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THE  
UNIVERSITY OF CALIFORNIA  
PROGRAM  
 in  
CANCER RESEARCH

Eighth Annual Report  
January 1955

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Cancer Research Coordinating Committee  
University of California  
January 14, 1955

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Robert Gordon Sproul, President  
University of California  
Berkeley 4, California

My dear President Sproul:

I take great pleasure in submitting to you the Eighth Annual Report of the University of California Program in Cancer Research.

As in the past it is beneficial to take stock of how the program of Cancer Research of the University is functioning and to gauge how favorably it compares with the programs in other first rate institutions of the land.

There are three levels of effort in a thorough, complete, and logical program of cancer research; namely, 1) clinical research on cancer patients, 2) research on neoplasms and the cancer host by animal experiments, and 3) basic research on the fundamentals of the natural sciences. Each of the underlying activities feeds the one above it. The raw materials for the ideas to attack the cancer problem must come from advances in the natural sciences. These ideas must then be tried and developed by means of experiments on animals, until finally the refined and established values obtained in this way are suitable for human trial. By the above test the University Cancer Research Program measures up well. Cancer research is being vigorously carried on all of the three mentioned levels.

The University of California, or no other institution, stands alone or works in isolation in the attack on the cancer problem. The activities of every laboratory and clinic engaged in pertinent work are motivated, guided and affected by the continuous exchange of ideas and information that constantly goes on. This occurs by many means: publication in journals, meetings of scientific societies, personal communications, etc. There is no more important element in the research attack on cancer than that of the utmost freedom of communication in science.

To the extent that one can foresee, the conquest of cancer will be a long, slow, laborious process, marked by individually small but repeated advances and successes. This means that infinite patience is required on the part of all: investigators, legislators, administrators, and above all the public. No easy road can be seen ahead and miracle cures are not discernible on the horizon.

Gains are constantly being made in improved methods of diagnosis, methods of treatment and in prevention. In these the University has made significant contributions and the record of these contributions for the

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Robert Gordon Sproul, President

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January 14, 1955

past year is contained in the current Cancer Research report.

A few significant items from the report may be singled out. The cancer teaching program sponsored by the United States Public Health Service, in which our University plays a leading part, is doing outstanding work in emphasizing the importance of early diagnosis of cancer and in alerting both the medical profession and the public to an awareness of this. The cytological method of cancer diagnosis, to which our University has contributed immensely, is being expanded and is finding new fields of application. Improvements in the applications of radiology to cancer are forecast in the reports of investigations now under way in the Donner Laboratory, the Radiological Laboratory and Department of Radiology of the School of Medicine, San Francisco, and in the several departments of the School of Medicine, Los Angeles. Chemotherapy has had but limited success in the treatment of cancer to date. However, there are high hopes of eventual success. New compounds that are active against some neoplasms are being developed regularly. Perhaps more important, some of the structural features required for therapeutic activity against cancer are being brought to light. In this program the University is taking an active part both in the development of new drugs and in the clinical evaluation of compounds that have passed scrutiny in animal tests. In addition many important contributions to the advance of the natural sciences and to the understanding of the nature of the neoplastic transformation are contained in the report.

Cancer research in the University of California continues to grow. This is shown by the increase in the number of reports submitted this year over last year. This increase has taken place in spite of the regrettable loss to the University of a very active laboratory, The Laboratory of Experimental Oncology of the United States Public Health Service. This steady growth has taken place in the face of some formidable obstacles and it is readily apparent that we are far from the peak of the development in the Cancer Research Program of the University. Only just now are the quarters for the Cancer Research Institutes both in the North and South reaching completion. Once suitably housed and with adequate facilities it can be confidently predicted that the research activities in cancer will be mightily increased.

This notable enterprise of the University, embarked upon some eight years ago, has expanded greatly and is flourishing. Results of great value to the health and well-being of the people of California have already been achieved and there is high promise of better things to come.

Respectfully submitted,

  
 David M. Greenberg  
 Chairman, Cancer Research Coordinating  
 Committee

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**THE UNIVERSITY OF CALIFORNIA PROGRAM IN CANCER RESEARCH**  
**EIGHTH ANNUAL REPORT, JANUARY 1955**

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Dauben, W. G.	Chemistry & Chemical Engineering
Dekker, C. A.	Biochemistry
DeOme, K. B.; Bern, Howard A.; & Alfert, Max.	Cancer Research Genetics Laboratory & Zoology
Greenberg, D. M.	Physiological Chemistry
Harris, M.	Zoology
Kirk, P. L.	Biochemistry
Krueger, A. P.	Bacteriology
Lawrence, J.H.; Gofman, J. W.; Jones, H.B.; Tobias, C. A.; Born, J.L.; Berlin, N.I.; Elmlinger, P.J.;	Donner Laboratory of Medical Physics
Dobson, E.L.; Kelly, L.S.;	
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Simpson, M. E.	Institute of Experimental Biology
Stanier, R. Y.	Bacteriology

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Williams, R. C.	Virus Laboratory
<u>Davis:</u>	
Julian, L. M.	Veterinary Medicine
 <u>Los Angeles:</u>	
Adams, W. S. & Bassett, S. H.	Medicine
Adams, J. M. & Imagawa, D. T.	Pediatrics
Appleman, D.	Plant Nutrition
Bennett, L. R.	Radiology
Biale, J. B.	Subtropical Horticulture
Dowdy, A. H.; Bellamy, A. W.; Hall, G. C.; & Penn, H. S.	Radiology
Dunn, M. S.	Chemistry
Fink, K. F.	Biophysics
Flickinger, R.	Zoology
Garst, J. B.	Physiological Chemistry
Geary, J. R., Jr.	Pathology
Geissman, T. A.	Chemistry
Goodwin, W. E.	Surgery
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<u>Responsible Investigator</u>	<u>University Department</u>
Morton, D. G.	Obstetrics & Gynecology
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Pressman, J. J. & Longmire, W. P., Jr.	Surgery
Roberts, C. S.	Zoology
Roberts, S.	Physiological Chemistry
Schechtman, A. M.	Zoology
Selle, W. A.	Biophysics
Swendseid, M. E.	Home Economics
Valentine, W. N.	Medicine
Weimer, H. E.	Infectious Diseases
West, P. M.	Biophysics
Wilman, S. G.	Botany
<u>San Francisco:</u>	
Bostick, W. L.	Pathology
Lindsay, S. & Dailey, M. E.	Pathology & Medicine
Low-Beer, B. V. A.; Allen, F. W.; Smith, K. C.; & Low-Beer, A. G.	Radiology & Biochemistry
Low-Beer, B. V. A. & Bell, H. G.	Radiology & Surgery
Low-Beer, B. V. A.; Bell, H. G.; Boldrey, E.; Crane, J.; & Mott, C.	Radiology, Surgery, Neuro- surgery, & Pathology
Low-Beer, B. V. A.; Low-Beer, A. G.; & Scott, K. G.	Radiology
Low-Beer, B. V. A. & Morrison, L. F.	Radiology & Ear, Nose & Throat Surgery
Low-Beer, B. V. A. & Mott, C. J.	Radiology
McCorkle, H. J.	Surgery
Miller, E. R.	Radiology
Moon, H. D.	Pathology
Rinehart, J. F.	Pathology
Scott, K. G.	Radiology
Steinbach, H. L. & Brodie, D. C.	Radiology

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<u>Responsible Investigator</u>	<u>University Department</u>
Stone, R. S.; & Adams, G. D.	Radiology
<u>Santa Barbara:</u>	
Walters, M. S.	Biological Sciences

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### INTRODUCTION

The Eighth Annual Report of the Cancer Research Program of the University of California differs from previous Reports in that an attempt has been made to include all of the cancer research activities of the University rather than only those supported entirely, or in part by University funds. The projects financed by University funds are clearly indicated in each project under the heading "Financial Support".

The work of some individuals on groups of individual may have been omitted; to these people the secretary wishes to express his apology.

The financial report includes known funds available to cancer research workers exclusive of funds included in the regular University budget. Two exceptions should be noted; namely, the inclusion of the regular budgets of the Cancer Research Genetics Laboratory and of the Cancer Research Institute, San Francisco. The data were compiled from the Regents' Roster, reports of investigators, reports of granting agencies, and the files of the Cancer Research Coordinating Committee. The research grants are those reported by the investigators, whose decision as to which ones should be classified as "Cancer Research", was accepted without question.

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The funds appropriated for cancer research by the  
 Legislature of The State of California, plus the income  
 from endowed funds, was the financial hard core of the  
 Cancer Research Program of The University. It should  
 be noted that a greater number of research projects  
 were supported entirely, or in part, by these funds than  
 by funds from all other sources.

*K. B. DeOme*

K. B. DeOme  
 Secretary of the Cancer Research  
 Coordinating Committee

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### FINANCIAL REPORT 1954

#### I. Research

1. University of California Funds		
A. California State Appropriation	\$	258,287
B. Cancer Research Genetics Laboratory		36,890
C. Cancer Research Institute, San Francisco		24,984
D. Income from Endowed Funds		28,356
E. Donations and Gifts		56,339
Sub-total (1)	\$	404,856

#### 2. Grants from Foundations, Agencies, and Industries

A. U. S. Public Health Service		345,126
B. American Cancer Society (National)		238,096
C. American Cancer Society (Cal.Div.)		29,160
D. Atomic Energy Commission		316,500
a. Radiation Laboratory	265,000	
b. Donnor Laboratory	36,000	
c. Others	15,500	
E. Damon Runyon Memorial Fund		12,000
F. California Institute for Cancer Research		6,002
G. Others		141,054
Sub-total (2)	\$	1,087,938

#### II. Teaching Grants

1. U. S. Public Health Service		101,968
2. California Institute for Cancer Research		12,490
Sub-total (3)	\$	114,458

#### III. Fellowships and Traineeships

1. U. S. Public Health Service (10)		27,450
2. Damon Runyon Memorial Fund (1)		4,800
3. American Cancer Society (National) (3)		10,800
4. American Cancer Society (Cal.Div.) (10)		7,000
Sub-total (4)	\$	50,050

**Total**

**\$ 1,657,302**

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Responsible Investigator: Frank Worthington Allen  
University Department: Physiological Chemistry  
Financial Support 1954-55: UC(SF) \$ 5,100.00; UC(B) \$ 500.00;  
 PHS \$ 6,199.00.

