOR (Furnish SSAN if U.S. Academic Institution)
NAME: Evans, Wayne O. LTC
TELEPHONE: 955-2824
SOCIAL SECURITY ACCOUNT NUMBER:
ASSOCIATE INVESTIGATORS
NAME:
NAME:

21. GENERAL USE

Foreign Intelligence not Considered

DA

22. KEYWORDS (Precede EACH with Security Classification Code)

(U) Analgesia; (U) Drugs; (U) Clinical Testing; (U) Combat Casualties

23. TECHNICAL OBJECTIVE, 24. APPROACH, 25. PROGRESS (Furnish individual paragraphs identified by number. Precede text of each with Security Classification Code.)

23. (U) A formal requirement has been established by the Combat Developments Command for an analgesic compound which will provide adequate relief from pain without producing sleep, mental confusion or a depression of vital bodily functions. The objective of this research is to help in the development of such a compound.

24. (U) It has been shown that a mixture of a stimulant of the amphetamine type when mixed with an opiate, such as morphine, will produce a potent analgesic compound which does not produce sleep, mental confusion or a depression of vital bodily functions as does morphine alone. Studies also indicate that a lower liability for physical dependence may be found for this mixture than for morphine alone. Further, side effects of nausea, headache or other bodily discomforts are reduced. Potential for abuse with this mixture will be evaluated in monkeys. To see if an oral form of the mixture can be developed, we will test a mixture of anileridine, an opiate with a fairly good absorption from the stomach, with amphetamine. The effects of the dextro, levo and racimic forms of amphetamine will be compared. In addition to analgesia, tests will also include rest-taking behavior, mood and social interaction.

25. (U) 70 07 - 71 06 In studies designed to determine potential for abuse of this mixture, monkeys when self-infusing, show signs of amphetamine toxicity. This suggests that the compound does have some potential for abuse. When evaluating the orally administered mixture of anileridine plus amphetamine by the ischemic arm pain test, we found that the mixture significantly enhanced the tolerance of pain as compared to a placebo or either compound alone. Preliminary findings also show an anti-depressant effect from this mixture.

*Applicable to contractors upon originator's approval

DD FORM 1 MAR 68 1498 PREVIOUS EDITIONS OF THIS FORM ARE OBSOLETE. DD FORMS 1498A 1 NOV 65 AND 1498-1, 1 MAR 68 (FOR ARMY USE) ARE OBSOLETE

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Title of Study: The Development of a Non-Sedating Analgesic for Military Use

Investigator: Wayne O. Evans, LTC, MSC

The following is an account only of the studies directly sponsored by this Institute. It does not include studies under the monitorship of LTC Hammond, Surgical Directorate, MRDC, to which the Principal Investigator is Technical Advisor. Also, it does not include independent studies, not funded by the Army, being conducted at USPHS Hospital, Lexington, Kentucky; Rockland State Hospital, Orangeburg, New York; Douglas Hospital, Montreal, Canada; Sloan-Kettering Institute, New York, New York; and the Medical School of the University of Chicago, Chicago, Illinois. Although these are not described, their initiation resulted from discussion of other Investigators with the Principal Investigator on this project.

During the past year, a service contract has been completed with the Southern Research Institute conducted by Dr. Gerald Deaneu as Principal Investigator to determine any possible potential for abuse of a mixture of an amphetamine and morphine. The monkeys appetitively sought to self-infuse the mixture for three months, reaching a peak dose of 30 mg per kilogram per day. They entered abrupt withdrawal without sleep. The mixture showed an abstinence syndrome similar to morphine, whereas during the self-infusion period, the syndrome more resembled amphetamine toxicity. From this we must assume the compound to have some potential for abuse. Data from the USPHS Hospital at Lexington will provide further information.

At this Institute, we investigated a mixture of anileridine at 25 mg plus dl-amphetamine at 7.5 mg by oral administration, using the method of Smith and Beecher, of pain produced by an exercised, ischemic arm in normal volunteers. This mixture, by the oral route, significantly enhanced the tolerance of pain as compared to a placebo, either compound alone or 15 mg of injected morphine. Further, no evidence of depression of vital bodily functions or sedation was witnessed with the mixture. Also, the mixture seems to have anti-depressant effects. Studies at some of the hospitals previously mentioned have confirmed the utility of this compound for episodic use in both reactive and endogenous depression. A notification of discovery has been submitted to the CG, MRDC, describing the efficacy and novelty of this compound.

