

RESEARCH AND DEVELOPMENT PROJECT CARD (NEW PROJECTS)		2. SEC. U	3. PROJ NO NR 120-000	
1. PROJECT TITLE Clinical and Nutritional Biochemistry			4. INDEX NO	5. REPORT DATE 30 Jun '50
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8. COGNIZANT AGENCY ONR	12. CONTRACTOR AND/OR LABORATORY See 21c		CONTRACT/W. O. NO.	
9. DIRECTING AGENCY Research Group 443	13. RELATED PROJECTS		17. EST. COMPL. DATES	
10. REQUESTING AGENCY	14. DATE APPROVED		RES.	
11. PARTICIPATION AND/OR COORDINATION	15. PRIORITY		DEV.	
	16. MAJ. CAT.		TEST	
19.		18. FISCAL EST'S.		OP. EVAL.
20. REQUIREMENT AND/OR JUSTIFICATION a. No change b. Block 12 changed				
21. BRIEF OF PROJECT AND OBJECTIVE (a) (b) (d) (e) no change. (c) Modified.  NR 120-002 (aided) - Amino Acids in Wound Healing. M. B. Williamson, Loyola University. NR 120-012 (aided) - Methylene Blue and the Mammalian Erythrocytes. H. G. Strack, Creighton University. NR-120-019 (transferred to project NR-122-000) - Proline and Hydroxyproline. J. H. Howard, University of Connecticut. NR-120-110 (transferred to project NR-115-000) - Enzymatic Activity in the Psychotic State. H. Hoagland, Worcester Foundation for Experimental Biology. (f) See task progress report for future plans. (g) See task progress report for complete bibliography of reports and articles.				
22. J RDB	SN.	FC.	IC & P.	X. I. C.

JRDB FORM 1A, 1 APR 1947

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CLINICAL AND NUTRITIONAL BIOCHEMISTRY--CODE 442

PROJECT NO. NR-120-000

CLINIC

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NR-120-150: (Continued)

15. Bordley, J. E., Harvey, A. M., Howard, J. E. and Newman, E. V., Preliminary report on the use of ACTH in the hypersensitive state, Proc. of the First Clinical ACTH Conference, John R. Mote, M. D., Editor, The Blackiston Company, Philadelphia, 1950, pp. 469-478.
16. Howard, J. E., Harvey, A. M., Carey, R. A. and Winkenwerder, W. L., Effects of ACTH on the hypersensitive state, read before the Section on Experimental Medicine and Therapeutics of the American Medical Association, June 28, 1950 in San Francisco (to be published in J.A.M.A.)
17. Howard, J. E., Some observations and thoughts on the therapy of diabetic acidosis, read before the American Diabetes Association, June 25, 1950 in San Francisco (to be published in Proceedings of the American Diabetes Association, 1950).
18. Rubin, P. S. and Howard, J. E., Histochemical studies on the role of acid mucopolysaccharides in calcifiability and calcification, Trans. of Second Conference on Metabolic Interrelations, sponsored by Josiah Macy, Jr. Foundation, New York, Jan. 9-10, 1950, in press.

\* \* \*

NR-120-299: Circulatory-Respiratory Changes as a Function of Environment (Unclassified)  
CONTRACTOR: University of Pennsylvania, Philadelphia, Pa.  
CONTRACT: N6onr-24901 (3/1/47 to 2/28/51)  
INVESTIGATORS: G. J. Lambertsen and G. F. Schmidt

OBJECTIVES: The objectives of this study are (a) to determine in human subjects the effects of inhaling oxygen at partial pressures above one atmosphere upon the cerebral circulation, cerebral, metabolism, and respiratory-tissue gas exchange; (b) to measure

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the pulmonary diffusion coefficient for oxygen (i. e., the quantity of oxygen taken up in the lungs per minute per millimeter of mercury difference in oxygen tension between alveolar air and pulmonary capillary blood); (c) miscellaneous related problems.