Title of Project: Nucleic Acids.

During the year designs for the construction and  
 operation of an apparatus for electrophoresis on paper have  
 been published. The apparatus has many general uses in  
 chemical and biological problems and information which has  
 been received indicates that many laboratories throughout  
 the United States have constructed this apparatus from our  
 plans and have placed it in successful operation. The  
 apparatus was designed in this laboratory to aid us in the  
 study of certain aspects of the chemistry of nucleic acids  
 and nucleotides.

By the use of the apparatus we have been able to  
 accomplish the first successful resolution of the twelve  
 isomeric mononucleotides of ribonucleic acid by zone  
 electrophoresis. Formerly used procedures required as  
 much as one week to resolve these substances. Their  
 resolution can now be accomplished in from 30 minutes to  
 1 hour.

The electrophoresis apparatus has permitted us to  
 develop a method which can be applied to the study of the  
 many enzymes that are known to be concerned in the

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metabolism of the nucleic acids of tissues. In contrast  
 to heretofore published methods this technique is specific  
 in that specific intermediary products as well as end-  
 products can be detected and characterized. This method  
 was specifically developed in order to study the nucleic  
 acid metabolism in normal and neoplastic tissues and the  
 effects of x-irradiation in directing or eliminating such  
 reactions. This latter study has been undertaken in  
 collaboration with Dr. B. V. A. Low-Beer (Department of  
 Radiology). The method has already been used by this  
 laboratory to study the activation and inactivation of  
 ribonuclease upon the specific substrates uridine-2'-3'-  
 phosphate and cytosine-2'-3'-phosphate. It will be  
 prepared for publication during the coming year.

Publications:

Allen, F. W. Nucleic Acids. Ann. Rev. Biochem.,  
 23:98-124, 1954.

Crestfield, A. M., and Allen, F. W. The Resolution  
 of Isomeric Ribonucleotides by Electrophoresis on Paper.  
 Federation Proc., 13:195, 1954.

Crestfield, A. M., and Allen, F. W. An Improved  
 Appartus for Zone Electrophoresis. Analytical Chemistry  
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Allen

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Crestfield, A. M. and Allen, F. W. Studies of the  
Mobility of Ribonuclease by Zone Electrophoresis. J.  
Biol. Chem., 211:363-366, 1954.

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Responsible Investigator: C. E. Ballou

University Department: Biochemistry

Financial Support 1954-55: UC \$ 3,000.00

Title of Project: The Synthesis of Glycolytic Intermediates  
and a Study of Enzyme Specificity.

The aim of this research program is to study the reactions of enolase, an enzyme involved in the metabolism of carbohydrates, and, through the use of specific inhibitors of structures closely related to that of the natural substrate, try to learn something about the mechanism by which this enzyme works.

During the four months this project has been in effect we have reinvestigated the normal reactions of enolase, and determined certain constants that will be necessary as a point of comparison. In addition we have synthesized three inhibitors of the enzyme, and measured the inhibition by a number of other substances. In general, the work on this project is progressing rapidly, and shows much promise.

Publications To Date: None.

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Responsible Investigator: Spencer W. Brown

University Department: Genetics

Financial Support 1954-55: UC \$ 3,100.00

Title of Project: Studies of Some Genetic and Physiological Factors Influencing the Stability of Ring and Rod Chromosomes.

The carcinogenic activity of x-rays and mustard gas provide an excellent indication that cancers arise from genetic changes during development. The essential genetic change is mutation but the effects of most mutations will remain masked by the presence of a non-mutated homologous chromosome. However, on elimination of the non-mutated chromosome or on crossing over between the homologous chromosomes, the effects of the prior mutation would be expected to become manifest. Our work on this problem is devoted to studies of the environmental, genetic, and developmental factors affecting chromosome elimination and somatic crossing over. The organism used, Drosophila melanogaster, is most ideally suited to studies of this sort.

Our data show a remarkable fluctuation in the frequency of somatic crossing over, from 13 to 300 percent mosaic spots per fly. Environmental and genetic differences otherwise minor seem to form the basis for

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Brown

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this wide range of variation. Somatic crossing over occurs at a disproportionately high rate during the very late developmental stages.

Since no carcinogenesis is involved here, work of this sort cannot provide direct evidence on the origin of cancer but it can be expected to provide models which can be tested against experience. In the present instance, the wide fluctuations in somatic crossing over would help to account for familial tendency toward carcinogenesis of a non-specific nature: the "high cancer" families would be those with a high frequency of somatic crossing over leading to the expression of any type of carcinogenic mutation in any type of tissue in which it might occur. The occurrence of somatic crossing over preponderantly in late developmental stages would parallel the observations in humans that neoplasms occur much more frequently in older people when tissue growth and replacement has reached a low rate.

During the course of these investigations, Dr. Drew Schwartz of the Oak Ridge National Laboratory published his evidence for a two-step mechanism of crossing over. Dr. Schwartz based his argument on studies of somatic crossing over in the fruit fly somewhat similar to those being conducted in this laboratory. Because an understanding of the mechanism of crossing over would

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Brown

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aid appreciably in defining the factors influencing somatic crossing over, Dr. Schwartz' experiments were repeated in cooperation with Mr. William Welshons of the Zoology Department. The results obtained are not in agreement with those offered by Dr. Schwartz, and indicate that the extreme fluctuation in somatic crossing over is probably the factor which led him to erroneous conclusions. A report on this problem is being prepared for publication.

At present, work is progressing along several lines. A determination of the time in development at which somatic crossing over occurs is being made by means of high temperature treatments. Preliminary results have shown that the frequency of somatic crossing over may be affected by variation in mineral nutrition. Statistical comparisons are being made of the developmental stages at which somatic crossing over and ring chromosome elimination take place. A large scale analysis of the number and distribution of genetic factors affecting the frequency of somatic crossing over is being projected for a thesis problem for a graduate student.

Publications To Date: None

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Responsible Investigator: I. L. Chaikoff  
University Department: Physiology  
Financial Support 1954-55: UC \$ 6,624.00.

Title of Project: A) Metabolic Patterns in Tumor Tissues  
 B) Pituitary Tumorigenesis

**A. METABOLIC PATTERNS IN TUMOR TISSUES**

The ultimate aim of certain investigators in the field of carcinogenesis is to obtain an answer to the problem as to why a tissue or organ that, after maintaining a constant size for a period of, say, 50 years, suddenly takes on new growth which may result in death of the host. It is not unreasonable to argue that an altered metabolic pattern is responsible for the turn of events. But regardless of the point of view, there can be no doubt at this time that the peculiarities, if such exist, in the metabolism of tumors must be explored. For this reason we are pursuing the various metabolic paths in normal and tumor tissues. We are doing this with the aid of C<sup>14</sup>-labeled glucose, fructose, acetate, short and long chain fatty acids of the even series and of the odd series. Other C<sup>14</sup>-labeled compounds are in the course of synthesis.

1. A Chromatographic-Radioautographic Approach to the Study  
 of Acetate Metabolism in Tumors

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Progress in the study of the metabolism of any tissue, normal or neoplastic, depends upon the availability of methods for detecting and for obtaining a quantitative estimate of intermediates involved in the utilization of carbohydrate, fats, and protein. It is for this reason that we are devoting much time to the development of a method for detecting and measuring the compounds involved in the fate of acetate in normal and tumor tissues. It should be recalled here that acetate represents, as closely as we can get to it, the two-carbon fragment, acetyl-S-CoA, which is a meeting point in the pathway of breakdown of fats, carbohydrate, and amino acids, and in the pathway of synthesis of these same compounds.

During the year under review we have succeeded in developing such a method. It involves filter paper chromatography, and since our starting material is radioactive acetate, we also make use of radioautographs of the chromatograms.

## 2. Fat Oxidation in a Mouse Hepatoma

The ability of normal tissues or their enzyme preparations to oxidize fatty acids via  $C_2$  fragments (acetyl-S-CoA) has been demonstrated convincingly by many workers. Curiously enough, the view has appeared in the literature that ketogenesis does not occur in tumor

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cells. Since the formation and accumulation of acetoacetate have important implications as to the manner by which that tissue oxidizes fatty acids, we undertook a study of acetoacetate formation by a tumor, the mouse hepatoma. In this study we made use of octanoate- $1-C^{14}$ . We found that isotopic acetoacetate accumulated in measurable quantities, and that the distribution of the isotope in the ketone body is consistent with the view that fatty acids are degraded to two-carbon fragments which then recondense to form acetoacetate. The hepatoma, in its metabolism of octanoate- $1-C^{14}$ , resembles extrahepatic tissues in that the acetoacetate which is formed is readily utilized. This explains why so little ketone bodies accumulate in tumors.

#### B. PITUITARY TUMORIGENESIS

Some time ago we observed that pituitary tumors can be induced by  $I^{131}$  injections. Since these are slow in development, we have imported a transplantable pituitary tumor from Dr. J. Furth, and these are providing the material for our present studies.

#### Publications:

Brown, G. W., Jr.; Chaikoff, I. L.; and Chapman, D. D.  
 Demonstration of  $\beta$ -Oxidation and Acetoacetate Formation in

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a Mouse Hepatoma. Proc. Soc. Exp. Biol. Med., 84:586-588,  
 December 1953.  
 Katz, J., and Chaikoff, I. L. A Chromatographic-  
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 in Animal Tissues, J. Biol. Chem., 206:887-900, February  
 1954.

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Responsible Investigator: William G. Dauben  
University Department: Chemistry and Chemical Engineering  
Financial Support 1954-55: UC \$ 2,600.00.

Title of Project: A Study of the Effects of Radiation on  
 Cholesterol.

The purpose of the project is to investigate further  
 the nature of the products formed by the irradiation of  
 cholesterol, a normal body constituent. From such a study  
 it is hoped to be able to evaluate the possible routes  
 whereby irradiation products can arise and to ascertain if  
 such products can be related to known chemical carcinogens.

It has been found that cholesterol upon irradiation  
 with soft beta rays undergoes decomposition when the reaction  
 is conducted in the presence of water or air. The nature  
 of the products produced suggests that certain portions of  
 the molecule are more susceptible than others. Of the  
 positions attacked, it is of interest to note that the  
 products formed can be viewed as being possible precursors  
 of the chemical carcinogen, methylcholanthrene.

