

NAV1.960101.004

OP-098E/jwh
Ser 10 P098

6500 B

SECOND ENDORSEMENT on BUMED-71-1:ml 6500 of 9 Feb 1971

From: Chief of Naval Operations
To: Secretary of the Navy

Subj: Use of human volunteers as subjects in research on
Splanchnic Metabolism during Chronic Stress in Active Duty
Personnel

1. Forwarded recommending approval of the use of human volunteers for studies of liver metabolism while undergoing the stress of seventy-two hour fasting which is similar to that occurring in combat situations.
2. The capability for regulating glucose and fat metabolism in the combat Marine or Navy crew member under conditions of restricted food intake is desired.
3. The basic correspondence has been carefully reviewed. The Chief, Bureau of Medicine and Surgery considers the risk of injury to volunteer subjects as minimal and indicates that adequate safety precautions will be taken.
4. A letter of implementation has been prepared and your signature is recommended.

E. A. P.

Research, Development, Test & Evaluation

Copy to:
BUMED (Code 712)
CHNAVPERS (A-242)

NAV1.9601010.007G



DEPARTMENT OF THE NAVY
BUREAU OF MEDICINE AND SURGERY

IN REPLY REFER TO

BUMED-71-1:ml

~~6500~~ 1090

9 FEB 1971

From: Chief, Bureau of Medicine and Surgery
To: Assistant Secretary of the Navy (Research and Development)
Via: (1) Chief of Naval Personnel
(2) Chief of Naval Operations (OP-07)

Subj: Use of Human Volunteers as Subjects in research; request for

Ref: (a) SECNAV INSTRUCTION 3900.39 of 28 April 1969

Encl: (1) CO, US Hosp Oakland, Calif ltr 3900:5213 of 1 Sep 1970
(2) L-1498 entitled: "Splanchnic Metabolism During Chronic Stress
in Active Duty Personnel"
(3) Sample consent form

1. In accordance with reference (a), enclosure (1) is submitted for approval.
2. Enclosure (2) states the purpose of the study and benefits which may accrue. The study cannot be satisfactorily conducted on animals since the metabolic responses are not similar.
3. The risks entailed in the study are minimal to the human volunteers. Adequate precautions will be taken to ensure maximal safety of the volunteers.
4. Enclosure (3) is a sample consent form as required by reference (a).

G. M. DAVIS

Yellow

Memorandum

DATE : 19 January 1971

FROM : Code 712
 VIA : Code 71 *from (see below)*
 TO : Code 7
 Code 2 *QT*

*Indy SG M info
 to base letter
 VR 100*

SUBJECT : Further information from Dr. Weinstein concerning proposed study
 "Splanchnic Metabolism During Chronic Stress in Active Duty Personnel"

1. Clinical Investigation Center, Oakland, California has been active in the study of liver metabolism in stress situations. They have demonstrated that starvation leads to lipolysis then to ketosis and decreased carbohydrate tolerance. Amelioration of ketosis using nicotinic acid (inhibits lipolysis), appeared to lessen the carbohydrate intolerance but did not substantially correct it.

During exercise (mile run), the parameters of carbohydrate utilization are increased with enhanced carbohydrate tolerance. Yet during exercise, a ketotic state occurs similar to that seen during caloric deprivation.

The Randle hypothesis states that increased levels of fatty acids and/or ketone bodies inhibit carbohydrate utilization by muscle tissue.

This hypothesis seems contradictory when laboratory studies from C-I-C indicate that both increased and decreased carbohydrate tolerance exist during ketotic states. Thus preliminary studies suggest that the primary defect may lie in liver metabolism and its ability to utilize carbohydrate. This question can be answered by observing arterio-venous differences across the liver.

The clinical methodology to measure such changes, the mechanical expertise to place the catheter and the valuable assistance of Dr. Richard Havel (Professor of Medicine, University of California) as co-investigator are present. Dr. Havel is an authority on carbohydrate and lipid interaction during fasted states. He has performed the procedure of hepatic vein catheterization in 35 individuals without complications due to the procedure. He will be present at Oakland when the initial procedure is performed and will be readily available for consultation throughout the study.

Finally, it should be noted that animal models with the exception of the rat do not exist for the study of ketosis. The rat is unsatisfactory for this study since their metabolic pathway for carbohydrate is different from the human.

Very respectfully,

R. L. Bernstine
 R. L. BERNSTINE

This study may shed some light on how or if the liver is involved in the high glucose levels and tolerance absent in Viet Nam casualties (trauma).



