4/9/65

ARM1.941209.162

TITLE PAGE

ANNUAL PROGRESS REPORT

PERIOD COVERED: 1 JANUARY 1964 THROUGH 1 APRIL 1965

PRINCIPAL INVESTIGATOR: PAUL E. CARSON, M. D.

INSTITUTION: THE UNIVERSITY OF CHICAGO

SUBJECT: THE RELATIONSHIP OF BIOCHEMICAL AND ENZYMIC ABNORMALITIES OF CELLS TO RADIATION SUSCEPTIBILITY AND TO THEIR INJURY BY OTHER AGENTS

CONTRACT NO: DA-49-007-MD-968

QUALIFIED REQUESTORS MAY OBTAIN COPIES OF THIS REPORT FROM DDC.

KEY WORDS FOR INDEXING: ERYTHROCYTES, G6PD, GLUTATHIONE REDUCTASE, CARBOHYDRATE METABOLISM, HEMOLYTIC ANEMIA, MALARIA, DRUG TOXICITY, CELLULAR INJURY

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 67A-4813
Box #: 43
File: Dr. Paul E. Carson MD-968
University of Chicago
Reports & Manuscripts

ABSTRACT

1. Preparing Institution: The University of Chicago

2. Title of Report: The Relationship of Biochemical and Enzymic Abnormalities of Cells to Radiation Susceptibility and to their Injury by Other Agents

3. Principal Investigator: Paul E. Carson, M. D.

4. Number of pages, illustrations, and date: 4 pages, no illustrations, 1 April 1965.

5. Contract Number: DA-49-007-MD-968

6. Supported by: U. S. Army Medical Research and Development Command, Department of the Army, Washington 25, D. C.

Investigations are continuing utilizing the comparison among enzyme deficient individuals and those without deficiency. These investigations include the considerations of whole body metabolism, clinical drug toxicity effects, cellular, and molecular changes. At the whole body and clinical levels the chief differences noted are hemolytic susceptibility and alterations of carbohydrate metabolism. These differences also apply at the cellular level but also effects of membranes on enzyme activities and cellular metabolism as well as actual molecular variation of the enzymes and proteins themselves are being studied. Publications have appeared giving data on these points as well as relationships to schizophrenia and to certain hemoglobinopathies. Field tests have been developed for use in these studies in terms of incidence of malaria, population genetics, and susceptibility to drug toxicities in populations.

Note: Copies of this report are filed with the Defense Documentation Center (DDC), Building 5, Cameron Station, Alexandria, Virginia, and may be obtained from that agency by qualified requestors.

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 67A-4813
Box #: 43
File: Dr. Paul E. Carson MD-968
University of Chicago
Reports & Manuscripts

The bulk of this annual report is contained in the attached reprints which have appeared during this period or are in press.

I. Carson, P. E., Okita, G. T., Frischer, H., Hirasa, J., Long, W. K., Brewer, G. J.: Patterns of Hemolytic Susceptibility and Metabolism, Proc. 9th Congr. europ. Soc. Haemat. Lisbon 1963 (S. Karger, Basel/ New York 1963), p. 655.

This paper presents data concerning $C^{14}O_2$ expired after injection of C^{14} labeled glucoses, glutathione reductase activities in hemolysates of G6PD and glutathione reductase deficient erythrocytes, and a set of stromal effects on hemolysate enzymes. Such data obtained at the whole body, cellular, and molecular levels give a pattern of hemolytic susceptibility and metabolism relating especially to carbohydrate metabolism. Although there clearly are changes in the whole body carbohydrate metabolism in G6PD deficiency we have been unable to confirm the recent report by Chanmugam and Frumin purporting to show abnormal oral glucose tolerance responses in G6PD deficiency. (The New England Journal of Medicine, vol. 271, 23, 1202, Dec. 1964). Data on this point have been obtained both in this hospital and at the Stateville Project in 1956-57, 1960-61, and most recently in 1964 and early 1965. A manuscript concerning this subject is being prepared.

II. Bowman, J. E., Brewer, G. J., Frischer, H., Carter, J. L., Eisenstein, R. B., and Bayrakci, C.: A Re-Evaluation of the Relationship Between Glucose-6-Phosphate Dehydrogenase Deficiency and the Behavioral Manifestations of Schizophrenia. J. Lab. & Clin. Med., vol. 65, 222, 1965.

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 67A-4813
Box #: 43
File: Dr. Paul E. Carson MD-968
University of Chicago
Reports & Manuscripts

A relationship between G6PD deficiency and schizophrenia had earlier been suggested. (Dern, R. J. and Brewer, F. J., Clin. Res., 10: 80, 1962, Abstract: Dern, R. J. et al, J. Lab. & Clin. Med., 62: 319, 1963). On the other hand Dr. W. K. Long (who obtained part of his recent training with us) was unable to confirm this. A definitive study of this important question appeared necessary and is given in the attached reprint. These results clearly indicate no statistically significant correlation between these two conditions. Other possible relationships between metabolic derangements and schizophrenia probably do exist and may, indeed, be different in G6PD deficiency. This would, however, have to be in a far more subtle fashion than a simple correlation.

III. Bowman, J. E., Carson, P. E., Frischer, H., Kahn, M., and Ajmar, F. A.: A capillary Tube, Nile Blue Methemoglobin Reduction Test for Glucose-6-Phosphate Dehydrogenase Deficiency, Proc. 10th Cong. Int. Soc. Blood Transf. Stockholm 1964. (S. Karger, Basel/New York) in press.

