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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 February 1950 to 31 January 1951

Nello Pace, Project Supervisor

RESEARCH AIMS

The general program of research is directed at the basic problem of mechanisms of transfer of materials in the human body. Within this broad problem it is possible to formulate a well-defined approach to an understanding of many of the fundamental processes regulating transfer. The specific approach is through the study of the dynamics of a variety of substances whose time-space distribution characteristics may be measured readily in the normal human when introduced into the body. Radioisotopes have greatly expanded the number of materials which may now be used for the purpose, and it is no longer necessary to rely ~~about~~ almost exclusively on substances foreign to the normal body metabolism in order to examine the behavior of a chemical population introduced suddenly into the body.

A further delimitation has been made for the present by employing only substances either not participating at all or participating only minimally in the processes of intermediary energy metabolism. It is in this sense, then, that certain gases, electrolytes, and water form the principal objects of study.

Although the literature records numerous experiments along these lines conducted on laboratory animals, and many profitable analogies may be drawn for the human, there exists a relative scarcity of data for the latter. It is of considerable interest and of some ultimate practical import, therefore, that such data be obtained. In this regard the radioisotopes are invaluable in enabling the detection and semi-quantitative determination of the distribution of atomic species by means of body surface measurements of radioactivity in the normal, intact human. Measurements at the body surface, coupled with blood level determinations and excretion measurements, form a precise and effective mode of attack on the general problem of transfer.

In addition to studies on normal humans, a number of individuals suffering various clinical disorders will also be examined. No particular clinical entity will be stressed, but rather abnormal conditions will be selected where one or more factors affecting transfer are involved. In this way, hypotheses and conclusions regarding the principles governing transfer may be tested. It is believed, of course, that information of value concerning the clinical entity will be obtained as well.

The actual procedure consists in obtaining serial arterial blood samples immediately after introduction of the experimental material into the body either intravenously or through the lungs. Collection of blood samples is continued at varying intervals for a total time period of two to three hours following administration, and in some instances the collection is made for several days. In certain experiments, when a suitable substance is used measurements at the body surface are carried out simultaneously over tissue regions such as the heart, liver, lung, thigh muscle and ankle bone. These measurements allow the detection of specific sites of accumulation of the substance and the correlation of the rate characteristics of accumulation components in the tissue curves with disappearance components in the blood curves.

From a study of the comparative distribution characteristics of various types of substances introduced into normal individuals and patients it is believed that many of the mechanisms regulating transfer of materials in the body will be clarified.

SPECIFIC EXPERIMENTAL PLAN

In the forthcoming year the work will consist essentially of a direct continuation of the present research, and it appears most practical to subdivide it primarily according to the materials to be examined.

(1). Carbon monoxide. Several aspects of the carbon monoxide problem will be studied. The mechanism of the sex difference in CO elimination rate is being approached by a comparative study of the properties of hemoglobin from men and women. Absorption spectrum comparison in the visible and near infra-red is being made, and it is expected that comparative carboxyhemoglobin dissociation curves will also be obtained. A study of carbon monoxide uptake rates by men and women is contemplated. The role of CO_2 as a factor in determining CO elimination rate will be studied. Finally, it is hoped that a few simultaneous arterial blood CO concentration curves and body surface measurement curves can be obtained using C 11 labeled CO.

(2). S 35 labeled sulfate. Plasma disappearance curves of labeled sulfate ion will be obtained from normal individuals and a few patients suffering disturbances in fluid balance. These curves will be analyzed for components and compared with those already at hand for sodium ion, CO, and radio-phosphorus labeled erythrocytes.

(3). H 3 labeled water. Plasma disappearance curves of tritium labeled water will be compared in the same way as described for the labeled sulfate. Much of the experimental material, i. e. plasma samples containing labeled water, is stored at present awaiting analysis. It has been necessary to develop a suitable method for tritium measurement; however, the method is now at hand and the analyses are proceeding. It will be at least several months before the results are available, and additional experiments may have to be performed at that time. Besides studies of the dynamics of transfer, labeled water will also be used for estimation of total body water.

(4). Gamma-ray labeled erythrocytes. Gratifying results have been obtained by the use of radio-phosphorus phosphate labeled erythrocytes in examining the rate of mixing the materials within the vascular system. Because erythrocytes leave the circulatory system at a very slow rate, introduction of labeled erythrocytes provides an excellent means for the study of the dynamics of intravascular mixing. An attempt will be made to label erythrocytes with a gamma emitting radioisotope rather than the beta emitting radio-phosphorus so that body surface measurements may be made of blood mixing in various tissue regions simultaneous with obtaining of blood curves.