PROGRESS THROUGH 30 JUNE 1950: The most significant results of breathing oxygen at increased pressures (3 to 4 atmospheres) have been: a twenty-seven percent decrease in cerebral blood flow, constriction of cerebral vessels, increased internal jugular carbon dioxide tension with normal or subnormal arterial carbon dioxide tension, and an unchanged rate of oxygen consumption. While providing no explanation of the cerebral manifestations of oxygen poisoning the results do argue against explanations hitherto proposed. The results of this completed work were published as two abstracts in Federation Proceedings, 9: 1950 (see bibliography) and were presented as two papers at the Thirty-Fourth Annual Meeting of the Federation of American Societies for Experimental Biology in Atlantic City, April 17-21, 1950.

Measurements of the pulmonary oxygen diffusion coefficient in man (medical students and submariners) reveal that the coefficient measured directly is higher than the coefficient obtained by indirect measurement. Direct measurement comprises the simultaneous estimation of oxygen consumption, oxygen tension of alveolar air, oxygen tension of mixed venous blood obtained from the right heart by catheterization, an oxygen tension of arterial blood. Indirect measurement as by others involves carbon monoxide inhalation. An oxygen coefficient of 60 and a mean alveolar-pulmonary capillary oxygen tension gradient of 5.4 was obtained by direct measurement in normal, resting subjects, compared to a diffusion coefficient of 30 with a gradient of 10 obtained by the indirect carbon monoxide technique. Arterial oxygen tension in submariners was found to be approximately 7 mm. Hg. below that observed in medical students, while the alveolar gas tensions measured approximately the same in the two groups.

An unreported series of experiments was carried out on human subjects to determine the relationship between respiratory minute volume and arterial and internal jugular blood pH and pCO<sub>2</sub> during inhalation of increasing concentrations of carbon dioxide.

A comparison of the respiratory depressant effects of Morphine and Demerol was completed in man, using the

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relationships between arterial  $pCO_2$  and respiratory minute volume as a highly sensitive index of the degree of respiratory depression. As a result of this series of experiments it was found that, contrary to general belief, Demerol is as potent a respiratory depressant as Morphine.

Preliminary experiments designed to complete the direct quantitative evaluation of the possible occurrence of retention of dangerous levels of carbon dioxide in the tissues during oxygen inhalation at 4 atmospheres pressure have been carried out in dogs. No evidence of such retention has been found, in contradiction to the high tissue  $pCO_2$  levels observed by others using less direct methods.

Two presentations of work carried out under task NR-120-299 will be presented at the International Congress of Physiology in Copenhagen, Denmark, in August 1950. The first paper is entitled, "The Pulmonary Oxygen Diffusion Coefficient" and the second, "Some Effects of High Partial Pressures of Oxygen in Man."

Two professional investigators have left after working on this task for the past year. Two new professional investigators have replaced them and are currently being indoctrinated with the methods and concepts of work under the task.

FUTURE PLANS: To continue task per objectives.

LIST OF TECHNICAL REPORTS AND PUBLISHED ARTICLES:

1. Barker, E. S., Pontius, R. G., Aviado, D. M., Lambertsen, C. J. Simultaneous comparisons of alveolar gas tensions obtained by various methods. American Journal of the Medical Sciences, 218:15, 1949.
2. Barker, E. S., Pontius, R. G., Aviado, D. M., Lambertsen, C. J. Comparative evaluation of several methods for determining alveolar gas tensions in man. Federation Proceedings, 8:7, 1949.
3. Lambertsen, C. J., Clark, J. K., Aviado, D. M., Pontius, R. G., and Barker, E. S. Attempt at direct measurement of values required for calculating the pulmonary diffusion coefficient for oxygen. Federation Proceedings, 8:90, 1949.