Work now in progress is to determine the possible  
 route followed in such an irradiation in the absence of  
 air and water. Further, it is hoped to evaluate the role  
 of the irradiation in the decomposition of cholesterol so  
 that a better idea may be gained as to the general aging

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properties of this sterol.

Publications To Date: None.

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I

Responsible Investigator: Dr. Charles A. Dekker

University Department: Biochemistry

Financial Support 1954-55: ACS \$ 4,600.00.  
(grant-in-aid CH-23)

Title of Project: The Chemical Synthesis of Dinucleoside  
Phosphates and Dinucleotides.

APPROACH

Reaction of nucleoside 2':3'-cyclic phosphates and nucleoside (2' or 3') phosphoryl ureas with suitably protected nucleosides and nucleotides.

PROGRESS

(1) The reaction of the cyclic phosphates with simpler alcohols and amino alcohols has been examined. In aqueous solution at pH 7 to 9 good yields of nucleotide esters have been obtained with amino-alcohols. The mechanism of this reaction has been investigated in view of its possible relation to enzyme catalyzed transesterification reactions.

(2) Self-condensation of the cyclic phosphates in non-aqueous systems has been investigated with the finding that modest yields of di- and tri-nucleotides can be formed in this manner.

(3) New methods of phosphorylation have been sought which would simplify the preparation of the intermediates in the reaction. In particular, salicylyl phosphate and

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o-phenylene phosphate have been investigated. The former  
 has proved useful for a simple and rapid preparation of  
 uridine diphosphate (UDP) from uridine monophosphate  
 (UMP) although in small yield. The o-phenylene phosphate  
 has certain advantages as a phosphorylating agent, since  
 the protecting group (o-phenylene) can be easily removed.

Publications:

Dekker, C. A., and Khorena, H. G. Carbodiimides.  
 VI. The Reaction of Dicyclohexylcarbodiimide with Yeast  
 Adenylic Acid. A New Method for the Preparation of  
 Monoesters of Ribonucleoside 2'- and 3'- Phosphates.  
 J. Am. Chem. Soc., 76:3522, 1954.

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Responsible Investigator: Dr. Charles A. Dekker

University Department: Biochemistry

Financial Support 1954-55: UC \$ 4,024.00.

Title of Project: Study of the Specificity of the  
Phosphatases Involved in the Degradation of Nucleic Acids.

AIM

Further knowledge regarding the structure of nucleic acids and regarding the mechanism of action of the various enzymes.

APPROACH

Synthetic substrates are prepared and the action of the enzymes studied.

PROGRESS

A clearer understanding of the specificity of the phosphodiesterase obtained from Crotalus adamanteus venom has been gained using synthetic nucleoside 2':3'-cyclic phosphates and esters of nucleotides. The same derivatives have been tested as possible substrates for other phosphodiesterases. This work has resulted in the discovery of an ideal substrate for ribonuclease which should have value as a means of assaying for this important enzyme.

The action of deoxyribonuclease on deoxyribonucleic acid (DNA) has been studied and a mechanism has been

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proposed which explains the changes in physical properties of the DNA which are observed during the hydrolysis.

Publications:

Dekker, C. A. Action of Snake Venom Phosphodiesterase on Nucleoside 2':3'-cyclic Phosphates and Related Compounds. Fed. Proc., 13:197, 1954.

Dekker, C. A. and Schachman, H. K. On the Macromolecular Structure of Deoxyribonucleic Acid: An Interrupted Two-strand Model. Proc. Natl. Acad. Sci., 40:894, 1954.

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Responsible Investigators: K. B. DeOme; Howard A. Berni;  
Max Alfert.

University Department: Zoology and Its Cancer Research  
Genetics Laboratory.

Financial Support 1954-55: UC \$10,100.00; ACS \$ 3,098.00.

Title of Project: The Cancer Research Program of the Cancer  
Research Genetics Laboratory.

The research program intrinsic to the Cancer Research Genetics Laboratory is supplemented by cooperative projects in which Laboratory research personnel and facilities are employed to varying degrees. Larger cooperative projects are separately reviewed and are referred to throughout the text of the report.

#### STUDY OF THE "PRECANCEROUS LESIONS"

##### OF THE MAMMARY GLANDS OF THE MOUSE

The hyperplastic nodules found in the mammary glands of mice belonging to strains destined to have mammary tumors, are usually referred to as "precancerous lesions." Because little is known of the morphologic and physiologic characteristics of these nodules, an organized effort is being made to characterize them definitively and to determine the factors involved in their induction, maintenance, and transformation into tumors. Thus, the "precancerous lesion" is being investigated with regard to: 1) growth potential

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DeOme et al. <sup>2</sup>

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in terms of transplantability, 2) metabolic and cytochemical characteristics, and 3) response to endocrine factors in the living animal and in organ culture.

### I. Transplantation Studies.

The precancerous nature of the hyperplastic nodules found in the mammary glands of virus-infected mice which develop mammary tumors has been inferred from several types of evidence. The "precancerous lesions" could be either mammary gland areas altered by the virus, which are not yet neoplastic; or areas which have already undergone the neoplastic transformation. A comparison of the transplantability of hyperplastic nodules, normal glands, and known tumors should be helpful in distinguishing between these two possibilities.

A single hyperplastic nodule, a sample of normal mammary gland, and a sample of tumor, all from the same donor mouse, were simultaneously implanted into a series of test animals. The fate of these transplanted tissues is being determined. To date, all of the tumors, only a few of the hyperplastic nodules, and none of the normal glands have shown tumor-like growth. The results suggest that most of these hyperplastic nodules had not undergone the neoplastic transformation.

(DeOme, Wellings, Faulkin)

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DeOme et al. <sup>3</sup>

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## II. Characterization of the Hyperplastic Nodule.

### 1. Morphologic and Cytochemical Studies.

It has been possible to establish some criteria for hyperplastic nodules, and various cytologic and cytochemical methods have been employed in comparing them with normal, prelactating, lactating, and tumorous mammary tissue. It is apparent that there is a family of structures referred to as "hyperplastic nodules."

In general, in the inactive gland the "average" hyperplastic nodule closely resembles prelactating tissue in regard to cytoplasmic vacuolation (and therefore lipid distribution) and in the distribution of alkaline phosphatase. Microspectrophotometric studies using the Feulgen reaction for DNA demonstrate no difference between normal gland and hyperplastic nodule; both contain predominantly diploid cells and a small proportion of presumably premitotic tetraploid cells (with twice the "normal" DNA value). In tumors, the frequency of tetraploid cells is greatly increased; this is probably correlated with the higher mitotic activity of this tissue. In addition, tumor tissue contains some highly polyploid cells which are not found in corresponding non-neoplastic tissues.

(Alfert, Bern, DeOme, Nishi)

### 2. Metabolic Studies.

A comparison has been made of the uptake of radioactive phosphorus ( $P^{32}$ ) of normal, nodular, and tumorous mammary

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DeOme et al. <sup>4</sup>

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tissue from the same female C<sub>3</sub>H mice. Analysis of the paired data from untreated multiparous animals demonstrates that the nodule has a significantly higher P<sup>32</sup> uptake than normal tissue and a significantly lower P<sup>32</sup> uptake than the tumor, thus establishing an intermediate metabolic position for the nodules. Nodular tissue shows a P<sup>32</sup> uptake not significantly different from that of lactating tissue.

Data have been obtained on the effects of pregnancy, ovariectomy, and estradiol administration. In the pregnant animal there is an elevation of P<sup>32</sup> uptake of non-tumorous tissue approaching the level found in tumorous tissue. In addition, the difference between nodular and normal (i.e., pre-lactating) tissue is less apparent. The relationship between normal, nodular, and tumorous tissues observed in untreated mice is not appreciably altered by estrogen treatment for two weeks.

(DeOme, Bern, Pissott; with the collaboration of W. E. Berg)

### III. Investigation of Endocrine Control Factors.

#### 1. In vivo Studies

Preparations of mammary glands from about 400 young male and female C<sub>3</sub>H mice, with and without milk factor, are being studied with respect to the influence of various hormonal treatments upon the incidence and morphology of the hyperplastic nodules. Administration of estradiol, prolactin, hydrocortisone, and testosterone; ovariectomy;

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and various combinations of these treatments have been employed. To date, observations indicate that definite glandular abnormalities result from estrogen treatment. Some are indistinguishable from typical hyperplastic nodules; others appear to be atypical growths developed from terminal buds. In addition, unique alveolar hyperplasias appear after month-long hydrocortisone treatment.

The effect of castration on the nodule incidence in virgin female C<sub>3</sub>H mice is also being determined. Castration at an age when the tumor incidence is not affected appreciably will provide information as to whether the nodules are independent of ovarian control or regress in the absence of ovarian hormones.

Some success has been attained in the development of technics for routine adrenalectomy and hypophysectomy of mice. The use of the triply operated mouse (hypophysectomized-adrenalectomized-ovariectomized) will eventually be required to analyze fully the hormonal interactions involved in nodule and tumor induction.

Nodules, particularly in prelactating glands, are often filled with a secretion frequently indistinguishable from milk. Studies with oxytocin are being conducted to see whether or not these nodules will "let-down" milk in the same way as normal lactating glands. Some evidence for the existence of non-reactive nodules has been obtained, and an

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DeOme et al.

attempt is being made to correlate the response with presence or absence of myoepithelial cells in the nodules.

The possible role of the adrenal cortex in the mammary response to estrogen administration is being investigated. Although no significant adrenal hypertrophy occurred in estrogen-treated C<sub>3</sub>H mice, B Alb C mice show notable adrenal hypertrophy coupled with so-called "brown degeneration" of the inner cortical zones. Studies have been completed which show that estrogen reduces the resistance of mice to stressors (formalin, cold, inanition) and that the relation of adrenocortical stimulation to continued estrogen dosage needs to be considered.

(Bern, DeOme, Frunk, Wellings, Campbell, Blair, Harkness, Nandi, Rosen, Crosby. Professor C. H. Li kindly supplied the prolactin employed.)