During the next year, we intend to test the effects of two doses (25 mg and 15 mg of anileridine) of the mixture, the effects of the

dextro, levo, and racimic forms of amphetamine. Tests will include analgesia, risk taking behavior, mood and social interaction.

From the developments that have taken place, it would seem that the qualities demanded in the Small Development Requirements from the Combat Developments Command for a Non-Sedating Analgesic to the Surgeon General have been fulfilled. If the development phase is expedited (phase III testing initiated and planning for issue, instructions for use, problems for supply, control, and purchase in quantity), it should be possible to have this effective analgesic in use by specified units, such as special forces or specially selected combat medics, within a year.

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King, A. B., G. S. Pechet, and L. Pechet. Intravenous injection of crude marihuana. J.A.M.A. 214: 1711, 1970.

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Stamper, D. A., R. A. Kinsman, and W. O. Evans. Subjective symptomatology and cognitive performance at high altitude. Percep. Mot. Skls. 31: 247-261, 1970. This paper was co-authored by LTC Wayne O. Evans while a member of the USAMR&NL in 1968.

ABSTRACTS

Research Performed Predominantly or Exclusively Before Joining USARIEM:

Boyd, A. E. and H. E. Lebovitz. Effects of L-DOPA on endocrine function in man. Clin. Res. 19:348, 1971.

Feldman, J. M., A. E. Boyd, and H. E. Lebovitz. Sites of catecholamine structure that determine effects on insulin secretion. Diabetes 19: 384, 1970. Supplement 1.

PRESENTATIONS

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Cahoon, R. L. Human performance under environmental stress. Middlebury College, Middlebury, VT, 11 March 1971.

Cahoon, R. L. Simple decision making at high altitude. Annual Meeting of Eastern Psychological Association, New York, NY, 15 April 1971.

Cipriano, L. F. and N. Pace. Effects of altitude on glycolytic intermediates and adenosine phosphates in the liver of the rat. Federation of American Societies for Experimental Biology (FASEB), Chicago, IL, 12-17 April 1971.

Presentations (Cont'd)

Cymerman, A., S. M. Robinson, and D. O. McCullough. Effect of hypobaric hypoxia on brain catecholamine metabolism in rats. Federation of American Societies of Experimental Biology (FASEB), Chicago, IL, 12-17 April 1971.

Doolittle, W. H., the Director of AMRLA, and several members of his staff gave eleven presentations to various civic organizations and schools of Fairbanks, AK, on Cold Weather Indoctrination, Arctic Biology and Arctic Survival.

Dusek, E. R. Research in Behavioral Sciences Laboratory, USARIEM. Current Trends in AMEDD Psychology Conference, Fitzsimons General Hospital, Denver, CO, 15 December 1970.

Dusek, E. R. Participant in Symposium: Current Trends in Army Medical Department Psychology, Fitzsimons General Hospital, Denver, CO, December 1970.

Dusek, E. R. Applications of Behavioral Science Research in the Military Service, Harvard School of Public Health, Boston, MA, March 1971.

Evans, W. O. Research in Military Stress Laboratory at USARIEM. Current Trends in AMEDD Psychology Conference, Fitzsimons General Hospital, Denver, CO, 15 December 1970.

Evans, W. O. Patterns of use of mind-altering drugs. Armed Forces Management Association Meeting, US Army Natick Laboratories, Natick, MA, 11 May 1971.

Evans, W. O. Hypoxia. Boston University School of Medicine, Boston, MA, 5 March 1971.

Evans, W. O. Drug structures. Northeastern University, Boston, MA, 27 April 1971.

Evans, W. O. Chairman, Study Group on Normal Humans, American College of Neuropsychopharmacology Annual Meeting, San Juan, PR. Chaired discussion on "Use of psychotropic chemicals in non-western cultures and historically".