(5). Radiosodium 24. Additional experiments utilizing Na 24 for transfer dynamics studies are contemplated which will fall into at least two categories. One is the effect of age on transfer, and will consist of a comparison of the component rate characteristics between young and old normal adults. The other will be the estimation of true extracellular fluid space by extrapolating the pure mixing components back to zero time.

(6). Radiocalcium 45. Preliminary experiments may be carried out on the feasibility of using Ca 45 for the determination of skeletal mass in vivo. Recent experiments in another laboratory have demonstrated that Ca 45 distributes itself uniformly in the normal Ca 40 of the body, even of the skeleton, after several days. Because the vast bulk of body calcium exists in the form of bone mineral, the equilibrium level of labeled Ca in body fluid should allow computation of skeletal mass from so-called Ca space. Ca 45 suffers a disadvantage in exhibiting a relatively long half-life of 180 days, so that its use in normal humans must be approached with caution; however, it may prove to be entirely safe to use it for human experimentation.

(7). Total body fat determination. The estimation of total body fat, while not directly related to the dynamics of transfer, is important in order that the fat-free body mass may be utilized as the reference unit for comparison of individual physiological variables. For this reason it is essential that a suitable means for estimation of body fat be found. It is planned to continue work on the methods under development in this laboratory at present. Both the foreign gas dilution method and the pressure differential method appear to hold promise as ultimate measures of body volume, and hence of total body fat as computed from the body specific gravity.

PARTICIPATING PERSONNEL

(1). With salary.

Nello Pace, Ph. D., Project Supervisor, Assistant Professor of Physiology and Research Associate, Division of Medical Physics and Donner Laboratory. 12.5 per cent of salary.

George F. Warner, M. D., Clinical Instructor in Medicine and Research Fellow, Donner Laboratory of Medical Physics. Half-time.

Elaine L. Walker, A. B., Technician. Full time.

Robert A. San Souci, A. B., Business Manager Donner Laboratory. 10 per cent of salary.

George J. Hecht, M. A., Graduate Student. Half-time plus full time in summer.

Julius T. Hanson, A. B., Graduate Student. Half-time plus full time in summer.

(2). Without salary. (Note: the following personnel contribute directly and materially to the pursuit of work under this contract at no cost to the Contract).

John H. Lawrence, M. D., Associate Professor of Medical Physics and Experimental Medicine and Director of Donner Laboratory

Hardin B. Jones, Ph. D., Associate Professor of Medical Physics and Physiology and Assistant Director of Donner Laboratory

Ernest L. Dobson, Ph. D., Research Fellow - Donner Laboratory

William Siri, A. B., Physicist in the Radiation Laboratory.

Muriel E. Johnston, A. A., Technician.

Caroline E. Rodgers, A. B. Technician.

Ellis H. Myers, B. S., Draftsman.

Peter J. Miljenich, A. B., Graduate Student.

Burton E. Vaughan, A. B., Graduate Student.

BUDGET

A.	Salaries		
	(1) Project Supervisor at 12.5%	$ 800.00	
	(2) M. D. - Physiologist at 50% time	$3,000.00	
	(3) Technician at full time	$3,120.00	
	(4) Administrator at 10% time	$ 552.00	
	(5) 2 Graduate Students at 50% time	$3,000.00	
			$10,472.00
B.	Overhead at 23% of Salaries		
C.	Special Expenses		
	(1) State retirement system at 8% of salary plus $4.00 fee per person, exclusive of students	$ 613.76	
	(2) Workmen's Compensation Insurance at $.04 per $100 for administrative salaries and $.92 per $100 for research salaries	$ 63.88	
			$ 677.64
D.	General Expenses and Equipment		
	(1) Cyclotron bombardment time for C11 and Na 24 at $35 per hour, two hours per month	$ 840.00	
	(2) Shop work (glass and mechanical)	$ 500.00	
	(3) Laboratory supplies (chemicals, glassware and minor mechanical apparatus, etc.)	$ 500.00	
	(4) Travel	$ 500.00	
	(5) Compensation for human subjects at ~~$25.00~~ $2.00 per hour	$ 250.00	
			$ 2,590.00
	TOTAL		$16,148.20