The effect of castration at different ages upon the incidence of mammary tumors in female C<sub>3</sub>H mice is being studied. Previous studies have shown that castration at an early age (less than 2 months) will prevent the appearance of mammary tumors, whereas castration at later ages will not prevent the development of tumors. Studies now in progress indicate that the older the mice at the time they are castrated, the higher the tumor incidence. For example, no tumors appeared in animals castrated at 60 days of age, whereas a large number appeared in those

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castrated at 150 days of age. An attempt is being made to ascertain the influence of the adrenal upon tumor incidence in castrated mice.

(Pilgrim)

2. In vitro Studies.

Surgical difficulties make it impossible to observe the neoplastic transformation in living mice. Because of these difficulties it would be useful to maintain normal and precancerous mammary gland tissue in culture so that changes could be observed. Initial attempts to culture the mammary hyperplastic nodule in vitro by Fell's organ-culture method have been successful. Nodules removed from the mammary gland under sterile conditions have been maintained for several weeks by subculturing. Fortunately such cultures exhibit only a slight tendency to form cellular outgrowths.

Experiments are now being set up which will allow us to determine the following: 1) the course of development of nodules in vitro and their subsequent transplantability; 2) the effects in vitro of hormones known to affect mammary tissue in vivo; 3) the development of nodules from mice pretreated with various hormonal combinations; 4) the effects of carcinogens added to the culture medium; 5) the influence of high pH of the culture medium, reported to cause epithelial proliferation in tissue cultures of mammary tumor cells. It is hoped that these studies will provide information

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on the development potential of hyperplastic nodules.  
(Elias, DeOme, Bern, Frunk)

THE STATUS OF THE MAMMARY TUMOR VIRUS IN STRAIN A/Cal MICE.

The lack of correspondence between the increasing incidence of mammary tumors and the demonstrated presence of mammary tumor virus in A/Cal mice has been studied for several years. Prior to four years ago this strain had been essentially free of mammary tumors and of virus. Since that time the mammary tumor incidence has increased as the result of selection to more than 75%. Three successive virus tests during the last four years have shown that the demonstrable mammary tumor virus has not increased in proportion to the incidence of mammary tumors. The presence of "precancerous lesions" in the mammary glands of these mice, and the present high incidence of breast cancer suggest that some virus-like inciting agent is present, but possibly in a changed state. Additional experiments are being carried out to clarify this situation.

(DeOme, Frunk, Barnawell)

THE TUMOR SPECTRUM OF WILD MICE.

The need for experimental animals with tumors of the gastrointestinal and reproductive tracts prompted a search for new strains of mice which might have tumors of these types. Since laboratory mice have been selected for other types of tumors for many generations, it seemed possible

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that unselected wild mice might show the desired tumor types, and could be used to establish new laboratory strains. Wild mice were collected from the salt marshes adjacent to San Francisco Bay and were maintained in the laboratory until they died. Several inbred lines were started to establish whatever new characteristics might be present in the wild mouse population. A sufficient number of wild mice and their immediate descendants have died so that a preliminary picture of their tumor incidence can be presented. Unfortunately, the spectrum of tumors among wild mice does not differ significantly from that found in laboratory mice. The inbred lines are not yet old enough to reveal differences in tumor incidence.

Tests for the presence of the mammary tumor virus among wild mice are nearly complete and reveal that little if any virus is present; however, mammary gland preparations from some wild mice show "precancerous lesions" similar to those found in virus-infected laboratory mice. Tests for genetic resistance to mammary tumor are not yet complete, but suggest that the wild mice are resistant.

The resistance of wild mice to X-ray irradiation has been studied, but again the wild mice do not differ significantly from the laboratory mice.

(DeOme, Barnawell)

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### EXPERIMENTS ON CELL SELECTION

The degree of variability existing among the individual cells within the cell population comprising a tumor is of both theoretical and practical significance. For example, the search for a chemotherapeutic agent for cancer depends upon the assumption that all of the cells within a tumor cell population are sufficiently alike so that they will respond to a given agent. Whether or not cell variability is sufficiently low to make successful chemotherapy likely, has not been demonstrated by actual test.

Several years ago we started a series of experiments to test the variability of mammary tumor cell populations, using transplantability to different but closely related strains as the criterion of variability. However, the experimental design was so rigorous as to exclude most of the tumors tested; hence, the results obtained to date are not representative of mammary tumors of the mouse. The results obtained from the "atypical" tumors indicate that the variability is very great. Less rigorous tests have been started which will allow inclusion of a greater number of spontaneous tumors.

(DeOme, Frunk, Finster)

### AN ATTEMPT TO TRACE THE MAMMARY TUMOR VIRUS IN TISSUES OF MICE.

The mechanism by which the mammary tumor virus produces mammary tumors in the mouse is unknown. Mice infected with

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virus during the first month of life develop tumors 8 to 11 months later. A knowledge of the fate of the virus during the period between infection and tumor formation might give some clues to the method by which the virus initiates tumors. The "fluorescent antibody" method of Coons is being developed as a promising approach to the location of virus in the host. (Alfert, DeOme, Goldstein, with the collaboration of R. C. Backus of the Virus Laboratory)

REASON FOR THE EARLY ONSET OF MAMMARY TUMORS IN A/Ne MICE.

A new substrain of A/He mice has appeared in this laboratory. The new substrain (A/Ne) is characterized by a very early age of onset of mammary tumors but retains the same high incidence as its parent strain (A/He). Since an early age of onset of tumors usually implies an increased genetic susceptibility to tumors or an increased potency of the tumor-inducing agent, it follows that an investigation of the difference between A/Ne and A/He mice should yield valuable information pertinent to these two points. A series of experiments is under way designed to reveal possible differences in genetic susceptibility, in the quantity or quality of the mammary tumor virus, and in endocrine activity in these two strains.

(Beebe)

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#### SUBSTITUTION OF X-RAY IRRADIATION FOR MAMMARY TUMOR VIRUS IN MICE.

Mammary tumors can be produced in mice by means of either virus or chemical carcinogens. X-ray irradiation is also known to produce tumors in mice, but it is not known whether or not X-ray irradiation can produce mammary tumors in the absence of chemical carcinogens or the mammary tumor virus. Experiments were conducted to answer this question.

A hybrid mouse was produced with full genetic susceptibility to mammary tumor but without the mammary tumor virus. These hybrid mice were irradiated with doses of X-ray varying from 0-700 r. The experiment is not completed, but it is already clear that X-ray irradiation is not comparable to either virus or chemical carcinogens as in incitor of mammary tumors in these hybrid virgin female mice. A similar experiment has been started using breeding female mice of the same genetic composition.

(DeOme, with the collaboration of Henry Kohn and Robert Kallman of the Radiological Laboratory)

#### STUDIES OF NORMAL AND ABNORMAL KERATINIZATION.

Cytochemical studies of keratin formation in the vagina, in metaplastic lesions, and in the epidermis have been continued. Vaginal keratinization in the rat resulting from estrogen treatment has been distinguished from that

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occurring in vitamin A deficiency on the basis of certain histologic criteria and of cytochemical differences in the distribution of alkaline phosphatase, RNA, sulfhydryl groups, etc. In estrogen-induced keratinizing lesions in the mouse prostate, microspectrophotometric measurements of nuclear DNA and protein reveal a pattern of nuclear degeneration differing from that typical of pycnotic degeneration. Epidermal studies have resulted in some information on the nature of the keratohyalin granules of the stratum granulosum, which evidently include a RNA component along with considerable phospholipid and show little evidence for any direct relation to the keratinization process.

Radioautographic studies with S<sup>35</sup>-cystine, P<sup>32</sup>-phosphate, C<sup>14</sup>-amino acids and carbonate have been completed and allow us to present a working hypothesis of the chemistry of keratin formation. In the formation of both "soft" keratin (estrogen-treated vagina, esophagus, epidermis) and "hard" keratin (hair shaft, tongue papillae) in the mouse, similar processes seem to occur. There is a specific concentration of radiocystine (presumably as cysteine) by the keratogenous zone in hair formation and by an analogous sub-corneal zone in "soft" keratin-forming tissues. This concentration is evidently accomplished by cells which, although dying, are nevertheless capable of carrying on protein synthesis in the form of keratin. Proteins moving up in cells from

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the proliferating layers would seem to undergo hydrolytic decomposition in the keratogenous zone where cysteine is incorporated in the synthesis of new protein. The sulfhydryl groups of cysteine are then evidently oxidized to disulfide to form cross-linkages between the polypeptide chains.

Additional radioautographic studies on the distribution of radiocystine during the hair cycle, in the female genital tract in various endocrine states, and in the normal organism generally are being completed.

(Bern, Alfert, Harkness, Blair)

#### HUMAN CERVICAL TUMORS.

Human tumors, like the well known animal tumors, are probably the result of the interaction between hereditary and environmental factors. Previous studies have failed to reveal consistently strong hereditary predisposing factors in the occurrence of cancer of the uterine cervix in the human female; hence, a search for environmental factors was undertaken. Environmental factors which might influence the incidence of cervical cancer were sought in the histories of women who had recovered from cervical cancer. More than fifty patients and a like number of controls (matched for age, race, sex, and religion) were interviewed by one questioner. Complete family histories were obtained, and the presence or absence of the selected environmental



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Responsible Investigator: David M. Greenberg  
University Department: Physiological Chemistry  
Financial Support 1954-55: UC \$12,500.00; ACS \$12,242.00;  
 PHS \$ 9,500.00; Runyon \$12,000.00.

Title of Project: Biochemical Studies on the Nature and  
 Regression of Neoplastic Growth.

PURPOSE OF INVESTIGATION

The major topics that are being investigated in our  
 cancer research program are: 1) A comparative study of the  
 metabolic reactions and biochemical properties of normal  
 and neoplastic cells. 2) Study of the effect of the  
 neoplastic process on the metabolic reactions and biochemical  
 properties of the host. 3) Chemotherapy studies on cancer  
 based on the principles of metabolite antagonism and  
 radiomimetic action. 4) Study of the mechanisms of the  
 development of drug resistance in cancer.

Through the comparative study of the metabolic  
 reactions and chemical properties of neoplastic and normal  
 cells, it is hoped that eventually differences between  
 the cancer and the normal will be discovered that can be  
 employed for the development of effective measures for  
 the diagnosis, treatment, and control of neoplasms.

