14 February 1951

Mr. William V. Consolazio
Head, Biochemistry Branch
Office of Naval Research
Washington 25, D. C.

Dear Mr. Consolazio:

Enclosed please find 15 advance copies of a proposal for continuation of studies on the Distribution of Gases, Water and Electrolytes in the Human Body as being conducted under Contract N7onr-295, Task Order IV, Project No. NR 122-307, for the three year period 1 September 1951 through 31 August 1954.

This proposal, although it has been approved by the University Assistant Business Manager, is not to be construed as official or binding and is intended only for your information.

The official proposal has been submitted to the President of the University and the Board of Regents for their approval, and if satisfactory to them will be forwarded to the Office of Naval Research.

Thank you for your interest in this matter.

Sincerely,

Nello Pace,
Assistant Professor of Physiology

NP:ew
cc: J. M. Miller
W. B. Reynolds
W. K. Ball (Attn: W. Mini)

Proposal for continuation of studies on the distribution of gases, water and electrolytes in the human body as being conducted under Contract N7onr-295, Task Order IV, Project No. NR 122-307, for the period 1 September 1951 to 31 August 1954.

Nello Pace, Project Supervisor

OBJECT

To define the physiological factors controlling the dynamics of the distribution of gases, water and electrolytes in the human body.

BACKGROUND

Previous work under this Contract has led to the description of the dynamic distribution behavior of a number of simple substances, following intravenous administration into the human body, in terms of the arterial plasma time-concentration curves. These curves have been resolved into multiple simple exponential rate expressions, some of which appear to be common to all substances injected and others which seem to be characteristic of each separate substance. For the substances of small molecular size examined thus far, the limiting factors in the rate of distribution are believed to be the rate of blood supply to the various tissue regions and the magnitude of the space in these tissue regions available to the substance in which to distribute itself.

In order to verify and expand this simple hypothesis it is necessary to obtain more distribution curves from normal individuals in various physiological states as well as from patients suffering circulatory disorders. Furthermore, it is of importance to measure the physiological

spaces of the body, such as the total body fat, skeletal mass, extracellular fluid, etc., so that more quantitative evaluation of the distribution curves may be made. Finally, it is of interest to examine the detailed distribution of materials at the cellular level, which is now possible by means of the differential centrifugation technic for cell fractionation.

In addition to the present work on distribution dynamics, it is anticipated that with the availability of the White Mountain Research Station some research will be initiated on the problems of high altitude physiology. Besides this research, which is quite limited at present, the administration of the White Mountain Research Station itself also falls within the framework of the Contract. In order to clearly dissociate the basic research done under the Contract from the more strictly administrative problem of the operation of the White Mountain Station, completely separate accountability has been maintained locally for the research and for the operation of the Station. For this reason, two separate Budgets have been set up and are included in the following.

EXPERIMENTAL PLAN

In planning a research program for a three year period it is manifestly difficult to outline the experiments to be done in any great detail. Hence, the following plan is to be regarded as tentative and general in scope.

I. Radiosodium 24 distribution. An extension of the present measurements on cardiac patients is planned so that the effect of an impaired

circulation and altered fluid spaces on the radiosodium distribution curve may be clearly seen. It is further planned to investigate in more detail the recent finding under this Contract that the total body sodium space is almost double the normal in cardiac patients. Studies will also be made of radiosodium clearance from a limb as measured by the in vivo counting technic following intra-arterial injection of the limb with radiosodium. This method holds promise as a criterion of regional muscle circulation.

II. Radiopotassium 42 distribution. Arterial plasma concentration curves of K42 following intravenous injection have been obtained on normal individuals, and in the future studies similar to those described above with Na24 will be carried out using K42. The comparison of the behavior of K42 and Na24 is desirable because of the predominantly intracellular distribution of potassium in contrast to the predominantly extracellular distribution of sodium.

III. Gamma-ray labeled erythrocytes. An unsuccessful attempt has been made to label human erythrocytes with K42, which emits gamma rays sufficiently energetic to be detected by the in vivo counting technic. Further attempts will be made using other gamma emitting isotopes to label erythrocytes so that the dynamics of blood mixing may be studied in various tissue regions.

IV. Estimation of body skeletal mass. Preliminary experiments have been carried out on the feasibility of using radiocalcium 45 for measuring the total calcium space of the body in laboratory mice, so that the skeletal mass may be computed. This work is expected to

continue. As an adjunct to this problem, the intracellular distribution of calcium is being studied by means of the cell fractionation technic.

V. Total body fat determination. Work continues on the development of an air displacement method for measuring total body volume so that total body fat may be estimated from the computed value of body specific gravity. Progress on this problem has been slow because very little time has been devoted to it; however, it is anticipated that more time can be spent in the near future.