A capillary tube methemoglobin reduction test has been developed which is by far the most practical and easy test yet devised for determining G6PD deficiency. Not only does it require little blood but for reasons not as yet understood appears to distinguish heterozygotes better than by enzyme assay and as well or better than the original Brewer's macro test. Furthermore, it is, of course, not only useful in pediatric cases,

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 67A-4813
Box #: 43
File: Dr. Paul E. Carson MD-968
University of Chicago
Reports & Manuscripts

adapted for field work.

IV. Frischer, H., Carson, P. E., and Bowman, J. E.: Methemoglobin Reduction in Intact G6PD Deficient and HbM Erythrocytes, Proc. 10th Cong. Int. Soc. Haemat. Stockholm 1964, (S. Karger, Basel/New York) in press.

The methemoglobin elution of intact cells has been developed by Dr. Frischer as indicated in the attached paper and as has been previously described in proposals and reports concerning this contract. The addition of this technique has several very significant consequences for our work. It adds the parameter of intact cell study to whole body and hemolysate and molecular studies. The technique can be used to show that the Lyon hypothesis of x-inactivation is not proven in human erythrocytes. It is especially adapted for field work in terms of several disorders particularly methemoglobin disorders and enzyme deficiencies. It has a very possible application to malaria and drug toxicity which is being explored, and finally its use in certain pretreatments of cells before applying this technique will be of especial value in connection with earlier studies on radiation effects. Namely, after treatment by ultra or x-radiation this technique more than any other offers the opportunity for revealing changes induced by such treatment. This, of course, is in addition to various other treatments of cells in terms of serum, plasma,

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 67A-4813
Box #: 43
File: Dr. Paul E. Carson MD-968
University of Chicago
Reports & Manuscripts

ionic, and drug effects. In addition, this technique has revealed several very new findings concerning HgbM disease and the structure of hemoglobin especially as related to cyanide reactivity. This work is in progress and will be published during the next year.

V. Additional investigations of previously described projects are continuing and will be presented in both interim reports and in the next annual report. These include further studies of membrane effects, of drug toxicity with labeled tritiated DDS in connection with hemolysis, carbohydrate metabolism, and antimalarial activity, and of genetic and molecular variants of several enzymes as revealed by vertical starch gel electrophoresis.

VI. Bowman, J. E. and Frischer, H.: Malaria, G6PD Deficiency and Sickle-Cell Trait. Brit. Med. J., 1378, 1964.

VII. General reorganization of the program and facilities for work being done under this contract.

New expanded facilities for our group have been made available by the University. The principals who will use the new facilities include Dr. Robin D. Powell, Dr. James E. Bowman, Dr. Henri Frischer, and Dr. Franco Ajmar. This expansion and coordination of previously segregated effort is expected to be completed in July 1965.

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 67A-4813
Box #: 43
File: Dr. Paul E. Carson MD-968
University of Chicago
Reports & Manuscripts

DISTRIBUTION LIST

Director
Walter Reed Army Institute of Research
Walter Reed Army Medical Center
Washington 12, D. C.

Director
Armed Forces Institute of Pathology
Walter Reed Army Medical Center
Washington 12, D. C.

Commanding Officer
US Army Tropical Research Medical Laboratory
APO 851, New York, New York

Commanding Officer
US Army Environment Hygiene Agency
Army Chemical Center, Maryland

Dr. Mary H. Aldridge
The American University
Massachusetts & Nebraska Avenues, N. W.
Washington, D. C.

Dr. George W. Beran
Silliman University
Mission Hospital
Dumaguette City, Negros Oriental
Republic of the Philippines

Dr. Robert J. Byrne
University of Maryland
College Park, Maryland

Dr. D. H. Connor
Makerere College
The University College of East Africa
P. O. Box 262
Kampala, Uganda

Professor J. B. Duguid
Institute for Medical Research
Kuala Lumpur, Malaya

Dr. Lorenzo Galindo
University of Puerto Rico
San Juan, Puerto Rico

Dr. Chamlong Harinasuta
The Bangkok School of Tropical Medicine
Rajvithi Road, Phyathai
Bangkok, Thailand

Dr. H. F. Hsu
State University of Iowa
Iowa City, Iowa

Dr. Mongkol Kruatrachue
The Bangkok School of Tropical Medicine
Rajvithi Road, Phyathai
Bangkok, Thailand

Dr. Edward P. Mumford
Palo Alto Medical Research Foundation
860 Bryant Street
Palo Alto, California

Dr. William P. Murphy, Jr.
Cordis Corporation
241 N. E. 36th Street
Miami 37, Florida

Dr. Augustine N. Njoku-Obi
Tuskegee Institute
Alabama

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 67A-4813
Box #: 43
File: Dr. Paul E. Carson MD-968
University of Chicago
Reports & Manuscripts

Dr. Francisco Ramos-Morales
University of Puerto Rico
San Juan, Puerto Rico

Dr. Leo Rane
University of Miami
Coral Gables, Florida

Dr. Suvajra Vajrasthira
The Bangkok School of Tropical Medicine
Rajavithi Road, Phyathai
Bangkok, Thailand

Dr. Robert Charles Wood
Department of Microbiology
The George Washington University
Washington 5, D. C.

Dr. Wen-Hsien Huang
College of Medicine
National Taiwan University
Taipei, Taiwan

Professor O. K. Khaw
National Defense Medical Center
Taipei, Taiwan

Dr. Tongchai Papasarathron
Faculty of Public Health
University of Medical Sciences
Bangkok, Thailand

Professor Yun-Tao Sun
College of Medicine
National Taiwan University
Taipei, Taiwan

Dr. Winston H. Price
Johns Hopkins University
School of Hygiene & Public Health
615 North Wolfe Street
Baltimore 5, Maryland

Washington National Record Center
Office of the Army Surgeon General
Record Group 112
Accession #: 67A-4813
Box #: 43
File: Dr. Paul E. Carson MD-968
University of Chicago
Reports & Manuscripts