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4. Lambertsen, C. J., Clark, J. K., Aviado, D. M., Pontius, R. G., Moyer, J. H., and Schmidt, C. F., The pulmonary oxygen diffusion coefficient. American Journal of the Medical Sciences, 220:715, 1949.
5. Lambertsen, C. J., Emmel, G. L., Cooper, D. Y., Loeschcke, H. H., and Kough, R. H. Effects of inhalation of oxygen at high partial pressures upon arterial and internal jugular blood gas content, tension and pH. Federation Proceedings, 9:73, 1950.
6. Kough, R. H., Cooper, D. Y., Jr., Emmel, G. L., Loeschcke, H. H., Lambertsen, C. J., and Schmidt, C. F. Effect of inhalation of oxygen at high partial pressure upon cerebral circulation and cerebral oxygen consumption in man. Federation Proceedings, 9:72, 1950.
7. Lambertsen, C. J., Kough, R. H., Cooper, D. Y., Emmel, G. L., Loeschcke, H. H., and Schmidt, C. F. Some effects upon man of oxygen inhalation at high partial pressures. To be published in Proceedings of International Congress of Physiology, 1950.
8. Schmidt, C. F., Lambertsen, C. J., Aviado, D. M., Jr., Pontius, R. G., Barker, E. S., and Moyer, J. H., Jr. The Pulmonary Diffusion Coefficient for Oxygen (DO<sub>2</sub>). To be published in Proceedings of International Congress of Physiology, 1950.

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NR-120-307: Distribution of Gases, Electrolytes, and Water in the Box (Unclassified)  
 CONTRACTOR: University of California, Berkeley, California  
 CONTRACT: N70nr-29504 (2/1/47 to 8/30/51)  
 INVESTIGATOR: E. Pace

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**OBJECTIVES:** The objectives of this study are: (a) to determine the distribution, retention, and elimination of inhaled carbon monoxide; and (b) to elucidate the physiological processes involved in the distribution of intravenously administered substances throughout the body fluids, cells, and cell accretions.

**PROGRESS THROUGH 30 JUNE 1950:** Studies of the tissue distribution of inhaled radioactive carbon monoxide ( $C^{11}O$ ) reveal, in addition to the known fast and slow distribution components, a very fast component (half-time of 0.28 to 0.88 minute) which is believed to represent the mixing of carbon monoxide with blood. No liver retention of the labelled carbon monoxide has been observed, which suggests that the temporary liver retention sometimes is the result of liver engorgement during transitory local anoxia. The rate of release of carbon monoxide by human subjects has been found to decrease with age, the half-time increasing 1% with each year. The rate of carbon monoxide elimination from the blood has been found to be a simple function of the alveolar oxygen partial pressure and the administration of pure oxygen in a recompression chamber at 2.5 atmospheres has been found to double the rate of elimination. Women have been found to eliminate carbon monoxide 30% faster than men, under comparable circumstances.

A technique for studying the distribution dynamics of intravenously administered substances has been perfected and applied to radioactive sodium ( $Na^{24}$ ), radioactive sulfate ( $S^{35}$ ), radioactive water ( $Tr^{20}$ ), and red blood cells labelled with radio-phosphorus ( $P^{32}$ ). Individual components of the distribution curves for these substances have revealed a relationship, of diagnostic interest, between the distribution time and cardio-vascular disease. The distribution curve components (from very fast to slow) are believed to represent such phases of mixing as intra-vascular blood mixing, extra-vascular fluid mixing, penetration into cells and cell accretions (such as bone), and elimination (through the lungs, kidneys, sweat, feces, etc.).

Arterial plasma concentration curves of  $S^{35}$  labeled sulfate ion following intravenous administration have been obtained on five young normal men and one young normal woman, and these in general confirm the characteristics of the single sulfate curve reported previously. The presence of, at least six components is clear, and the arterial plasma concentration of labeled sulfate,  $X$ , may be expressed as a function of time in hours,  $t$ , following intravenous injection by the equation:

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$$X = 0.25e^{-76t} + 0.31e^{-20t} + 0.14e^{-4.4t} + 0.13e^{-0.40t} + 0.15e^{-0.12t} + 0.02e^{-0.03t}$$