VI. Intracellular radiophosphorus distribution in the liver. The technics have been developed for the cellular fractionation of liver cells of laboratory rats into nuclei, mitochondria, microsomes and aqueous cytoplasm. It is also possible to carry out the chemical fractionation of each of these cell fractions into the various major groups of phosphorus compounds, viz., the acid soluble compounds, fat soluble compounds or phospholipids, nucleoproteins, and phosphoproteins. Work has already started on a study of radiophosphorus turnover rates in the various chemical and cell fractions after the injection of P32 labeled phosphate. By this means it is hoped to obtain more specific information concerning the intracellular sites of phosphorus metabolism. Following these preliminary experiments it is expected that the principle of the study of turnover at the cellular level will be applied in other problems as yet not clearly formulated.

VII. Myoglobin metabolism. Although hemoglobin metabolism has been studied extensively, very little is known of the metabolic origin, turnover, and fate of the companion respiratory pigment myoglobin.

Experiments are in progress by which some measure may be had of the normal rate of turnover of radioiron in rat myoglobin. In addition, it is expected that there will be available shortly at the White Mountain Research Station rats of the same strain which have been bred at altitude through at least one generation, so that the myoglobin concentration and turnover may be compared with the sea level counterparts. Preparations are being made to carry out these measurements at White Mountain within the year.

PARTICIPATING PERSONNEL

BERKELEY RESEARCH

Principal Investigator

Nello Pace, Ph.D., Assistant Professor of Physiology

Salaried Personnel

Salary provisions are being made for the following: one research M.D., half time; two graduate students, half time; and one administrative assistant, 20 per cent time.

Without Salary

At least six members of the Donner Laboratory of Medical Physics contribute directly and materially to the pursuit of the work under this Contract at no cost to the Contract. In addition, it is anticipated that the services of some of the members of U.S. Naval Volunteer Research Unit 12-2, Berkeley, will be available to the Contract if they are voluntarily recalled to active duty with the Office of Naval Research, San Francisco, for additional duty with this Contract.

WHITE MOUNTAIN RESEARCH STATION

In Charge

S. F. Cook, Ph.D., Professor of Physiology

Nello Pace, Ph.D., Assistant Professor of Physiology

Salaried Personnel

The only personnel who receive salary in direct connection with the White Mountain Research Station are two caretakers and maintenance men at full time. The duties of these individuals include the care of the physical facilities and equipment of the Station, as well as the care of the animal colony. They are also responsible for daily meteorological observations.

BUDGET

Although the research under this proposal is to continue for a three year period, it is more convenient to formulate the budget on a yearly basis. Furthermore, as mentioned above, the budget is subdivided into two sections, one dealing with the basic research under the Contract, and the other dealing with the administration of the White Mountain Research Station.

Part I - Berkeley Research

PERSONNEL

Salaries

Research M.D. at half time	$ 3,300.00
Two Graduate Students at half time	$ 3,120.00
Administrative Assistant at 20 per cent time	$ 1,128.00
Total	$ 7,548.00

Overhead

26 per cent of Salaries	$ 1,962.48	
Retirement and Insurance		
State retirement system at 8 per cent of salary, plus $4.00 per person, exclusive of students.	$ 354.24	
Workmen's Compensation Insurance at $.04 per $100 administrative salary and $.92 per $100 research salary.	$ 59.52	
TOTAL PERSONNEL COSTS		$ 9,924.24
EXPENSES AND EQUIPMENT		
Radioisotopes, including shipping charges from Oak Ridge, Tennessee	$ 900.00	
Shop work (glass and mechanical)	$ 600.00	
Laboratory supplies (Chemicals, glassware, and minor apparatus)	$ 500.00	
Compensation for human subjects, at $2.50 per hour	$ 500.00	
Travel and charges for research at White Mountain Research Station.	$ 575.76	
TOTAL EXPENSES AND EQUIPMENT		$ 3,075.76
YEARLY TOTAL FOR BERKELEY RESEARCH		$13,000.00
3 YEAR TOTAL FOR BERKELEY RESEARCH		$39,000.00

Part II - White Mountain

PERSONNEL

Salaries

Two Caretakers at $280 per month	$ 6,720.00

Overhead

8 per cent of Salaries (off-campus rate)	$

Retirement and Insurance

State retirement system	$ 545.60
Workmen's Compensation Insurance	$ 2.69
TOTAL PERSONNEL COSTS	$ 7,305.89

EXPENSES AND EQUIPMENT

6000 gallons of Diesel fuel for power, heat and bulldozer operation at $.175 per gallon, delivered.	$ 1,050.00
2000 gallons of gasoline for automotive equipment at $.30 per gallon, delivered.	$ 600.00
Repairs and maintenance supplies (automotive repairs, generator repairs and overhaul, oil grease, anti-freeze, tires, etc.)	$ 1,944.11

Administrative travel between
Berkeley and White Mountain at
$.05 per mile (for transportation)
and $3.00 per diem. for $ 600.00

TOTAL EXPENSES AND EQUIPMENT	$ 4,194.11	
YEARLY TOTAL FOR WHITE MOUNTAIN	$12,000.00	
3 YEAR TOTAL FOR WHITE MOUNTAIN		$36,000.00
TOTAL COST OF 3 YEAR CONTRACT		$75,000.00