Presentations (Cont'd)

Francesconi, R. P. and M. Mager. Effects of sleep deprivation on the periodicity of tryptophan and tyrosine metabolism in mice. Federation of American Societies of Experimental Biology (FASEB), Chicago, IL, 12-17 April 1971.

Gerben, M. J., L. G. Jones, and J. A. Smoake. A high altitude syndrome in the squirrel monkey. Annual Meeting of the American Physiological Society, Bloomington, IN, August-September 1970.

Givoni, B. and R. F. Goldman. Prediction of rectal temperature response to work environment and clothing. Symposium of Environmental Physiology Beer-Sheva, Israel, July 1970.

Goldman, R. F. Physical fitness flight requirements and age. 27th Aerospace Medical Panel Meeting, Garmisch-Partenkirschen, Germany, September 1970.

Goldman, R. F. Promising new approaches for Arctic clothing Second International Symposium on Circumpolar Health, Oulu, Finland, 21-24 June 1971.

Goldman, R. F. Assessing the environment and its impact on man. Global Medicine Course, WRAIR, Washington, DC, 2 February 1971.

Goldman, R. F. Military performance, clothing and environment. Global Medicine Course, WRAIR, Washington, DC, 8 February 1971.

Goldman, R. F. Physical agents in the environment. Environmental Hygiene Course, Edgewood Arsenal, January 1971.

Goldman, R. F. Clothing design for comfort and work performance in extreme thermal environments. Third Shirley International Seminar on Textiles for Comfort, Manchester, England, June 1971.

Goldman, R. F. Assessing the environment and its impact on man. Global Medicine Course, WRAIR, Washington, DC, 28 June 1971.

Hansen, J. E. High altitude. Global Medicine Course, WRAIR, Washington, DC, 2 February 1971.

Presentations (Cont'd)

Hansen, J. E. Acclimatization to high elevations. Hahnemann Medical College, Philadelphia, PA, 19 May 1971.

Hartley, L. H. Cardiovascular response to exercise at high altitude. Presented to the Medical Staff and guests of Hospital Obrero of Cerro De Pasco, Peru, August 1970.

Hartley, L. H. Cardiovascular and metabolic factors which affect physical performance at high altitude. Presented to the Physiology Group and guests, Universidad Peruana, Cayetano Heredia, September 1970.

Hartley, L. H. Physical training and the physiology of exercise. Global Medicine Course, Walter Reed Army Institute of Research, Washington, DC, 8 February 1971.

Hartley, L. H. Exercise physiology. Lecture at Boston University, Boston, MA, 22 October 1970.

Hartley, L. H. Observations on the cardiovascular response to exercise. Boston City Hospital, Boston, MA, 13 October 1970.

Hartley, L. H. Effects of physical training on the cardiovascular system of man. Cardiology Conference, University of Missouri, Columbia, MO, 18 December 1970.

Hartley, L. H. Chronic hypoxia and decreased cardiac performance. Institute of Environmental Medicine, University of California, Santa Barbara, CA, 21 January 1971.

Hartley, L. H. Effects of hypoxia on the cardiovascular system of man. Goleta Valley Community Hospital Staff, Santa Barbara, CA, 22 January 1971.

Hartley, L. H. Physiology of high altitude. University of Massachusetts Medical School, Worcester, MA, 24 March 1971.

Hartley, L. H. Effects of muscular exercise and physical training on the cardiovascular system of man. Harvard Medical School, Boston, MA, 24-26 April 1971.

Presentations (Cont'd)

Hartley, L. H. Working capacity in high altitude natives. Physiology Interest Group, Boston University, Boston, MA, 1 May 1971.

Hubbard, R. The relationship of carbohydrate and lipid metabolism to human physical performance. Northeastern University, Boston-Bouve College, Boston, MA, January 1971.

Huibregtse, W. H., W. H. Doolittle, and L. H. Hartley. Improvement in physical fitness associated with walking six miles per hour for t days. Annual Meeting of the American Physiological Society, Bloomington, IN, August-September 1970.

Jones, L. G., L. H. Hartley, and J. W. Mason. The effects of muscular leg exercise on plasma levels of growth hormone insulin epinephrine, norepinephrine and cortisol. Annual Meeting of the American Physiological Society, Bloomington, IN, August-September 1970.