IV 21101

DATE : 11 January 1971

FROM : CODE 712

TO : CODE 7 *5*

SUBJECT : Reference Memo from Code 2 to Code 7

1. Dr. Weinstein will be in Washington on 13-14 January 1971.
2. He will be prepared to discuss his background in hepatic vein catheterization and their previous work in liver function during stress.
3. *Could* he present a briefing in person or submit a written report?

Very respectfully,

R. L. Bernstein
R. L. BERNSTINE

*please as it must be given to SA for his consideration.
R*

Code 7

What has Oakland
been doing along these
lines in the past in
connection with
function in stress studies

gma
2

12-2-26

DEPUTY SURGEON GENERAL

712 -

Any info
on what CIC
has been doing
in the past

See Code 2

mine
HR

UNITED STATES GOVERNMENT

DEPARTMENT OF THE NAVY

BUBBLE 12:00

DATE : 1 December 1970

Memorandum

FROM : Code 712

TO : Code 71

SUBJECT : NH Oakland request for use of human volunteers on effect of stress as measured by certain hepatic functions monitored via hepatic vein catheterization

1. The expertise of the co-investigators stems from "a thorough familiarization with the procedure by the primary investigator". In addition, "support has been elicited from co-investigators (Departments of Surgery and Radiology, Naval Hospital, Oakland) to perform the catheterizations and assume responsibility for care of the subject during and after the study". (Statements quoted are from ADM Makin's letter.)
2. Their experience with this particular technique of liver catheterization stems from their contact and instruction in Dr. Havel's laboratory.
3. In order to compare peripheral and splanchnic samples (i.e. liver metabolism), a catheter must be placed in the hepatic vein.
4. I talked with other surgeons at NMRI and none expresses any serious concern with the procedure as such. Whether it should be performed in healthy volunteers depends upon weighing the "minimal" risk and discomfort against possible benefits (i.e. biochemical mechanisms which are altered in chronic stress of fasting).
5. Dr. Weinstein will be in town sometime within the next two weeks.

Very respectfully,

R. L. Bernstein

R. L. BERNSTINE



Buy U.S. Savings Bonds Regularly on the Payroll Savings Plan

This form must accompany all correspondence submitted for approval to the Deputy Chief of the Bureau

| | APPROVED | DATE | INFORMATION OR COMMENTS | DATE SIGNED |
|-----------------|-------------------------------------|-------------------------------------|-------------------------|-------------|
| ASSISTANT CHIEF | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <i>RSW</i> | 3 Nov 70 |
| DEPUTY CHIEF | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <i>Jick</i> | |
| CHIEF OF BUREAU | <input checked="" type="checkbox"/> | | | |

PREPARED BY: CAPT L. Bernstine, MC, USN, CODE 712

PREPARED IN CONNECTION WITH: SECTION OF, OR IN REPLY TO

SEC: NSTR 3900.39 of 28 Apr 1970 and CO NH Oakland ltr 78-cw of 1 Sep 1970

BRIEF

Permission is requested to use human volunteers in a research proposal submitted by Naval Hospital, Oakland.

Human volunteers are essential to the project since metabolic responses in animals are not sufficiently similar to those of man to produce reliable guidelines.

Volunteers will be healthy young males who are patients recovering from mild conditions such as simple fractures.

SIGNIFICANT ASPECTS OF MATERIAL FOR SIGNATURE

Use of human volunteers.

CLEARANCES (Explain nonconcurrences or clearances indicated but not obtained)

SIGNATURE: *L. Bernstine*, CAPT MC USN, Director, Research Division DATE: 5 Oct 1970

Approved: [Signature]
1 December 1970

Case 712

Case 71

NI Cabland request for use of human volunteers on effect of stress as measured by certain hepatic functions monitored via hepatic vein catheterization

1. The expertise of the co-investigators stems from "a thorough familiarization with the procedure by the primary investigator". In addition, "support has been elicited from co-investigators (Departments of Surgery and Radiology, Mc Hospital, Oakland) to perform the catheterizations and assume responsibility for the subject during and after the study". (Statements quoted are from AMM in a letter.)
2. Their experience with this particular technique of liver catheterization stems from their contact and instruction in Dr. Havel's laboratory.
3. In order to compare peripheral and splanchnic samples (i.e. liver metabolism), a catheter must be placed in the hepatic vein.
4. I talked with other suspects at NRE and none expressed any serious concern with the procedure as such. Others in the field performed on healthy volunteers depend upon weighing the "minimal" risk and discomfort against possible benefits (i.e. biochemical mechanisms which are altered in chronic stress of fasting).
5. Dr. Weinstein will be in town sometime within the next two weeks.