METABOLIC STUDIES ON TUMORS

A spectrum of mouse and rat tumors are being studied  
 for differences in chemical and metabolic properties.

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Wide differences have been observed in the contents of the free amino acids and nucleic acids. The differences are of such a magnitude that they warrant comparative studies on the effect of widely different tumors on the metabolism of the tumor-bearing host. Such an investigation should distinguish between metabolic derangements which may be related to the specific metabolic pattern of the tumor and those which are a general condition of neoplasia.

#### MECHANISMS OF PROTEIN SYNTHESIS

This is being approached by investigation of the effects of chemical analogues of certain amino acids on the incorporation of radioactive amino acids into the protein of the Ehrlich ascites carcinoma. Two types of metabolite antagonists appear to be emerging from this work. One type exerts an independent inhibition on its congener and does not interfere with the incorporation of unrelated amino acids. The other type appears to block incorporation of all amino acids so long as the congener amino acid remains unavailable. Evidence has also been obtained of the manner of utilization of phosphate bond energy in peptide synthesis. We feel that this investigation should throw new light on the mechanism of action of amino acid antagonists and consequently will contribute to the understanding of the use of antimetabolites in the control of neoplastic growth.

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CHEMOTHERAPY

In the field of cancer chemotherapy it is important to constantly test against the defects of present methods and to develop improved methods.

Since the free-cell ascitic form of a tumor has been shown to be more susceptible to chemotherapy via intraperitoneal injection, we have attempted to develop an assortment of these ascites tumors for preliminary screening tests. Three of our 5 mouse tumors (Ehrlich carcinoma, Gardner lymphosarcoma, and the C3H-SX mutation of the Shinkin mammary carcinoma) and the rat tumor (Walker-256 carcinosarcoma) have adapted to growth and transplanting in the ascitic form.

Evaluation of cancerostatic activity on these free-cell forms is based on 1) total weight gain, 2) ascitic fluid weight, 3) packed cell volume of the ascitic fluid, and 4) degree of solid tumor growth in the peritoneum.

All compounds screened here are now tested first against the ascitic tumor which has been shown to be most sensitive to a related known cancerostatic agent (See Table I). Compounds proving effective under these conditions are tested further on other ascites and solid tumors and via other routes of administration.

To date, this procedure has shown one sulfur-mustard analogue synthesized in our laboratories, to be as effective as N-mustard against the 3 ascitic tumors tested,

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i.e. both produced complete regression of the free cell forms of the Ehrlich and C3H-SX tumors. Further characterization of this compound, against solid tumors and by varying routes, is in progress.

TABLE I

Effect of Known Cancerostatic Agents on Different Forms of Some Mouse Tumors

	Ascitic Tumors						Barrett
	Ehrlich		Gardner		C3H-SX		Solid
	Free cell	Solid	Free cell	Solid	Free cell	Solid	Mamm. Carc.
<b>Mustards:</b>							
N-Mustard	++	+	+	-	++	+	+
SM-1	++	+	±	-	++	+	
<b>Ethylenimine Compds:</b>							
TEM		+					
TEP		++(toxic)					
TEP (thio)		++(toxic)	±	-	-	-	++
<b>Purine-Pyrimidine:</b>							
8-Azaguanine	+		+	=	=	-	+
6-Mercaptopurine	+		-	-	-	-	+
Thioguanine			+	-	+	-	
			(toxic)		(toxic)		
<b>Miscellaneous:</b>							
Aminopterin	++		-				
Urethan	+						
ACTH	-						
Hyleran (Timmis compd.)			-	+	-	-	+
++ complete regression (or 90% c solid tumors) + moderate regression ( 50-75% c " " ) ± slight regression ( 25-50% c " " ) - no effect = increased tumor growth							

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### GENERAL METABOLISM AND ENZYME STUDIES

There are three essential levels of cancer research:

1) Clinical research on cancer patients; 2) research on experimental cancer with neoplasms; and 3) research on the fundamental basis of life processes. The last named provides the pool of information upon which the other two must draw.

Basic research in our Laboratory consists of a study of the pathways of metabolism and reactions of the amino acids, phospholipid bases and one-carbon compounds. Gratifying progress is being made which is worth mentioning briefly here. An enzyme system has been obtained which synthesizes serine from glycine and formaldehyde. Coenzyme requirements of this enzyme system are tetrahydrofolic acid and pyridoxal phosphate. In the study of the metabolic degradation of the essential amino acid threonine, one enzyme, threonine dehydrase, which converts this amino acid to  $\alpha$ -ketobutyric acid has been crystallized. Another one, threonine aldolase, which splits threonine to acetaldehyde and glycine, has been considerably purified and its properties studied.

Progress is being made in developing the step-by-step pathways of the metabolism of valine, the leucines,  $\alpha$ -aminobutyric acid, methionine, histidine, etc. Significant results are also being developed in clarifying the metabolic cycle of transformation of serine to glycine to ethanolamine to choline and back to glycine.

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### SYNTHESIS OF COMPOUNDS FOR METABOLIC AND THERAPEUTIC STUDIES

The importance of our Laboratory for the synthesis of compounds for the metabolism and chemotherapy studies cannot be overemphasized. Compounds of potential interest are constantly being prepared. Many, of course, are isotopic compounds commonly containing  $C^{14}$  or  $S^{35}$ . Mention of these compounds appear in the list of publications given below.

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Chem., (in press).

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Responsible Investigator: Morgan Harris  
University Department: Zoology  
Financial Support 1954-55: ACS \$ 4,894.00.

Title of Project: Studies in Cell Nutrition.

This investigation was initiated in October 1954, and has not yet progressed to the point of yielding definite results. We are planning to study growth processes in tissue culture by a new cell suspension technique and at the present time are "retooling" the laboratory to permit the use of this new procedure. Cell counts, determination of DNA (desoxyribonucleic acid) and other quantitative criteria will be used to evaluate the role of protein and nonprotein factors for the nutrition of chick cells in vitro. As opportunity permits we plan also to study the variability in cell populations, using strains established from single cells as starting material.

Publications:

Harris, Morgan. The Role of Bicarbonate for Outgrowth of Chick Heart Fibroblasts in vitro. J. Exp. Zool., 125:85-98, 1954.  
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inoculated, freed of medium constituents for analytical purposes, and used for a variety of purposes that previously were limited to cancerous cells alone, which have been cultivated under similar conditions for some time.

Comparative studies of several cancer cell types with the normal human cells under comparable conditions, both morphologically and chemically, have been prosecuted and are being continued.

An effort is underway to locate a nutritional constituent of embryo extract ultrafiltrate that is believed to be present in impure vitamin B<sub>12</sub> samples. Such samples were highly effective in a synthetic medium additive, but purified vitamin B<sub>12</sub> samples did not have the same effect. This difficult problem is not yet to a point at which significant progress can be reported.

Publications:

Calleau, Relda, and Kirk, Paul L. The Influence of Various Culture Media on the Growth of Earle's Strain L Cells and Chick Heart Fibroblasts in vitro. J. Natl. Cancer Inst., 15:295-303, 1954.

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Kirk

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Responsible Investigator: Albert P. Krueger, M. D.

University Department: Bacteriology

Financial Support 1954-55: UC \$ 2,395.00; ONR \$17,125.96.

Title of Project: Studies of Fundamental Virus-Host Cell Relationships.

Until recently only two mechanisms for altering a host-virus equilibrium were generally recognized. On the part of a mammalian host this alteration could be achieved by change in the immunological status of the individual. On the part of the virus it was caused solely by the selection of spontaneous mutants. There has been general acceptance of the principle that the host has no influence on the properties of the virus whose growth it supports.

Some three years ago we reported the discovery of an unusual case of host control over viral properties. In this instance passage through a new host resulted in a non-inheritable ability of the viral particles to reproduce in some hosts but not in others. This subject of host-controlled variation is currently our major research project. Our work has been concerned with the following aspect of the phenomenon:

The properties of the host controllable phage.

The mechanism of the control effected by certain staphylococcal cells.

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The behaviour of altered virus with respect to the formerly susceptible host.

Extension of the phenomenon to other staphylococcal strains.

The altered virus was found to adsorb on the original host cells but only a small percentage of the viral particles produced cellular dissolution. The altered virus was produced in the first burst of singly infected host cells regardless of the previous host. Judging from the data presented in Reference 1 below the observed changes appear to be caused by host control over the formation of viral materials necessary for a successful infection of the original host.

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Ralston, D. J., and Krueger, A. P. The Isolation of a Staphylococcal Phage Variant Susceptible to an Unusual Host Control. J. Gen. Physiol., 37:685-716, 1954.

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Responsible Investigators:    STAFF OF DONNER LABORATORY AND  
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John H. Lawrence, John W. Gofman, Hardin B. Jones,  
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 Paul J. Elmlinger, Ernest L. Dobson, Lola S. Kelly,  
 Roman Kutsky, N. K. Freeman, Ann C. Birge, Robert  
 Mortimer, Hal O. Anger, Thomas L. Hayes, John E.  
 Hewitt, Carl A. Beam, R. Lowry Dobson, and James E.  
 Roberts.

University Department:            Division of Medical Physics  
 and Biophysics and Donner Laboratory

Financial Support 1954-55:    UC \$50,000.00; PHS \$15,832.00;  
 AEC \$36,000.00, (Cyclotron time,  
 pile use, etc.);  
 Various Donors \$ 475.00.