The elimination curve of labeled sulfate by the kidneys, as estimated from urine concentration curves, appears to involve at least four components and is expressible by the following equation:

$$U = 0.49e^{-0.33t} + 0.24e^{-0.14t} + 0.11e^{-0.069t} + 0.16e^{-0.0018t}$$

where U is the fraction of labeled sulfate injected which remains to be excreted in the urine. It will be noted that the last two rate constants in this equation bracket the final rate constant in the plasma equation, and that the first two urine rate constants match the fourth and fifth plasma rate constants, respectively. It appears, therefore, that urine concentration measurements with labeled sulfate reflect in part the behavior of plasma concentration. The significance of this correspondence will be discussed in detail in a forthcoming publication. It is also noteworthy that even four days after the intravenous administration of labeled sulfate more than 13 percent of the dose is not eliminated by way of the urine. Simultaneous measurement of labeled sulfate excretion by way of the feces revealed that only 1.5 percent of the total administered was lost by this route. Therefore it appears that approximately 15 percent of labeled sulfate injected intravenously is incorporated into a body pool of sulfur, possibly organic, from which it is released slowly with a half-time of about 16 days.

Progress is also being made in the other areas of research under this contract, but only mention of the direction of effort will be made at this time. Work continues on the measurement of labeled water arterial plasma curves. The technic for obtaining radiopotassium by cyclotron bombardment is now in hand, and it is anticipated that labeled potassium ion arterial plasma curves will soon be obtained. Preliminary experiments have also been carried out on the feasibility of labeling erythrocytes with radiopotassium.

Data is being obtained on the behavior of radiosodium ion when injected intramuscularly, as measured by a Geiger-Muller tube on the body surface over the site of injection. A technic

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has been developed for measurement of the activity of Ca 45 in biological material by direct plating, so that preliminary chemical separation of the calcium is not necessary. Finally, a nylon diaphragm less than 0.001 inch thick with an effective cross-sectional diameter of 2.5 inches has been developed which permits the detection of pressure changes of less than 0.002 mm Hg. The application of this pressure sensing device to the measurement of body volume continues.

FUTURE PLANS: To continue task per objectives.

As an aid to the distribution studies, the estimation of total body water, fat, and bone has been attempted. Body density appears to be an index of total body fat, and total extra-vascular body water has been quantitated by measuring the dilution of radioactive water, administered intravenously.

LIST OF TECHNICAL REPORTS AND PUBLISHED ARTICLES:

1. Pace, Nello; Loevinger, Robert; and Strajman, Enrique. In vivo Geiger-Muller gamma-ray counter for radioisotope distribution studies. Science, 107:71-73, 1948.
2. Pace, Nello; Strajman, Enrique; and Walker Elaine. Influence of age on carbon monoxide desaturation in man. Federation Proceedings, 7:89, 1948.
3. Pace, Nello; Strajman, Enrique; and Walker, Elaine. Acceleration of carbon monoxide elimination in humans by high pressure oxygen. Science, 111: In press, 1950.
4. Warner, George F.; Pace, Nello.; Strajman, Enrique; Siri, William E.; Johnston, Muriel E.; and Walker, Elaine L. Dynamics of the distribution of substances when introduced acutely into the human circulation. I. Arterial blood concentration of radiosodium 24 as a criterion of distributive events in normal individuals. In preparation.

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PROJECT NO. NR-120-000

NR-120-324: Protein Metabolism (Unclassified)  
 CONTRACTOR: George Washington University, Washington, D. C.  
 CONTRACT: N70nr-41901 (6/20/47 to 6/30/50)  
 INVESTIGATOR: L. K. Sweet

OBJECTIVE: The objective of this task is to investigate the effectiveness of protein dietary supplements in raising the protein plasma concentration of hospitalized individuals.

PROGRESS THROUGH 30 JUNE 1950: The value of concentrated human serum albumin for very small premature infants has been evaluated by the clinical means of giving albumin to alternate infants whose birth weight is below 1500 grams. The results of this study have not been evaluated.

The statistical analysis of the results of the previous two years work on the use of concentrated human albumin in premature infants whose birth weight is between 1251 and 2000 grams has been completed and work on the preparation of the manuscript for publication is almost complete.

FUTURE PLANS: This contract has expired. A final report is awaited.

LIST OF TECHNICAL REPORTS AND PUBLISHED ARTICLES:

Reports:

None

Publications:

None

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NR-120-509: Human Calorimetry (Unclassified)  
 CONTRACTOR: American Society of Heating and Ventilating Engineers  
 CONTRACT: N80nr-64901 (6/20/48 to 6/30/52)  
 INVESTIGATOR: C. Tasker

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