Kobrick, J. L. Environmental factors affecting visual perception. 16th Annual Army Human Factors Research & Development Conference, Ft. Bliss, TX, 21 October 1970.

Kobrick, J. L. Effects of hypoxia on response time to peripheral visual signals. International Symposium on the Perception and Application of Flashing Lights, Imperial College of Science and Technology, London, England, 19-22 April 1971.

Kotchen, T. A., L. H. Hartley, T. W. Rice, E. H. Mougey, and J. W. Mason. Renin response to graded exercise. American Federation for Clinical Research, New York, NY, December 1970.

Landowne, M. Circulatory dynamics in exercise I. Revelation of cardiac output to oxygen uptake. Research Conference, Cardiovascular Unit, Boston City Hospital, Boston, MA, March 1971.

Landowne, M. Circulatory dynamics in exercise II. Vascular conductance in muscle: determinant of maximal oxygen uptake. Research Conference, Cardiovascular Unit, Boston City Hospital, Boston, MA, April 1971.

Landowne, M. Nonlinear relation of cardiac output to oxygen uptake in exercise. Federation of American Societies of Experimental Biology (FASEB), Chicago, IL, April 1971.

Presentations (Cont'd)

Maher, J., A. Goodman, and L. H. Hartley. Responses of rat myocardium to exhaustive exercise. Federation of American Societies of Experimental Biology (FASEB), Chicago, IL, April 1971.

Marshall, H. Development of human adaptation to cold. Second International Symposium on Circumpolar Health, Oulu, Finland, 21-24 June 1971.

Metzger, B., M. Mager, S. M. Robinson, E. Harris, and N. Freinkel. Factors influencing the hypothermia of hypoglycemia. Annual Meeting of the Endocrine Society, San Francisco, CA, 24-26 June 1971.

Molnar, G. W., R. F. Goldman, and O. Wilson. Analysis of the rate of digital cooling. International Symposium on Temperature Regulation, Lyon, France, September 1970.

Robinson, S. M. Central nervous system-pharmacodynamics. Massachusetts College of Pharmacy, Boston, MA, January to May 1971.

Shetshow, J. C. Visiting Lecturer, Alcoholism Training Institute, Massachusetts General Hospital and Harvard Medical School, Boston, MA, April 1971.

Soule, R. G. and R. F. Goldman. Voluntary march rate as a measure of work output in the heat. Annual Meeting of the American Physiological Society, Bloomington, IN, August-September 1970.

Soule, R. G. and R. F. Goldman. Terrain coefficients for energy cost prediction. Federation of American Societies of Experimental Biology (FASEB), Chicago, IL, April 1971.

Soule, R. G., R. F. Goldman, and W. L. Sembrowich. Single point estimation of mean weight skin temperature. American College of Sports Medicine Annual Meeting, Toronto, Canada, May 1971.

Therriault, D. G. Lipid mobilization in rats during starvation or exposure to cold. American Oil Chemists' Society Meeting, Chicago, IL, October 1970.

Presentations (Cont'd)

Vogel, J. A., M. A. Gleser, L. H. Hartley, and J. G. Lifton. Hypoxia-induced elevating cerebraspinal fluid pressure and its treatment with isosorbide and CO_2 replacement. XI International Congress of Internal Medicine, New Delhi, India, 25-30 October 1970.

Vogel, J. A., M. A. Gleser, and R. Mello. Oxygen transport during exercise with carbon monoxide exposure. Federation of American Societies of Experimental Biology (FASEB), Chicago, IL, April 1971.

Wheeler, R. C. and D. D. Heistad. A mechanism of adrenergic stimulation of respiration in man. American Federation of Clinical Research, Atlantic City, NJ, 1-4 May 1971.

Whitten, B. K., M. Posiviata, and W. D. Bowers. Influence of temperature on hepatic protein synthesis in homethems and hibernators. Annual Meeting of the American Physiological Society, Bloomington, IN, August-September 1970.

Wilson, O., A. L. Hughes, and R. F. Goldman. Skin temperatures change with crystallization health. Second International Symposium on Circumpolar Health, Oulu, Finland, 21-24 June 1971.