FUNDAMENTAL CANCER RESEARCH

This report reflects the varied approaches to the  
 problem of the fundamental nature of cancer and therapy  
 of malignant disease carried out in the Donner Laboratory.  
 These studies have ranged from a study of the biological  
 effectiveness of irradiation in yeast through studies on  
 various growth promotion factors, the rate of synthesis and  
 turnover of nucleic acids to investigations of metabolic  
 alterations in human cancer and the introduction of a new method  
 for the treatment of carcinoma of the breast in women by  
 radiation of the pituitary with 340 mev. protons. A  
 description of the work carried out in the various projects  
 follows:

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### PROJECTS

1. Studies of Nucleoprotein Metabolism
2. Blood Mixing Rates in Leukemia with Splenomegaly
3. Studies on Blood Volume, Iron Metabolism, and Red Cell Life in Malignancy
4. Use of Various Experimental Techniques for Evaluating Red Cell Life Span
5. Studies on Erythropoetic Hormone
6. Studies of Body Composition
7. Radiation Protection
8. The Problem of Leukemia in Polycythemia Vera
- \*\* 9. Radiation Studies Utilizing High Energy Protons and Deuterons
- \*\* 10. Diagnostic Techniques for Detection of Radioactive Isotopes in the Human Body
11. Biophysics of Growth and of Radiation Effects
12. A Biophysical Study of Factors Determining Survival of Cancer Populations
13. Lipoprotein Studies of Fat Metabolism in Cancer

\*\* These studies have been supported either in part or entirely by the Atomic Energy Commission. The particular types of instrumentation and research facilities necessitate directly the use of cyclotrons, piles, and related ancillary facilities. They are reported here in that they bear upon the full cancer research program of the Donner Laboratory of the University of California.

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1. Studies of Nucleoprotein Metabolism.

Studies on the rate of formation of desoxyribose nucleic acid (DNA) have continued under various metabolic conditions in an effort to learn more about the factors controlling the rate of cell division. It is now well established that DNA precursors, such as the phosphate (containing P<sup>32</sup>) are incorporated into DNA only when a cell is increasing its content of DNA in preparation for division. Hence the incorporation of P<sup>32</sup> into DNA is a good index of the overall rate of cell division.

An extensive series of measurements on the inhibition of DNA synthesis after irradiation of normal tissues, regenerating liver, and two tumors has been completed in the past year. The tentative conclusion has been reached that a major portion of the inhibition in DNA formation is due to death of cells shortly after irradiation rather than to a specific inhibition of DNA synthesis. Death of cells within a few hours after irradiation is a particularly prominent phenomenon in lymphoid tissues and probably accounts for the drastic inhibition of DNA synthesis in lymphosarcomas as compared to the moderate inhibition in mammary carcinomas. However, in order to confirm this hypothesis, radioautographic experiments are planned in which it will be possible to analyze events occurring in individual cells.

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The rate of DNA formation is being measured in various tissues of hypophysectomized rats to determine the influence of pituitary hormones or their absence on the rate of cell division. Preliminary results indicate that DNA formation is markedly reduced in all organs of hypophysectomized rats with the possible exception of intestine. Experiments are planned to test various hormone supplements in these rats for their ability to restore DNA formation and to compare the effects of hypophysectomy on normal tissues and transplanted tumors. It is hoped that some knowledge of endocrine influences will help explain the previously observed disturbances in DNA formation which occur in tumor-bearing animals.

The average cell life is being estimated in various tissues of normal and tumor-bearing mice in an effort to learn more about the influence of transplanted tumors on the metabolism of the host animal. This is done by measuring the amount of P<sup>32</sup> incorporated into DNA at many time intervals after injection. Since the tracer remains in DNA until the death of the cell, an estimate of cell life can be obtained from the rate of disappearance of P<sup>32</sup> from the DNA of a given tissue.

Studies of a chick embryo nucleoprotein fraction which stimulates growth in tissue culture have been carried out in the following manner.

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The chick embryo tissues and organs were separated by dissection and a nucleoprotein fraction (NPF) isolated from each tissue by precipitation with streptomycin. The NPF's are then tested for growth activity in a chick embryo heart tissue culture. These studies show that spine, cartilage and carcass NPF are more active than whole embryo NPF. Cartilage appears to be the most potent source of this nucleoprotein fraction. Ultraviolet analysis shows that these tissue NPF fractions contain from 2-1/2 to 10% nucleic acid. Further study of each tissue NPF by electrophoretic analysis revealed from 2 to 4 components. On the basis of electrophoretic mobility of the tissue NPF's there appears to be some differentiation of the more active NPF's. Ultraviolet analysis of electrophoretic subfractions of tissue NPF's indicates an increased mobility with increased nucleic acid content, the constituent nucleoproteins ranging from 1.5 to 80% nucleic acid. Assay of whole embryo NPF with the chick embryo heart culture technique shows that the active principle in this material is probably of intermediate mobility, but is not clearly defined electrophoretically and is probably present in very low concentrations. It is anticipated that in the near future human cancer tissue will be studied in the same manner--that is, after isolation with streptomycin. The nucleoprotein fractions will be studied

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for growth promoting activity and will be characterized as well as possible by known physical-chemical means.

2. Blood Mixing Rates in Leukemia with Splenomegaly.

When tagged red cells or labeled plasma proteins are injected intravenously and their mixing curves obtained by recording frequent timed samples in the post injection period, marked differences in the mixing behavior of the red cells as compared to the plasma proteins can be observed in certain patients with splenomegaly. Labeled red cells and labeled plasma proteins mix very rapidly, 90% in about 2 minutes, in normal individuals. Gross prolongation of the red cell mixing time has been observed in some, but not all patients with splenomegaly. Occasionally about 50% of the red cell population has been observed to mix with a half time of 10 minutes. This component has been completely eliminated by surgical removal of the spleen and greatly reduced by the administration of epinephrine which causes marked contraction of the spleen, thus reducing its size and the quantity of "sequestered" red cells.

3. Studies on Blood Volume, Iron Metabolism, and Red Cell Life in Malignancy.

Measurement of the blood volume in 66 patients with

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red cell formation is adequate to maintain the observed total red cell volume. In 7 of these 8 patients the iron turnover for red cell formation was normal or increased, and in one it was decreased. In the one patient in which it was decreased the total red cell volume was also decreased. This patient was also studied with radioactive glycine and a normal red cell life span obtained. The implications of these studies of iron metabolism are that a failure to produce a normal number of red cells is not a significant factor in the production of the anemia of malignancy. One inference from the iron studies is that the red cell life span may be shortened in cancer. However, in the one patient with carcinoma of the breast and three with lymphosarcoma that have been studied, all have had normal red cell life spans. This does not mean that a shortening of the red cell life span may not be a significant cause of anemia in cancer. However, no patient has yet been studied who was anemic by blood volume standards and has an increased iron turnover so that we cannot at the present time clearly define the mechanism for the development of anemia in cancer.

4. Use of Various Experimental Techniques for Evaluating Red Cell Life Span.

The life span of red cells may be measured in the

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following ways:

- A. The Ashby Differential Agglutination Technique.
- B. The use of Nitrogen-15 or Carbon-14 labeled glycine.
- C. Long-term follow-up of the uptake of Fe<sup>59</sup> in the red blood cells. An inference may also be drawn as to the life span of the red blood cell from the rate of formation of red cells; however, this requires a constant total red cell volume which is difficult to postulate in most cases.
- D. The use of Chromium-51 labeled red cells.

Simultaneous determination in 13 individuals of the life span of the red cell with the Ashby Technique, the Carbon-14 technique, and radio-iron technique shows that when the red cell life span is normal all three methods agree. However, when the red cell life span is shortened, these three methods may not agree. This arises from the fact that in the Ashby Technique normal cells are transfused into a diseased individual. If the red cell destructive processes are accelerated as a result of extra-corporeal factors, the destructive process of these transfused cells will then be comparable to that of the individual's own cells. However, if the individual is producing defective cells resulting in a shortening of the life span, the Ashby Technique will fail to show this. The evidence from these simultaneous studies would indicate that such a

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possibility does exist.

Studies are now underway with a view toward measurement of the life span of the red cell with Cr<sup>51</sup>. The patient's own red blood cells may be labeled in vitro with Cr<sup>51</sup> and then reinjected. Unfortunately, there is a slow elution of chromium from the red cells so that the red cell life span as measured by this technique is not the actual red cell life span. Data are now being accumulated on normals and pathological states. The most important problem is to determine whether the rate of elution of chromium from the red cell in pathology is the same as in the normal. Since this procedure is easier technically than the other methods, if it can be proven to be satisfactory this will be a significant advance in the study of the life span of the red blood cell. Although the actual red cell life span will not be obtained, a figure will be obtained which is directly related to the actual red cell life span.

5. Studies on Erythropoetic Hormone.

Studies carried out in collaboration with the Institute of Experimental Biology over the past several years have shown that following hypophysectomy in the rat the blood volume decreases such that at 100 days following hypophysectomy the total red cell volume is reduced approximately 45%. Studies on the removal of other

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endocrine organs show that this anemia is primarily a result of the hypophysectomy. Efforts have been made to extract a substance from the pituitary gland, which will repair this anemia. These extracts have been partially purified. Doses as low as 15 micrograms of this material will correct this anemia. At the present time studies are underway to purify further this material and to remove all remaining traces of ACTH activity. At present this material is assayed by determining the changes in the total red cell volume of animals receiving this extract. The utilization of plasma iron turnover as measured with radio-iron in hypophysectomized rats injected with this material is being explored as another assay method. It is hoped that this method will permit a more rapid assay.

Finally, studies of the plasma of patients with polycythemia vera have turned up an erythropoetic stimulating factor not present in normal blood. These studies are being extended.

#### 6. Studies of Body Composition.

Depot fat and lean tissue mass in humans are not readily accessible to direct measurement. In the past these have been estimated from the total body water of the mean body density. However, the relationships between fat and water or density presume a fixed percentage of water in lean

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tissue, and consequently, may be invalid in pathologic states. Studies in this laboratory indicate the depot fat and lean tissue mass may be measured in pathological states by simultaneous measurement of both body water and mean body density. Tritium labeled water has been used for the determination of body water in normal and in disease states. Recently a new method for measuring mean body density has been developed in this laboratory to circumvent the limitations of the older body immersion technique. This is a gas dilution technique providing a direct measure of body volume. The subject is placed at atmospheric pressure in a rigid closed chamber into which an accurately determined quantity of helium is injected. Following complete mixing, the helium concentration which is proportional to the tissue volume of the subject is determined by the change in the thermal conductivity of the chamber gases as measured by a hot wire Wheatstone bridge. Studies in 200 patients including patients with various neoplastic diseases and normal subjects, the latter ranging in age from 21 to 85, have been completed. Sufficient data now are at hand to establish the natural variations in body composition as a function of age, sex, and body type. Additional studies are in progress on changes in body composition in malignancy.