Very respectfully,

R. L. BRIDGEMAN

| | | | | | |
|-------------------|--------------------|--------------------|---------------------|------------------|----------------------------|
| 1. PROJECT NUMBER | 2. RIGIDITY NUMBER | 3. SUBJECT ELEMENT | 4. APPROVAL ELEMENT | 5. HEADQUARTERS | 6. DOD/DA/AF/USMC/USN/USAF |
| N/A | A | U | U | N/A | ML |
| 7. PRIORITY | 8. CONTRIBUTING | 9. CONTRIBUTING | 10. CONTRIBUTING | 11. CONTRIBUTING | 12. CONTRIBUTING |
| U | | | | | |

(U) Splanchnic Metabolism During Chronic Stress in Active Duty Personnel

12. SCIENTIFIC AND TECHNOLOGICAL AREAS:
003500 Clinical Medicine

| | | | |
|----------------|-------------------------------|--------------------|------------------------|
| 13. START DATE | 14. ESTIMATED COMPLETION DATE | 15. FUNDING AGENCY | 16. PERFORMANCE METHOD |
| 70 07 01 | 71 07 01 | DNO | C. In-House |

| | | | |
|----------------------|------------------------|------------------------------|------------------------------|
| 17. CONTRACT/GRANT | 18. RESOURCES ESTIMATE | 19. PROFESSIONAL MAN-YEARS | 20. FUNDS (\$ IN MILLIONS) |
| | PRECEDING | | |
| 21. DATES EFFECTIVE: | 22. EXPIRATION: | 23. SCAL YEAR | 24. CURRENT |
| | | N/A | 1971 |
| 25. NUMBER: | 26. KIND OF AWARD: | 27. PERFORMING ORGANIZATION: | 28. PERFORMING ORGANIZATION: |
| | | | |

| | |
|---|--|
| 29. RESPONSIBLE DOD ORGANIZATION: | 30. RESPONSIBLE DOD ORGANIZATION: |
| NAME: Naval Hospital | NAME: Clinical Investigation Center |
| ADDRESS: 8750 Mountain Boulevard Oakland, California 94627 | ADDRESS: Naval Hospital Oakland, California 94627 |
| RESPONSIBLE INDIVIDUAL | PRINCIPAL INVESTIGATOR (Furnish SSAN if U.S. Academic Institution) |
| NAME: H. P. Mahin, RADM MC USN | NAME: H. V. Werner, LT MC USNR |
| TELEPHONE: 415-639-2111 Autovon 855-2111 | TELEPHONE: 415-639-2336 Autovon 855-2336 |
| 31. GENERAL USE: | SOCIAL SECURITY ACCOUNT NUMBER: |
| | |
| | ASSOCIATE INVESTIGATORS |
| | NAME: R. L. Weinstein, LCDR MC USNR |
| | NAME: |

22. KEYWORDS (Precede EACH with Security Classification Code)
(U) Glucose; (U) Fasting; (U) Splanchnic metabolism; (U) Stress

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

23. (U) This project is designed to define the biochemical mechanisms which are altered during a simulated combat situation, e.g. the chronic stress of fasting. With the onset of fasting, glucose storage deposits are depleted and fats are mobilized for energy maintenance. To utilize the fats efficiently, however, the body surrenders its ability to normally metabolize glucose; a temporary diabetic state results. Understanding of the biochemical alterations in liver that occur during stress could result in prophylactic treatment to maintain the pathways in a normal state.

24. (U) ^{TEX(10)} Individuals are fasted overnight (control state) and for 72 hours (stress state). Their psychological condition, alertness, and efficiency in the performance of tasks are observed for deviations from normal. The test proper consists of isolation of splanchnic metabolism by catheters in the hepatic vein and branchial artery and withdrawal of blood at timed intervals. Injection of labelled glucose and indocyanine green dye (for liver blood flow rate) is by a superficial arm vein. Separation of labelled glucose and lactate by column chromatography, counting by liquid glucose turnover values and rates of gluconeogenesis. Measurement of acetoacetate and 3-hydroxybutyrate levels determines rates of ketogenesis by liver and their utilization by extra hepatic tissues. Measurement of free fatty acids and glycerol estimates the rate of fat mobilization from adipose stores.

25. (U) New Work Unit.