Witherspoon, J. M. and R. F. Goldman. Spontaneous rewarming after cold water immersion. Annual Meeting of the American Physiological Society, Bloomington, IN, August-September 1970.

Witherspoon, J. M., R. F. Goldman, and J. R. Breckenridge. Heat transfer coefficients of humans in cold water. International Symposium on Temperature Regulation, Lyon, France, September 1970.

Witherspoon, J. M. and R. J. T. Joy. Sweating in a hot dry climate: the effect of post-exercise hyperventilation. Federation of American Societies of Experimental Biology (FASEB), Chicago, IL, April 1971.

Witherspoon, J. M. Indices of heat stress: criteria for limiting exercise in the heat. New England Exercise Physiology Interest Group, Boston University, Boston, MA, May 1971.

SEMINAR PROGRAM

14 October 1970
COL James E. Hansen, Commanding Officer, USARIEM.
Quo Vadimus

21 October 1970
LTC L. Howard Hartley, Physiology Laboratory, USARIEM.
Report on Peruvian Field Study

4 November 1970
Dr. Frank P. Ellis, Yale School of Medicine.
Environmental Warmth and its Measurement

18 November 1970
Dr. Roger W. Hubbard, Biochemistry & Pharmacology Laboratory, USARIEM.
Growth and Lipolysis of Rat Adipose Tissue

2 December 1970
Dr. Wilbert D. Bowers, Experimental Pathology Laboratory, USARIEM.
Ultrastructural Studies of Liver for Mice Exposed to Normal and Low Ambient Temperatures During Infection or Endotoxin Poisoning

9 December 1970
Dr. Howard G. Knuttgen, Boston University.
Muscle Metabolism in Exercise

16 December 1970
Dr. Milton Landowne, Medicine Laboratory, USARIEM.
An Innovative Analysis of Circulatory and Metabolic Responses to Exercise - A Playboy's Guide to Models, Figures, and Curves

20 January 1971
Dr. Oscar Bing, Boston City Hospital.
Effects of Hypoxia on Isolated Heart Muscle

10 February 1971
Dr. James A. Vogel, Military Stress Laboratory, USARIEM.
Trip to India and Review of Medicine in the Indian Army

10 March 1971
Dr. Frank P. Ellis, Yale School of Medicine.
First Thoughts on the Epidemiology of Heat Illness in the United States

18 March 1971
CPT's Hartlin and Grey, Canadian Medical Corps.
Review of Hypoxia Research on Mount Logan

31 March 1971
Dr. Richard L. Cahoon, Behavioral Sciences Laboratory, USARIEM.
Simple Decision Making Under Hypoxia

7 April 1971
MAJ Aubrey E. Boyd, Biochemistry & Pharmacology Laboratory, USARIEM.
Mechanism of Insulin Secretion

14 April 1971
Dr. Ove Wilson, Swedish Institute of Aviation Medicine.
Mission of Swedish Institute of Aviation Medicine

21 April 1971
CPT Malcolm Gleser, Military Stress Laboratory, USARIEM.
Observations on Prolonged Exhaustive Exercise

28 April 1971
WRAIR Course

3 May 1971
Dr. E. T. Angelakos, The Hahnemann Medical College.
Adrenergic Innervation of Blood Vessels of the Brain

5 May 1971
Dr. Bernard J. Fine, Behavioral Sciences Laboratory, USARIEM.
Field Dependence, Extraversion and Neuroticism

17 May 1971
Dr. Jo Ann Kinney, Submarine Medical Research Laboratory, Naval Submarine Base.
Effect of Nitrogen Narcosis on Visual Evoked Potentials

20 May 1971

Dr. Lee Caldwell, Army Medical Research Laboratory, Ft. Knox, KY.
Psychological Scaling of Effort Produced by Strenuous Physical Exertion

24 May 1971

Dr. Harwood Belding, University of Pittsburgh.
Heat Stress Indices

26 May 1971

Dr. Stanley M. Halpin, Military Stress Laboratory, USARIEM.
Experimental Bias Effects in Physiological Research

2 June 1971

Dr. E. Ralph Dusek, Behavioral Sciences Laboratory, USARIEM.
Problems in Applying Statistics in Medical Research