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comparison of blood volume is cc/kilogram of body weight. However, it has been found that in the extremes of body weight this may not be a satisfactory index. Particularly is this true in patients with malignancy or those who have lost weight. In the past in such patients we have tended to use the blood volume in terms of cc's per kilogram of actual body weight, recognizing that there is some controversy as to whether this is the best index. Certainly if used in this manner this gives some idea of the blood volume available to the tissue mass to which blood must flow and to which nutrients must be carried and catabolic products removed. In general, adipose tissue is of a low degree of vascularity and because the adipose tissue varies considerably in quantity in normals, it is found that the range of the normal blood volume in terms of cc's per kilogram of body weight is large. However, it is now evident that the range of normal blood volume in terms of cc's per kilogram of lean tissue is small. By measuring the blood volume and by measuring body water and body volume in patients with malignancy, we will then be in a better position to determine the presence or absence of anemia in terms of blood available to the lean tissue mass. This procedure should prove useful as an aid in determining the presence of anemia in these cases.

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7. Radiation Protection.

Observations including hematological studies are being carried out on persons exposed frequently over a long period of time in the course of their occupations to small but possibly significant levels of ionizing radiation within the accepted "tolerance" range. Special attention has been paid to cytological differences in the blood of the exposed group as compared to an unexposed control group. These studies confirm Ingram's earlier observation that low level exposure is correlated with an increase in the number of circulating double-nucleated and bi-lobed lymphocytes. Detailed studies on a few individuals covering the period before exposure and the period after exposure have been made. An increase in double-nucleated lymphocytes has been demonstrated. The exact time relationship between significant doses of radiation and the transient appearance of these abnormal cells in the peripheral blood is being further explored.

8. The Problem of Leukemia in Polycythemia Vera.

In recent years there has arisen some discussion as to the possibility that the use of P<sup>32</sup> in the treatment of polycythemia vera may induce leukemia. The evidence for this consists largely in the observation of certain groups of workers of the development of acute leukemia in a small

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percentage of patients. Actually, the problem is one of the natural history of the disease. Unfortunately, there are no statistics available on the life expectancy and the causes of death in any large series of patients who have not been treated with irradiation. However, there are isolated observations of the development of acute leukemia in patients with polycythemia vera who have not received any form of irradiation therapy. Long-term follow-ups have shown that in patients who have lived 15 years after onset, 80% die with a picture like that of myelogenous leukemia, and that of those who live 10 years, 62% die with leukemia. In the patients treated in this laboratory only 42% of those who have survived more than 10 years and who have died, die with leukemia. This lower figure is not thought to be statistically significant.

In an effort to determine if it is possible to predict whether a given patient will develop leukemia, a statistical analysis has been made of the white cell count, the differential count and the presence or absence of splenomegaly in the patients who do develop leukemia as compared to those who have not. This study shows that the incidence of leukemia is higher in certain patients. These are those patients who prior to any therapy have a markedly elevated white count and who show immature cells in the peripheral blood. There is no correlation between the presence or absence of

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splenomegaly and the development of leukemia. These studies, of course, do not prove or disprove that leukemia can be induced by x-irradiation treatment or with P<sup>32</sup>. However, with the remarkable prolongation of life in this disease, 14 years average survival when treated with P<sup>32</sup> as compared to 7 years in other series and the marked reduction in the incidence of vascular complications make P<sup>32</sup> the most satisfactory form of therapy in polycythemia vera. It is also our belief that we have not increased the incidence of leukemia in polycythemia vera as a result of P<sup>32</sup> therapy. The evidence cited makes it probable that the development of leukemia is a part of the natural history of the disease.

9. Radiation Studies Utilizing High Energy Protons and Deuterons.

I. INTRODUCTION

Some of the penetrating radiations produced by the Berkeley 184 inch cyclotron, chiefly 190 Mev deuterons and 340 Mev protons, have now been investigated over a period of about five years in physical and biological studies. (See previous progress reports). It has become increasingly evident that the physical properties of these radiations give somewhat unique advantages in several fields of biological research. In particular we wish to review briefly some applications in endocrinology, neurophysiology,

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and tumor therapy.

## II. PHYSICAL PROPERTIES OF HIGH ENERGY PROTONS AND DEUTERONS AND TECHNIQUES OF IRRADIATION

The use of these types of irradiation allows a high dose to be delivered to small, well defined volumes of tissue (located within the body), whereas the surrounding and intervening tissues receive much smaller doses. This localized destruction of tissue may be accomplished in one of the following ways:

A. The monoenergetic particles are allowed to stop in the region to be irradiated. The particles thus cause 3 to 6 times as much ionization near the end of their range as compared to the point of entry.

B. A collimated beam of particles is delivered through the volume to be irradiated, and then the body of the animal is rotated such that the volume element to be irradiated is at the center of rotation and hence remains essentially stationary. By using several planes of rotation the dose to intervening tissues is distributed over a solid angle, which materially reduces the dose outside the central volume. During the current year development was concentrated on the latter technique.

Most of the present work concerns the application of the high energy particles to pituitary irradiations in larger animals and man. Because of the vital and important

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structures surrounding this gland, an anatomical and physical scheme which would allow precise alignment of the rotational center and also high precision in the entire rotational apparatus and procedure was developed.

With this technique radiation dose to tissues outside the volume being specifically irradiated decreases very rapidly as a function of distance from the volume specifically irradiated. Moreover, the symmetry of dose distribution attained is such that doses to the surrounding structures and regions can be rather accurately predicted.

III. PRESENT FACILITIES (NEW HUMAN PROTON IRRADIATION FACILITY)

During the current year a new irradiation room was constructed to extend the utility of the 184 inch cyclotron for purposes of human pituitary irradiation.

#### IV. STUDIES OF PITUITARY IRRADIATION IN ANIMALS

##### A. Rats.

During the past three years a detailed study has been carried out on the effects of pituitary irradiation in young rats. Members of the Institute of Experimental Biology have collaborated in this work. Characteristic evidences of hypophysectomy appeared at doses as low as 3,000 Rad units (1 rad = 100 ergs/gm tissue) although a progressively higher dose was, in general, found to shorten the time at which hypophysectomy effects were evident.

A lower incidence of spontaneous tumors was observed

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irradiated rats than in the normal controls. This work was done in collaboration with Dr. M. Simpson.

Dogs.

Studies now in progress have been chiefly undertaken on (young adult) pure-bred Beagle dogs, in which the anatomical relations of the pituitary to the skull have been found to be relatively constant. Two forms of rotational techniques have been used and several dose levels delivered to the pituitary.

In general, it has been found that to depress or destroy the functional integrity of either the pituitary gland or the cranial nerves--both dose and time following irradiation are critical factors. 18,800 Rad delivered to the pituitary results in depression of function in one to two months; while cranial nerves 3, 4, and 6 ceased to function with smaller doses (11,000 to 13,200 Rad) in the same interval of time after irradiation. This dosage ratio, pituitary: cranial nerves 3, 4, and 6, is much less in man, of the order of 5:1, because of anatomical differences.

Most animal studies of this type have used single large doses. In view of the fact that clinical irradiation therapy utilizes fractionated dose methods, a program has been instituted to study the effects of fractionation of the dose on pituitary and brain. This program is in collaboration with Dr. B. Low-Beer.

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**Monkeys.**

Initial studies have been instituted on young animals given 0,400 Rad. using rotational therapy. Several more will be required to obtain the complete data in this experiment, but marked retardation of growth has been observed ten months post-irradiation.

**V. PITUITARY IRRADIATION AS A POSSIBLE THERAPEUTIC MEASURE IN CANCER**

Beginning in September 1954 a limited program was started on the therapy of breast cancer, using the 340 mev proton beam from the 184 inch cyclotron. The patients selected have had every other known form of therapy, and all have tumors responsive, in the past, to hormonal therapy.

The rationale for this type of therapy is that the growth and secretory functions of certain carcinomas are strongly influenced by hormonal substances, and removal of certain endocrine organs in man (especially testes, ovaries, and adrenals) has been shown to result in a regression of metastatic lesions and a definite remission. There are many reasons to suspect that pituitary hormones may influence certain malignant cells, and that hypophysectomy might result in remission.

The therapeutic procedure consists, in brief, of rigidly securing the head in the apparatus by means of a specially

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and plastic cast made for each individual patient, and aligning the desired point within the sella turcica to the beam such that this desired point is the center of rotation of the head. The accuracy of this alignment is held within  $\pm 0.5$  mm for each of the three axes of orthogonal alignment. Diagnostic x-rays are utilized for this procedure. Rotation of the head is carried out during therapy so that as a net result the beam is distributed through a solid angle ( $60^\circ \times 60^\circ$ ) with the pituitary at the vertex.

The patients are followed very closely clinically-- during and following therapy. A large number of laboratory studies are carried out at repeated intervals to assess the influences of the procedure on the disease process and the effects on the endocrine system. Probably at least three year follow-ups will be required for even a preliminary evaluation of the results.

#### VI. STUDIES OF HYPOTHALAMIC PHYSIOLOGY IN RATS

During recent years studies from several laboratories have indicated the importance of the hypothalamus on anterior as well as posterior pituitary function, and also hypothalamic influences on autonomic and other regulatory mechanisms.

Preliminary studies utilizing very small deuteron beams have indicated that this technique has advantages

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of electrolytic lesions produced by means of electrically located electrodes. One set of observations is worthy of mention here, namely that certain areas of the hypothalamus appear to have a significant influence on the normal growth of rats. The mechanism of this growth effect has been elucidated.

Diagnostic Techniques for Detection of Radioactive Isotopes in the Human Body.

A. Scintillation Crystal Scanner.

In the 1952 and 1953 reports a ten channel scintillation crystal scanner particularly suitable for study of the distribution of gamma ray-emitting isotopes administered in tracer doses to the human body was described. With this instrument a visual record of the distribution of radioactive substances in the body is obtained.

The following studies are in progress:

1. Detection of thyroid carcinoma metastases with <sup>131</sup>I.
2. Study of the fate of iodine labeled antibodies in the body.
3. Distribution of radiopotassium (chiefly into muscle masses).
4. A study of liver and spleen size using a radio-gold colloid, which is deposited in the reticulo-

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endothelial system.

Preliminary studies show that this is a

factory instrument for carrying out these studies.