NAVAL HOSPITAL
OAKLAND, CALIFORNIA 94617

IN 2581455555 70
70:cv
3900:5213
1 Sep 1970

From: Commanding Officer, Naval Hospital, Oakland, California
To: Chief, Bureau of Medicine and Surgery, Research Division (Code 71)
Subj: Proposed research project, "Splanchnic Metabolism during Chronic Stress in Active Duty Personnel;" additional information on
Ref: (a) Telecon with CAPT R. L. Bernstine, 28 August 1970

1 The proposed study requires a vascular isolation of the liver by an arterial catheter in the brachial artery, and a venous catheter in the hepatic vein to collect liver effluent. Among those using this technique in humans are listed:

- a. Bondy, P.K., et al.: Studies of the role of liver in human carbohydrate metabolism by the venous catheter technic. I. Normal subjects under fasting conditions and following the injection of glucose. *J. Clin. Invest.* 28:238, 1949.
- b. Myers, J.D.: Net splanchnic glucose production in normal man and in various disease states. *J. Clin. Invest.* 29:1421, 1950.
- c. Sanders, C.A., et al.: Effect of exercise on the peripheral utilization of glucose in man. *New Eng. J. Med.* 271:220, 1964.
- d. Wolfe, B.M., Havel, R.J., et al.: Effects of ethanol on splanchnic metabolism in healthy men. *J. Clin. Invest.* 49:104a, 1970.
- e. Havel, R.J.: Unpublished studies, 1969-1970.

2. Canine studies were contemplated but discarded since the definitive data required for application to humans might not be valid for the following reasons:

- a. The inherent excitability of dogs leads to rapid and prolonged changes in tissue lipid and carbohydrate metabolism, probably secondary to hormonal secretions, e.g., epinephrine (R. J. Havel, M.D., Professor of Medicine and Associate Director of the Cardiovascular Research Institute, University of California Medical School, San Francisco).

- b. Dietary variations result in profound changes in carbohydrate metabolism (*Physiol. Rev.* 36:164, 1956), and the "average" American diet (*J. Am. Dietet. Assoc.* 36:433, 1960) differs considerably in containing

20 (11)

Subj: Proposed research project, "Splanchnic Metabolism during Chronic Stress in Active Duty Personnel;" additional information on

higher quantities of protein and lower fat and carbohydrate than the usual dog diet (Am. J. Physiol. 201:41, 1961).

c. Anesthesia and surgery, which are needed in dog or rabbit studies, produce marked changes in carbohydrate metabolism (Metabolism 8:827, 1959; New Eng. J. Med. 244:615, 1951; and J. Biol. Chem. 225:225, 1957).

d. The anatomy (gross and microscopic) of the canine liver (Am. J. Anat. 84:311, 1949) and probably also its vascular supply (Am. J. Dig. Dis. 16:344, 1949; and Anatomie Anat. 103:246, 1956) differs from human liver.

3. Starvation of 72 hours was chosen as the prototype of stress since it is physiological and reproducible from subject to subject. Unpublished data from this laboratory indicate similar metabolic responses to the stresses of starvation, of exercise, and of heat-exercise. Thus, the data which result from these studies, on changes in human liver carbohydrate metabolism during the stress of fasting, should have valid application to other stressful situations, e.g., those of temperature extremes and exercise which are experienced in military situations, particularly in individuals under combat conditions.

4. This technique has been performed on forty-three (43) subjects by Dr. Havel's group without incident in those less than thirty years of age. To assure minimal morbidity in the proposed study, a thorough familiarization with the procedure by the primary investigator has been accomplished (via Dr. Havel's staff), and support has been elicited from co-investigators (Departments of Surgery and Radiology, Naval Hospital, Oakland) to perform the catheterizations and assume responsibility for care of the subject during and after the study.

H. P. MAHLIN

28 April 1969

RDT&E ACTIVITY

CONSENT TO PARTICIPATE VOLUNTARILY IN A RESEARCH,
DEVELOPMENT, TEST, OR EVALUATION (RDT&E) PROCEDURE

DATE _____

1. I hereby volunteer to participate as a subject in an RDT&E procedure being conducted under Element No. _____, Project No. _____, Work Unit Title " _____" which has been approved by _____ (sponsoring command). I understand

that the adequacy of safety measures has been certified by the Chief, Bureau of Medicine and Surgery, and that authority to use human volunteers has been granted by the Secretary of the Navy.

2. The nature and purpose of the procedures have been explained to me as follows: (See attached summary.)

3. In making my decision to volunteer, I am not relying upon any information or representation not set forth in this document, or attached summary. My consent is given as an exercise of free will, without any force or duress of any kind. I understand that my consent to participate does not constitute a release from any possible future liability by the United States attributable to the experiments.

SIGNED: _____

(TYPED NAME, RANK, RATE,
OR GRADE)

DATE OF BIRTH _____

WITNESSED: _____
(NOT DIRECTLY INVOLVED IN TEST)

APPROVED: _____

(TEST DIRECTOR)

Copy to:
Service record, jacket, or personnel file

Enclosure (1)

End (3)