**B. Gamma Ray Pinhole Camera and Image Amplifier.**

The system described in the report for 1953, for

direct visualization of a gamma ray source, has now been

thoroughly investigated. The present system has an

intrinsic image amplification of some 600 fold; however, it

is still not sensitive enough for medical tracer work.

Further progress awaits development of a better image

amplifier tube.

**11. Biophysics of Growth and of Radiation Effects.**

A study has been conducted for the past three years

on the general mechanisms of cell division and its inhibition

by penetrating radiations. Yeast cells are used exclusively.

Evidence has been accumulating to show that the inhibition

of cell division is mostly due to recessive lethals and in

addition a certain percentage of dominant lethals are

present. It was shown that cell division inhibition depends

on the mitotic state; budding cells are about 10 times more

resistant than resting cells. General relationships are

being sought between the deterministic role of the genes

and the wide morphological variations encountered in given

strains of microorganisms. A study was made of the

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Statistical fluctuations of cell division time under standard environmental conditions. This may be an index of the nucleocytoplasmic relationship. The root mean square fluctuation of cell division time in diploid yeasts is about 6% over a few degrees temperature range. When the cells are irradiated, cell division is delayed and its time fluctuations also increase. The delay occurs at lower doses than the inhibition of cell division, and is not very dependent on ploidy.

Statistical fluctuations in cell division time increase as the cell division delay increases. After irradiation usually one normal cell division occurs, then the following division is delayed; finally the cell division time returns to normal in subsequent divisions. These events are consistent with the idea that the mechanism of cell division delay differs from cell division inhibition; the former may be related to the inactivation of a number of essential molecules; until these molecules are resynthesized by the cell, the division cannot proceed.

Tracer experiments and other studies of the nature of cell division are usually hampered by the generally asynchronous state of cell division of growing colonies. Yet the small statistical fluctuations in cell division time, and the generally "periodic" nature of cell division suggest that experimentally cell division might be

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is synchronized in the laboratory by periodic applications of division promoting or retarding influences. An apparatus has been built to administer periodic changes of medium to a colony of yeast cells. By alternating dextrose buffer with complete medium, two states may be obtained: One with only 0.1% of the cells budding; the other with about 70% of cells in the budding state.

12. A Biophysical Study of Factors Determining Survival of Cancer Populations.

A survey of the survival tendencies of large cancer populations reported in the medical literature has been begun. Several facts and conclusions can already be pointed out.

A. All groups of cancer types present a uniform tendency to die at a fixed rate. This is essentially independent of the ages of the cancer group or the duration of the disease. The fixed rate of death is proportional only to the numbers in a cancer population at any time; this suggests possibly that the high death rate of cancer is a random occurrence as far as any individual member of a population is concerned and that the length of life already spent with his cancer may not predispose to any more rapid rate of death compared to a person who has just acquired a similar type of cancer.

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B. Since the lethal tendency is probably a random event and not related to duration of the disease, it is postulated that the cause of death is some metabolic change that has become likely because of the presence of cancer. This argues for an intensive search into metabolic changes in the cancer state as a means of preventing cancer mortality, since such a change may be the actual killer and not the presence of the cancer itself. The above argument, of course, is also answered by the random destruction of a vital center by a metastases. However, this latter mechanism appears to explain only a fraction of the deaths from cancer.

13. Lipoprotein Studies of Fat Metabolism in Cancer.

That the metabolic aging of the body is increasing at a logarithmic progression in the latter half of the life span is shown from the rapid exponential increase in the death rate as caused by various degenerative diseases that are the end results of metabolic disturbances incurred throughout life. Since each of the main killing diseases of our population, heart disease, cancer, cerebral vascular-renal disease as well as others are increasing at very nearly if not the same rate of progression, it is concluded that many inter-related factors of metabolism provide bases of relationship between physiologic vigor and the

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susceptibility to a given degenerative disease. It is  
 further predicted that any study which is a good general  
 measure of the vigor of body metabolism such as the lipoprotein  
 measurements will be of some use in predicting early death  
 from any of the degenerative diseases and that while the  
 lipoprotein studies are chiefly of interest with reference  
 to cardiovascular disease, it is now possible that they  
 may have general usefulness in relation to death from  
 cancer or other degenerative diseases. This concept will  
 be tested during the coming year during which time the  
 large pool of "normal" individuals that have had their  
 metabolism rated by the lipoprotein studies, will be  
 searched for those that have subsequently developed  
 disease.

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I

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Responsible Investigator: Daniel Mazia  
University Department: Zoology  
Financial Support 1954-55: ACS \$ 7,000.00.

Title of Project: Enzyme Chemistry of Chromosomes.

On this project, a number of lines of study are being pursued.

1. The structure of the chromosomes. One of the questions arising from genetic theory is to what extent is the chromosome a chemical continuum and to what extent is it particulate? The approach to the problem of how a structure is put together is to determine how it can be taken apart. I have now shown that the chromosome can be taken apart by treatments that do not involve the splitting of primary organic bonds. It appears that it is composed of desoxyribonucleoprotein particles held together entirely by ionic forces and especially by bridges of Ca or Mg ions. This has some interesting consequences for the theory of chromosome breakage and radiation sensitivity, which are now being tested.

2. Mitosis. Following our earlier successful isolation of the mitotic apparatus of dividing cells we have this year looked into the chemistry of its formation. It now appears to be composed of a single

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Mazia I 2

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protein or a group of very similar proteins, which we have analyzed. Basically, it seems to be a gel in which the protein molecules are linked together by sulfur atoms. Its remarkable fibrous structure seems to depend on the formation of bundles of these protein chains, the chains being held together by some secondary bond. The action of antimetabolic agents such as colchicine seems to be an inhibition of the formation of these secondary bonds.

3. Problems of nuclear function. Of the various lines of attack on nuclear function that have been followed this year, two have led to definite conclusions. A study of the incorporation of a labelled amino acid, methionine-<sup>35</sup>S, into cells from which the nucleus has been removed shows an immediate drop in incorporation. Therefore, the nucleus must directly control a certain part, but not all, of the synthesis of proteins in the cell (experiments on Amoeba). A second study was directed toward the question, does the nucleus continue to function during the time when the cell is dividing? The answer seems to be negative; at least with respect to the utilization of phosphorus, the dividing cell operates at the same depressed rate as does the cell from which the nucleus has been removed.

Publications: See Publications (I & II) following next report.

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II

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Responsible Investigator: Daniel Mazia  
University Department: Zoology  
Financial Support 1954-55: UC \$ 4,000.00.

Title of Project: Mechanism of Chromosome Duplication.

This project is directed toward answering the following questions. (1) When during the life cycle of the cell does the duplication of the genetic material take place, and what is its exact time course? (2) Does the hereditary system duplicate in such a way that the material of the parent chromosome is distributed between the two daughter chromosomes, or is a substantially new chromosome formed?

Our attempts to answer these questions experimentally are based on the technique of high resolution autoradiography: the photographic registration of the sites of radioactive atoms within the cell. Dr. Walter S. Plaut, who is supported in part by this grant, has been responsible for setting up the autoradiographic procedures.

A series of autoradiographic observations on the Amoeba cell suggests that  $P^{32}$  is incorporated into DNA, the suspected hereditary substance, during the period between divisions, especially during the twelfth to eighteenth hour of the twenty four hour cycle. We have established that  $C^{14}$  labelled adenine is readily

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2  
Mazia II

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incorporated, and this, plus the quantitative method mentioned below, will now permit us to settle question 1 with reasonable exactness.

In our first attempt to answer question 2, the sperm cells of Drosophila were labelled with P<sup>32</sup> and permitted to fertilize an egg that was not labelled. However, we found that it was not feasible to follow the labelled chromosomes, as we had hoped, because of their exceedingly small size and low P content. The development of a quantitative technique makes it possible to carry out this experiment on a type of cell with a larger chromosome number. We are now using the plant Crepis with six chromosomes that are fairly large, which looks as though it will be suitable for exact measurements of the distribution of parental DNA between daughter nuclei.

A great drawback of autoradiography in the past has been the lack of a quantitative method: in order to estimate the concentration of radioactive atoms, it is necessary to count the number of blackened silver grains in a microscopic area. In collaboration with Dr. Plaut and Mr. G. W. Ellis, an optical "grain counter" has been developed which now permits us to measure the autoradiographs quantitatively.

Publications: ACS and UC grant publications listed together. See next page.

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Publications I & II  
Mazia

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Publications:

Prescott, D. M., and Mazia, D. The Permeability of Membranes of Isolated and Enucleated Fragments of Amoeba proteus. Exp. Cell Res. 6:117-26, 1954.

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Responsible Investigator: Nello Pace  
University Department: Physiology  
Financial Support 1954-55: UC \$ 2,400.00.

Title of Project: Intracellular Constitution of Normal Rat  
 Liver, Regenerating Rat Liver and Butter Yellow Hepatoma in  
 the Rat

Although this project has only been in operation since  
 July of this year, progress may be reported. The aim of  
 the project is to compare the characteristics of the  
 intracellular constituents of a tissue under three  
 conditions: first, normal, adult tissue, where little  
 growth is occurring, i.e. normal rat liver; second, the  
 same tissue undergoing rapid, but controlled growth, i.e.  
 regenerating rat liver; and third, the same tissue  
 suffering deranged growth, i.e. a butter yellow induced  
 hepatoma.

It has been possible to obtain hepatomas in Long-  
 Evans strain rats by feeding butter yellow, the dye  
 p-dimethylaminoazobenzene, in the diet for three months.  
 Similarly, the surgical technic has been perfected for  
 removing the bulk, about two thirds, of the liver from a  
 rat so that successful regeneration of the liver tissue  
 takes place. Thus, animals are now available for making  
 the comparative studies on the liver as outlined above.

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Preliminary experiments have been carried out on liver  
 homogenates from the three types of rats, employing the  
 analytical ultracentrifuge to examine the characteristics of  
 the large-molecule complexes of the cell cytoplasm. On the  
 basis of these very primitive experiments it does appear  
 that the sedimentation pattern of the cancer cells shows  
 differences from the patterns obtained from normal and  
 regenerating liver. More work is required, however, before  
 the quantitative significance of these results may be  
 assessed.

Publications To Date: None.